European Handbook of Dermatological Treatments

Third Edition

Andreas D. Katsambas
Torello M. Lotti
Clio Dessinioti
Angelo Massimiliano D'Erme
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ISBN 978-3-662-45138-0 ISBN 978-3-662-45139-7 (eBook)
DOI 10.1007/978-3-662-45139-7

Library of Congress Control Number: 2015934002

Springer Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer-Verlag GmbH Berlin Heidelberg is part of Springer Science+Business Media (www.springer.com)

Preface

The third edition of the *European Handbook of Dermatological Treatments* follows the successful second edition published in 2003, providing concise yet comprehensive, up-to-date overviews of treatment guidelines and pearls in a plethora of skin diseases.

Over the last years, dermatology has achieved major breakthroughs in molecular and clinical research that have enabled the discovery of new treatments; our therapeutic armamentarium has been enriched with biological agents for psoriasis, also used as off-label promising treatments in other skin diseases, targeted agents for malignant melanoma and basal cell carcinoma, and new treatment modalities for rosacea, acne, atopic dermatitis, and urticaria, to name a few.

The three main sections of the third edition of the handbook are (i) diseases, (ii) drugs, and (iii) methods, encompassing different skin diseases, drugs available for dermatological treatments, and various methods applied in dermatology, including fillers, botulinum toxin, laser, dermoscopy, cryosurgery, and electrosurgery. Each chapter is focused on treatments, also providing a brief synopsis of the etiology and clinical presentation of the skin disease. Each chapter is structured with an abstract and a list of key points, while a comprehensive presentation of dermatological treatments, recent updated guidelines and recommendations, indications, contraindications, modes of action, and dosages are analyzed by our colleagues, experts in the field.

The third edition is enriched with clinical photos aiming to make the reading of the handbook a pleasurable as well as a learning experience. The skin is the most visible organ, and skin diseases can be challenging to effectively treat. The handbook focuses on dermatological treatments; indeed, treating patients is the essence of medicine, following the words of Hippocrates of Kos: "*Primum non nocere*."

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Part II Methods

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Part I

Diseases

Acne

1

Clio Dessinioti and Brigitte Dreno

Key Points

- Acne vulgaris (acne) is a chronic inflammatory dermatosis that requires long-term treatment.
- Topical treatments (retinoids, benzoyl peroxide [BPO], azelaic acid, or antibiotics) are recommended for mild comedonal or inflammatory acne and in combination with systemic treatment for moderate and severe acne.
- The use of systemic treatments is indicated for moderate to severe inflammatory acne vulgaris, for acne that is resistant to topical treatments, and for acne of the trunk.
- Combination treatments are recommended to enhance effectiveness and tolerability and to improve the patient's compliance to the proposed treatment regimen.
- Treatment should aim to reduce the risk of bacterial resistance. Antibiotics (oral or topical) should not be used for more than 3 months and always be combined with topical agents such as retinoids or BPO.
- The treatment choice should be individualized and should take into account the age and the medical history of the patient, the type and severity of acne, the impact of acne on the patient's quality of life, the risk of scarring, and the presence of prognostic factors such as a family history of acne, adult acne, hyperseborrhea, hyperandrogenemia, truncal acne, or a history of infantile acne.
- Topical treatment is recommended as maintenance therapy, usually with a topical retinoid, BPO, or azelaic acid.
- Conglobate acne is a rare but severe form of nodular acne mostly affecting adult males. It presents with numerous comedones, papules, pustules, nodules, abscesses, and draining sinus tracts on the chest, back, and buttocks. Oral isotretinoin is strongly recommended as a monotherapy for conglobate acne.
- Acne fulminans is a rare acne variant affecting adolescent boys. It is characterized by the sudden onset of painful, ulcerative crusting acne in association with systemic signs and symptoms including fever, weight loss, arthralgias, and myalgias.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_1, © Springer-Verlag Berlin Heidelberg 2015

Definition and Epidemiology

Acne vulgaris (acne) is the most common skin disorder, affecting more than 80 % of adolescents, although it may present at any age. It has been defined as a chronic inflammatory dermatosis characterized by comedones and inflammatory lesions, including papules, pustules, and nodules, on sebum-rich body areas such as the face and trunk. It may be associated with a severe psychological and social impairment, as it may result in dysmorphia and permanent scarring, with a risk of low self-esteem and depression.

Conglobate acne is a rare but severe form of nodular acne mostly affecting adult males. It presents with numerous comedones, papules, pustules, nodules, abscesses, and draining sinus tracts involving mainly the chest, back, and buttocks. It frequently results in extensive and disfiguring scarring.

Acne fulminans (also known as acute febrile ulcerative acne or acne maligna) is a rare acne variant affecting adolescent boys. It is characterized by the sudden onset of painful, ulcerative crusting acne in association with systemic signs and symptoms including fever, weight loss, arthralgias, and myalgias. Aseptic, osteolytic bone lesions, visible on radiographs, have also been reported. Acne fulminans can be the dermatologic manifestation of the synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome.

Basic Concepts of Pathogenesis

The four major pathophysiologic factors that influence acne pathogenesis include sebaceous gland hyperplasia with hyperseborrhea, follicular hyperkeratinization, hypercolonization of the pilosebaceous unit with *Propionibacterium acnes (P. acnes)*, inflammation, and immune reaction. Although each of these factors may represent a potential therapeutic target, the sequence of events has not been elucidated yet.

Androgens are central players in acne, as they increase the size of sebaceous glands and the sebum production, and they stimulate keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum, thus contributing to comedone formation. Sebaceous gland lipids exhibit direct pro-inflammatory properties playing a key role in acne pathogenesis. Although the relative amounts of *P. acnes* may not differ between acne patients and normal individuals, it has been proposed that specific *P. acnes* predominate in acne patients and possess specific genes that may increase virulence, promote stronger adherence to the human host, or induce a pathogenic host immune response.

Clinical Presentation

The clinical lesions in acne vulgaris are either non-inflamed lesions including open or closed comedones or inflamed lesions including papules, pustules, or nodules.

Acne may be classified based on the age of onset, into childhood, adolescent, or adult acne. This classification is important as there are age-related differences in the clinical presentation and the treatment approach.

Acne may present in childhood, and it is classified depending on the age of presentation, in neonatal, infantile, mid-childhood, and prepubertal acne.

In adolescents, acne presents around 12–14 years of age and usually resolves around 18–20 years of age.

Adult acne affects individuals older than 20–25 years. Adult acne is termed late-onset acne or acne tarda, when it first presents in adulthood, while persistent acne refers to acne continuing from adolescence to the adult years of life. Persistent acne is the most common form of adult acne, accounting for 80 % of cases. There are two clinical forms of adult acne: the inflammatory form consisting of papulopustules and deep inflammatory nodules and the comedonal form characterized by macrocomedones.

Also, acne may be classified according to severity as mild, moderate, or severe and according to the lesions that predominate in a given patient as comedonal, papulopustular, or nodular (Figs. 1.1, 1.2, and 1.3). When there are a similar

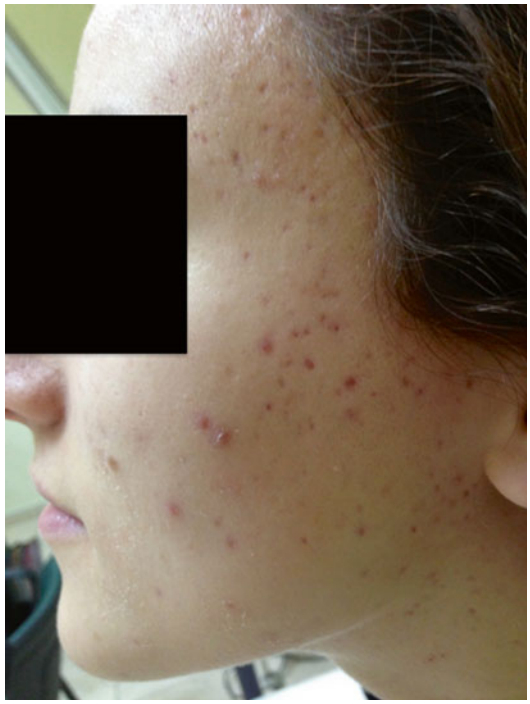


Fig. 1.1 Mild facial acne with few papules and pustules. Several acne scars are present

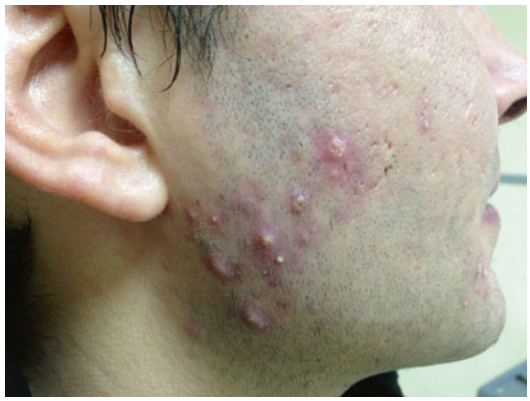


Fig. 1.2 Moderate facial acne with some papules and pustules. Acne scars are present

number of comedones and papules, it is referred as comedopapular acne, while in case of a similar number of papules and pustules, it is termed papulopustular acne. Severe cystic acne is characterized by the presence of cysts and numerous comedones, papules, and pustules.

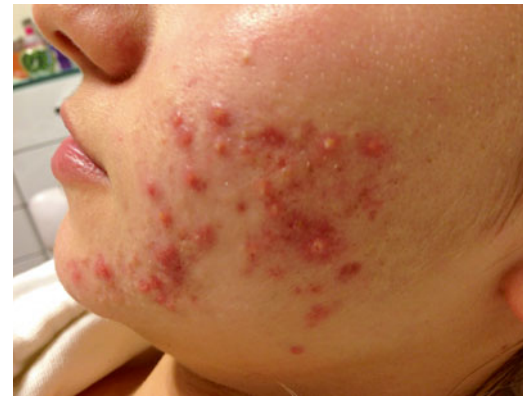


Fig. 1.3 Severe papulopustular acne

Differential Diagnosis

The diagnosis of acne is clinical. Acne is not an allergy or an infection, so laboratory evaluations are not necessary to confirm diagnosis, except if other conditions should be ruled out. The comedone is the sine qua non clinical lesion in acne. It is always present in acne and this is the key characteristic that establishes diagnosis.

Childhood acne should be differentiated from:

- Neonatal cephalic pustulosis: *Malassezia furfur* is found in microscopy, presents with pustules and no comedones, and responds to topical ketoconazole.
- Acne venenata infantum: is due to the application of topical oils and ointments.
- Milia: small cysts with keratin plugs. Spontaneous resolution.
- Acneiform eruption: due to maternal use of corticosteroids during pregnancy, no comedones, monomorphous lesions.
- Perioral dermatitis: may be due to the use of topical or inhaled corticosteroids. No comedones.

Adolescent acne should be differentiated from:

- Folliculitis: it presents with follicular pustules. Comedones are absent.

Adult acne should be differentiated from:

- Rosacea: it affects individuals after the age of 30 years. Comedones are absent.
- Perioral dermatitis: it affects individuals mainly after the age of 30 years. It is located around the mouth, nose, and eyes. Comedones are absent.

- Drug-induced acneiform eruptions due to glucocorticosteroids, antiepileptics, antidepressants, growth hormone, cyclosporine, vitamin B12, epidermal growth factor receptor (EGFR) inhibitors, and BRAF inhibitors: recent or current history of drug intake; comedones are absent.

General Principles of Treatment

Acne is a chronic disease, and patient education is critical to improve adherence to proposed treatment and optimize clinical results. It should be explained that acne treatment will continue over long periods of time and clinical improvement is not evident early but usually takes some (5–6) weeks to show. Topical treatments are fundamental for the management of acne, so the importance of applying topical agents should be communicated to patients. Topicals should be applied on the entire face and not just on the clinically visible lesions in order to effectively target the microcomedone, the primary acne lesion, that is not visible to the naked eye.

A mild cleanser may be used for washing the face twice daily. The use of noncomedogenic cosmetics and makeup products if camouflage is desired is encouraged. A suitable oil-free sunscreen during the summer and during oral isotretinoin treatment is advisable. Skin care products are often necessary to either complement the use of acne drugs or to counteract the drying effect of some acne medications, such as moisturizing creams during oral isotretinoin treatment and in combination with topical retinoids, in order to avoid topical irritation.

A common question often posed by acne patients is whether a specific food influences their acne. The intake of chocolate has been traditionally held as culprit for acne flare-ups. However, this has remained a myth and not a proven fact, and there are no evidence-based data to either support or refute an association of diet with acne. We suggest our acne patients to follow a balanced diet as part of a healthier mode of life in general.

Topical Treatments

Topical Antibiotics

Topical antibiotics include erythromycin, clindamycin, tetracycline, and nadifloxacin. They exert anti-inflammatory properties as well as antibacterial action against *P. acnes*.

Topical antibiotics are indicated for mild to moderate action. They should never be used as monotherapy but should be used in combination with another topical treatment such as retinoids, benzoyl peroxide, or azelaic acid, either in the context of alternate day regimens or as fixed-dose combinations. They are applied once or twice daily for a maximum period of 6 weeks.

Benzoyl Peroxide (BPO)

BPO has antibacterial, anti-inflammatory, and mild comedolytic actions. Topical BPO is indicated for mild papulopustular acne and for moderate to severe acne in combination with another topical treatment, such as retinoids, antibiotics, or azelaic acid. Also, it may be combined with systemic antibiotic therapy or, in women, with hormonal therapy. BPO is applied once or twice daily for a period that is determined by the treating dermatologist. It may be proposed as maintenance therapy.

Topical Retinoids

Topical retinoids include adapalene, isotretinoin, tazarotene, and tretinoin. They have comedolytic effects, and, in addition, adapalene exhibits mild anti-inflammatory action. Topical retinoids are indicated for comedonal and mild papulopustular acne. Also, they are indicated for moderate to severe acne in combination with another topical treatment, such as BPO, antibiotics, azelaic acid, and/or a systemic antibiotic or hormonal therapy. They are applied once or twice daily for a period that is determined by the treating dermatologist. They may be proposed as maintenance therapy.

Azelaic Acid (AZA)

Azelaic acid presents mild comedolytic, antimicrobial, and anti-inflammatory actions. AZA is indicated for comedonal and mild papulopustular acne. Also, it is recommended for moderate and severe acne in combination with another topical treatment such as BPO, retinoids, or antibiotic or in combination with a systemic antibiotic or hormonal therapy. It is applied twice daily, and treatment for at least 12 weeks is usually required for acne improvement.

Fixed-Dose Combination Topical Formulations

Fixed-dose combination topical agents combine two different agents used for acne treatment, such as combinations of antibiotic/retinoid or antibiotic/benzoyl peroxide or benzoyl peroxide/retinoid. Topical combination treatments target multiple pathogenetic factors at the same time, thus resulting in enhanced effectiveness and improved tolerability. Also, they present the advantage of a simpler application regimen, with a once- or twice-daily application of a single formulation, thus resulting in better adherence by the patient to the proposed treatment.

Topical retinoids in combination with topical antimicrobials have been shown to reduce inflammatory and noninflammatory acne lesions faster and to a greater degree than antimicrobial therapy alone. This may be explained by the fact that combination treatments target several areas of acne pathophysiology simultaneously. In addition, topical retinoids may affect skin permeability and facilitate the penetration of the topical antibiotic.

Clindamycin/zinc gel contains zinc acetate dehydrate applied once or twice daily in a formulation that reduces the extent of absorption of clindamycin through the skin while showing equivalent efficacy and safety to clindamycin lotion. Combinations of zinc with erythromycin may result in reduction of the risk of bacterial resistance.

Once-daily applied topical clindamycin/benzoyl peroxide and twice-daily applied erythromycin/zinc acetate are both effective treatments for acne, but clindamycin/benzoyl peroxide has an earlier onset of action. Also, a fixed clindamycin phosphate/tretinoin gel formulation applied once daily was more effective and faster acting in reducing acne lesions than clindamycin lotion formulation applied twice daily.

5 % Dapsone Gel

Dapsone is a sulfone with both anti-inflammatory and antimicrobial properties. Advances in cutaneous pharmacology have produced a new topical formulation of 5 % dapsone gel, which was shown to be an effective and safe treatment, when applied twice daily for 12 weeks. Glucose-6-phosphate dehydrogenase-deficient patients presented no laboratory abnormalities. It has been proposed that its action may be due to a direct inhibition of leukocyte trafficking and the generation of chemical mediators of inflammation by leukocytes. Alternatively, topical dapsone might act indirectly in acne, by altering the levels and/or activity of propionibacteria.

Topical Treatments at a Glance

- Topical treatments (retinoids, BPO, AZA, antibiotics) are recommended for mild comedonal or inflammatory acne and in combination with an oral treatment for moderate and severe acne.
- Topical antibiotics should not be used alone but in combination with another agent (e.g., retinoid or BPO) to avoid the risk of bacterial resistance.
- Topical treatments are recommended to be used in combination, either as separate agents or as fixed-dose combination agents.
- Fixed-dose combination agents aim to enhance effectiveness and tolerability and to improve patients' compliance to the propose treatment regimen.
- Topical treatment is recommended as maintenance therapy, usually with a retinoid, BPO, or AZA.

Systemic Treatments

The use of systemic treatments is indicated for moderate to severe inflammatory acne, for acne that is resistant to topical treatments, and for acne of the trunk. Established systemic acne treatments include oral antibiotics, isotretinoin, and hormonal therapies.

Antibiotics

Systemic antibiotics for acne treatment include tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, and minocycline) and macrolides (erythromycin, azithromycin).

Antibiotics such as tetracyclines (oxytetracycline, tetracycline chloride, doxycycline, and minocycline), trimethoprim, and macrolide antibiotics (erythromycin) have been a mainstay of treatment for moderate and severe acne and treatment-resistant forms of inflammatory acne, for more than 30 years. The efficacy of tetracycline derivatives in acne vulgaris is believed to be related, besides to their antibiotic effects, also to their anti-inflammatory effects. Anti-inflammatory action may be exerted via reduction in neutrophil chemotaxis, as well as via inhibition of proinflammatory cytokines and matrix metalloproteinase-9 (MMP-9). Nevertheless, data concerning antibiotic use in acne has been based on anecdotal reports, clinical experience, and small clinical trials.

Recommended dosage regimens are 500–1,000 mg/day for tetracycline and erythromycin, 300 mg/day for lymecycline, and 50–200 mg/day for doxycycline and minocycline. Treatment should not exceed 3 months.

Acne treatment with systemic antibiotics may be associated with vaginal candidiasis and gastrointestinal disturbances. Moreover, doxycycline has been associated with photosensitivity, while minocycline has been associated with pigment deposition in the skin, mucous membranes, and teeth, particularly among patients receiving long-term therapy and/or higher doses of minocycline. Rare adverse effects reported with minocycline use include autoimmune hepatitis, a systemic lupus erythematosus-like syndrome, and serum sickness-like reactions (Table 1.1). Tetracyclines are indicated for individuals older than 8 years, after permanent dentition has been completed, and they are contraindicated during pregnancy and lactation.

Bacterial resistance to antibiotics is an increasing health problem worldwide. Resistance of *P. acnes* is more common with erythromycin; less common with tetracycline, doxycycline, and trimethoprim; and rare with minocycline. Although acne itself is not infectious, antibiotic-resistant propionibacteria should be considered transmissible between susceptible individuals. The use of antibiotics may result not only in an increase of resistance of *P. acnes* but also in an increase in other resistant organisms, such as *Staphylococcus aureus.* In order to avoid this, it is recommended to avoid antibiotic monotherapy, to restrict antibiotic use to a minimum (up to 3 months), and to use combination treatments for acne.

Released in 2006, anti-inflammatory dose doxycycline (40 mg capsule containing 30 mg immediate-release and 10 mg delayed-release beads) administered once daily was approved by the US Food and Drug Administration (FDA) for the treatment of papulopustular rosacea. This formulation presents anti-inflammatory activity devoid of antibiotic effects, so that there is no evidence of antimicrobial selection pressure associated with its use. In patients with moderate acne, doxycycline at a subantimicrobial dose

Table 1.1 Adverse events associated with oral antibiotic use in acne vulgaris

Antibiotic	Adverse events
Tetracycline	Gastrointestinal upset
	Vaginal candidiasis
	Reduced absorption with food and dairy products
Doxycycline	Gastrointestinal upset
	Photosensitivity
Minocycline	Dizziness
	Rarely, intracranial hypertension
	Hyperpigmentation of skin, oral mucosa, teeth
	Autoimmune hepatitis
	Lupus-like syndrome
	Serum sickness-like reactions
Erythromycin	Gastrointestinal upset
	Vaginal candidiasis
	Resistance of *P. acnes*

(20 mg twice daily) has been shown to reduce both inflammatory and noninflammatory lesions, while no resistant strains of *P. acnes* were evident.

Moreover, an extended-release (ER) minocycline tablet, administered at a dosage of 1 mg/kg daily for 12 weeks, was FDA approved for moderate to severe inflammatory acne vulgaris in patients over 12 years old. This formulation produces a slower release of active drug, which is believed to reduce the risk of side effects such as acute vestibular adverse reactions, and overall drug exposure with time.

Azithromycin is a methyl derivative of erythromycin that effectively inhibits significant intracellular pathogens, as well as Gram-positive and Gram-negative aerobic and anaerobic bacteria, including *P. acnes*. It has been found to be effective in treating noninflammatory and inflammatory acne lesions. Whether its efficacy is mediated primarily through antimicrobial or anti-inflammatory action remains unclear. There is no data on azithromycin resistance developing in *P. acnes*; however, due to high bacterial resistance to azithromycin in the population (20–27.4 %), its use as a first-line antibiotic therapy for acne is not advised. However, it may be considered as an alternative to conventional anti-acne treatment.

Isotretinoin

Systemic isotretinoin (13-*cis* retinoic acid), a vitamin A derivative, is the only therapeutic agent that targets all four major factors involved in acne pathogenesis. The European Agency for the Evaluation of Medicinal Products (EMEA) recommends that its use should be limited to severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) that has proved resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. However, it has been proposed that oral isotretinoin may be considered as a first-line treatment, in the case of existing prognostic factors that have been proven to influence acne, such as family history, early onset of acne, trunk involvement, persistent and late-onset acne, hyperseborrhea, scarring potential, and severe psychological impact. Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first-line therapy (e.g., financial resources/reimbursement limitations, legal restrictions, availability, drug licensing).

Isotretinoin is recommended at a dose of 0.3–0.5 mg/kg/day, given in two divided doses, for at least 6 months and until there is sufficient response. A lower clinical response with oral isotretinoin 0.5 mg/kg/day for 6 months, for mild to moderate adult female acne, has been associated with a high-glycemic-load diet, smoking, and early acne onset. Relapse after treatment with oral isotretinoin has been reported in 15–45 % of patients, and it has been associated with early acne, young age at the moment of isotretinoin initiation, family history of acne, prepubertal acne, localization on the trunk, important seborrhea, and a high number of inflammatory lesions at the end of treatment.

Systemic isotretinoin has been associated with a plethora of adverse events, most of which are dose dependent and self-limited. Mucocutaneous xerosis is the most common adverse event, resulting in dermatitis, cheilitis, epistaxis, and conjunctivitis. Laboratory evaluations during therapy should include triglycerides, cholesterol, transaminase levels, creatine phosphokinase, and complete blood counts. Hypertriglyceridemia and hypercholesterolemia have been reported in 25 % of patients but are reversible when isotretinoin is stopped. Elevated liver function tests have also been reported, which return to normal within 2–4 weeks despite continued treatment, and only rarely is treatment discontinuation needed. The most important adverse events are teratogenicity and psychiatric disorders. Isotretinoin is a known teratogen for women, so pregnancy should be avoided during treatment and for 1 month after cessation of treatment. Before treatment initiation, women of childbearing potential should be informed about teratogenicity of isotretinoin and the absolute need of effective contraceptive measures throughout treatment and for 1 month after treatment completion. Some studies and case reports have reported mood disorders, depression, suicidal ideation, and suicides in patients taking isotretinoin, while other studies have failed to

show such an association. There is not enough evidence to establish a causal link between isotretinoin use and suicide or major depression. On the contrary, isotretinoin therapy has been shown to improve anxiety and depressive symptoms in acne patients. Oral isotretinoin should not be combined with oral tetracyclines as there is increased risk of benign intracranial hypertension.

New developments and future trends are low-dose long-term isotretinoin regimens and new isotretinoin formulations (micronized isotretinoin). Intermittent moderate-dose isotretinoin has been proposed for adult patients with mild acne unresponsive or rapidly relapsing after treatment with oral antibiotics. In a study of 80 patients, isotretinoin was used at a dose of 0.5 mg/kg per day for 1 week every 4 weeks for a total period of 6 months. The acne resolved in 88 % of the patients, but 12 months after treatment 39 % of the patients had relapsed. Another intermittent isotretinoin regimen which was found to be a safe and effective option for the treatment of mild to moderate acne consisted of isotretinoin 0.5–0.75 mg/kg/day for 1 week, every 4 weeks, for a total period of 6 months (cumulative dose 35 mg/kg). The importance of continuing effective contraception should be underlined for women taking intermittent isotretinoin regimens.

Hormonal Therapies

Hormonal agents for acne treatment are indicated for female patients only, and they include antiandrogens and combined oral contraceptives (OC). Hormonal therapies exert their beneficial effects in acne by reducing circulating and local androgens and by opposing the actions of androgens in the pilosebaceous unit.

Appropriate patient selection is important when considering initiating hormonal therapy. Contraindications should be ruled out and treatment should be individualized. Hormonal therapy in acne is indicated for women, when oral contraception is desirable, when repeated courses of isotretinoin are needed to control acne, and when there are clinical signs of hyperandrogenism, such as androgenic alopecia, and seborrhea/acne/hirsutism/alopecia (SAHA) syndrome. Also, hormonal therapy can be proposed for late-onset acne (acne tarda) and for cases of proven ovarian or adrenal hyperandrogenism. Hormonal therapy can be very effective in females with acne whether their serum androgens are abnormal or not. Most women with acne have normal serum androgen levels, yet will respond if treated with hormonal therapy.

Polycystic ovary syndrome (PCOS) may present with acne as a marker of hyperandrogenism. Oral contraceptive pill therapy is the first-line therapy for women with PCOS, hirsutism, and acne. The choice of OC is important as some progestins are more androgenic (norgestrel, levonorgestrel) and should be avoided, while others are less androgenic. The combination of ethinyl estradiol with drospirenone has the advantage of the antiandrogenic effects of drospirenone. Antiandrogens such as cyproterone acetate in the form of combined oral contraceptive are effective in the treatment of recalcitrant acne in PCOS.

Systemic Treatments at a Glance

- Among oral antibiotics, doxycycline is recommended as first-choice agent for the treatment of moderate to severe inflammatory acne.
- Oral antibiotic therapy should be discontinued when response is achieved and after a maximum period of 3 months.
- Oral antibiotics should always be combined with a topical agent such as a retinoid, BPO, AZA, or their combinations, to decrease the risk of bacterial resistance.
- Oral antibiotic should not be combined with a topical antibiotic alone.
- Oral isotretinoin is recommended at a dose of 0.3–0.5 mg/kg/day in the recent European Guidelines.
- Hormonal therapy should be individualized for female acne patients.

Other Treatment Options for Acne

Other therapeutic options that have been used for acne treatment include the extraction of closed and open comedones, laser, and light sources, while chemical peels and lasers may be used for acne scarring.

Laser and light therapies, including blue or red light, intense pulsed light (IPL), and pulsed-dye laser (PDL), have been used for acne. It is known that *P. acnes* produces porphyrins, particularly coproporphyrin III. Visible light is able to activate these porphyrins to produce a photodynamic reaction that has the potential to destroy bacteria. Topical photodynamic therapy (PDT) uses light-activated agents (photosensitizers) that are selectively absorbed into the pilosebaceous unit to amplify the response to light/laser therapy. Topical photosensitizers used for PDT in acne include 5-aminolaevulinic acid (ALA) and methyl aminolevulinate (MAL), although controlled randomized investigator-blinded trials are lacking. The recently published European Guidelines propose an "open recommendation" (neither for nor against) for the use of light, IPL, laser, PDT for the treatment of mild or severe papulopustular/moderate nodular acne, and moderate nodular/conglobate acne, as optimal treatment regimens, frequencies, and device settings remain to be clarified.

There is only a low strength of recommendation for blue light monotherapy for the treatment of mild to moderate papulopustular acne.

Zinc

Zinc sulfate and zinc gluconate have been used for the treatment of inflammatory acne vulgaris with conflicting results. Oral zinc salts have been used at a dose of 30–150 mg of elemental zinc daily for 3 months. Adverse events during zinc treatment involve the gastrointestinal tract.

The mechanism of action of zinc salts is only partially known. Zinc acts via inhibition of polymorphonuclear cell chemotaxis and inhibition of growth of *P. acnes*. Also, its anti-inflammatory activity could be related to a decrease in TNF-α production and the modulation of the expression of integrins and the inhibition of Toll-like receptor 2 (TLR2) surface expression by keratinocytes.

Zinc gluconate has been proposed as an alternative therapy for inflammatory acne; it may be a useful treatment for pregnant women due to its favorable safety profile, and it may be proposed during summer as it causes no photosensitivity. In addition, zinc gluconate does not induce bacterial resistance, and when combined in a topical formulation with erythromycin, it has been shown to prevent the growth of erythromycin-resistant *P. acnes* strains and to be more effective in inflammatory acne than erythromycin alone.

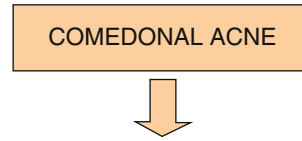
European Evidence-Based Guidelines for the Treatment of Acne

Treatment choice should be individualized and should take into account the age and the medical history of the patient, the type and severity of acne, the impact of acne on the patient's quality of life, the risk of scarring, and the presence of prognostic factors such as a family history of acne, adult acne, hyperseborrhea, hyperandrogenemia, truncal acne, or a history of infantile acne.

The recently published European Evidence-based (S3) Guidelines for the treatment of acne have systemically reviewed well-designed clinical trials of acne treatments and included a structured consensus process. Guidelines were based on the clinical form of acne.

For comedonal acne, topical retinoids are recommended as first-line therapy (Fig. 1.4). Available topical retinoids were found to have similar efficacy, but adapalene is superior due to its better tolerability profile.

For papulopustular acne, fixed-dose combination agents were more efficacious compared to their ingredients used alone. For mild to moderate papulopustular acne, there is high strength of recommendation for the use of fixed-dose combination BPO/adapalene or BPO/clindamycin. AZA, topical retinoids, or BPO is recommended with a medium strength of recommendation. For more widespread mild to moderate papulopustular



Strength of recommendation	Treatment
High	-
Medium	Topical retinodis
Low	BPO AZA
Negative recommendation	Topical antibiotics Hormonal therapy Systemic antibiotics Oral isotretinoin Artificial UVR
Open recommendation (neither for nor against)	Visible light Laser (visible, infrared wavelength) PDT, IPL

Fig. 1.4 Recommendations for comedonal acne based on the European evidence-based (S3) guidelines

acne, oral antibiotic combined with adapalene is recommended with a medium strength of recommendation. Blue light monotherapy has a low strength of recommendation (Fig. 1.5).

For severe papulopustular/moderate nodular acne, oral isotretinoin has been recommended, while there is medium strength recommendation for systemic antibiotics combined with adapalene, BPO/adapalene, or AZA (Fig. 1.6).

There are very few studies evaluating nodular or conglobate acne. The recommendations for nodular/conglobate acne are presented in Fig. 1.7.

It is recommended that oral antibiotic therapy should always be combined with topical therapy (other than antibiotics). Among oral antibiotics, doxycycline should be preferred as first-line antibiotic, compared to minocycline or tetracycline, as minocycline has been associated with more serious side effects and tetracycline has a more complicated dosage regimen. Topical antibiotic monotherapy is to be avoided due to increased risk of bacterial resistance.

Maintenance therapy (e.g., with a retinoid or BPO or AZA) is of cardinal importance in order to maintain acne remission.

Treatment Approach for Acne in Different Age Groups

The abovementioned guidelines apply for acne vulgaris during adolescence. Additional special considerations apply for childhood acne, adult acne, and acne during pregnancy and lactation. The proposed treatment approach for acne in different age groups is summarized in Fig. 1.8.

Special considerations of adult female acne include the resistance of acne to standard treatments, the fact that adult skin is more sensitive to possibly irritant topicals and there may be slower response, and the possibility of needing to treating acne during pregnancy or lactation. Patient education is important to increase therapeutic adherence.

MILD-TO-MODERATE PAPULOPUSTULAR ACNE

Strength of recommendation	Treatment
High	BPO/clindamycin BPO/adapalene
Medium	AZA BPO Topical retinoids Systemic antibiotics + adapalene, for widespread acne
Low	Blue light as monotherapy Erythromycin/tretinoin Erythromycin/isotretinoin Oral zinc Systemic antibiotics + BPO or +BPO/adapalene, for widespread acne
Negative recommendation	Topical antibiotics as monotherapy Systemic treatment with anti-androgens, antibiotics and/or isotretinoin Artificial UVR
Open recommendation	Red light, laser, PDT, IPL

Fig. 1.5 Recommendations for mild to moderate papulopustular acne based on the European evidence-based (S3) guidelines

Topical monotherapy usually is not sufficient to treat adult acne, as it fails to target the multiple factors implicated in acne pathogenesis. It is proposed to use combination topical treatments or combine oral and topical agents for optimizing results.

For adult women, topical retinoids are indicated for the treatment of mild comedonal and mild to moderate papulopustular acne. Adapalene is better tolerated. Given the oral teratogenicity of retinoids, it is recommended that women avoid pregnancy while using topical retinoids.

Azelaic acid (cream 20 %, gel 15 %) is proposed as first-line monotherapy for inflammatory and noninflammatory adult female acne, as it presents similar efficacy with other topicals, while it is characterized by a favorable tolerability profile. AZA has anti-tyrosinase action and is suitable to treat postinflammatory hyperpigmentation associated with acne. No harmful effects on fetuses have been reported during two decades of clinical experience with topical AZA.

In accordance with the European Guidelines, topical antibiotics are not proposed as monotherapy for adult female acne. They may be used as part of combination therapy.

BPO may cause photosensitivity and irritation to the adult female skin with erythema and dryness.

Topical combination treatments are indicated for inflammatory adult female acne. The application of a fixed-dose combination agent is easier to use compared to the combined use of different agents, and it may improve the patients' adherence to proposed treatment.

SEVERE PAPULOPUSTULAR ACNE (SPP) / MODERATE NODULAR ACNE (MNA)

Strength of recommendation	Treatment
High	Oral isotretinoin for SPP
Medium	Systemic antibiotics + adapalene, or + BPO/adapalene, or + AZA, for SPP
Low	Systemic antibiotics + BPO, for SPP, MNA Systemic antibiotics + oral anti-androgens for SPP, MNA (for females) Oral anti-androgens + topical treatment for SPP (for females)
Negative recommendation	Topical monotherapy Oral antibiotics as monotherapy Oral anti-androgens as monotherapy Visible light as monotherapy Artificial UVR
Open recommendation	PDT, IPL, laser

Fig. 1.6 Recommendations for severe papulopustular/moderate nodular acne based on the European evidence-based (S3) guidelines

NODULAR/CONGLOBATE ACNE (CA)

Strength of recommendation	Treatment
High	Oral isotretinoin for CA
Medium	Systemic antibiotics + AZA, for CA
Low	Systemic antibiotics + BPO, or + adapalene, or +BPO/adapalene, for nodular/conglobate acne Systemic antibiotics + oral anti-androgens, for CA (for females)
Negative recommendation	Topical monotherapy for CA Oral antibiotics as monotherapy for CA Oral anti-androgens as monotherapy for CA Visible light as monotherapy for CA Artificial UVR for CA
Open recommendation	IPL, laser for CA Although PDT is effective, it cannot yet be recommended for moderate nodular/conglobate acne due to a lack of stand treatment regiments that ensure a favourable profile of acute adverse reaction

Fig. 1.7 Recommendations for nodular/conglobate acne based on the European evidence-based (S3) guidelines

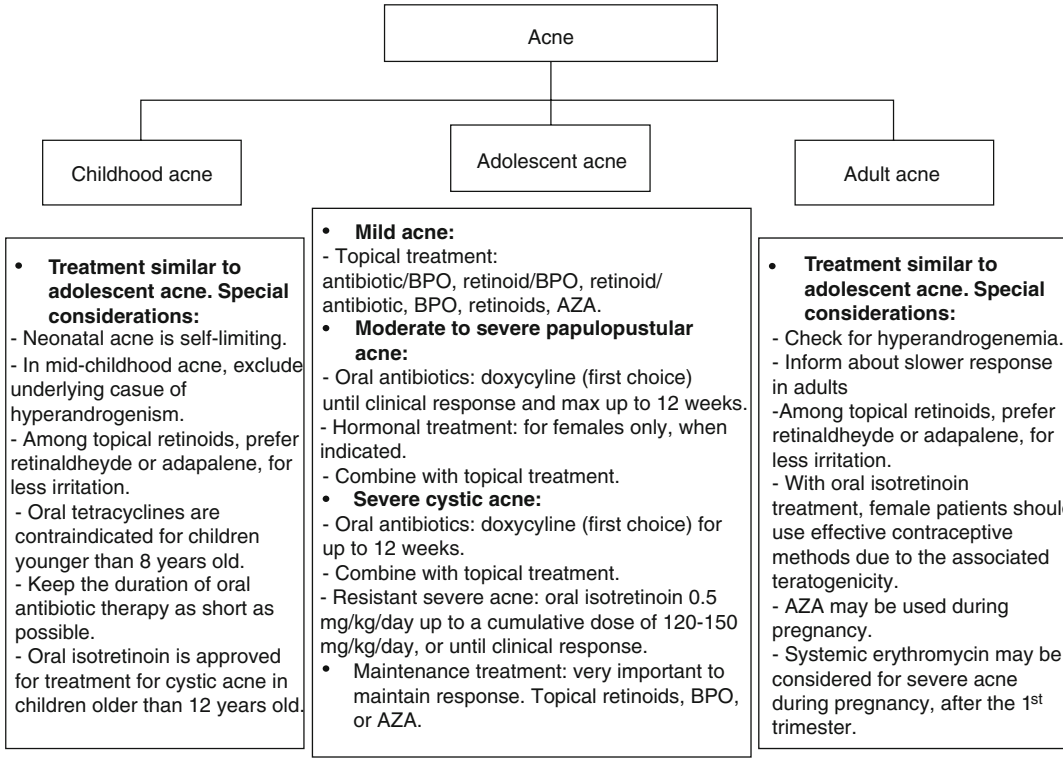


Fig. 1.8 Acne treatment in different age groups

For adult female acne, systemic treatment is indicated for moderate to severe acne, acne with risk of scarring, and acne resistant to therapies.

In accordance with the European S3 Guidelines for the treatment of acne, oral antibiotics are not recommended as monotherapy, but they should be combined with topical therapies, such as BPO, to decrease the risk of bacterial resistance, or azelaic (15 % or 20 %) as an alternative choice for adult women with intolerability to BPO. According to published guidelines, when indicated, oral erythromycin may be taken during pregnancy after the first trimester, whereas oral tetracyclines are contraindicated during pregnancy as they may inhibit the formation of the skeleton of the embryo.

Hormonal therapies (antiandrogens and/or oral contraceptives) are very effective for adult female acne, even when there are no underlying hormonal disorders. Hormonal therapy permits long-term therapy without any risk of emergence of bacterial resistance as is the risk with long-term antibiotic therapy. Also, hormonal therapy is an alternative choice for females that have relapsed after multiple oral isotretinoin treatments. Hormonal therapy should be combined with topical acne therapies such as antibiotics or BPO. Antiandrogens are contraindicated during pregnancy and lactation.

Topical maintenance treatment is necessary for adult female acne in order to decrease the risk of acne relapse after treatment discontinuation. For adult female acne, adapalene 0.1 % is proposed as first-line maintenance therapy and AZA 15 % or 20 % as an alternative. Topical antibiotics should not be used as maintenance therapy.

Future Perspectives

Future perspectives in acne treatment include insulin-sensitizing agents; selective inhibitors of key enzymes involved in cutaneous androgen metabolism, such as 5-α reductase type 1, as well

as Toll-like receptor antagonists; and agents targeting proinflammatory molecules that participate in acne pathogenesis.

Insulin-Sensitizing Agents

Hyperinsulinemia is an important factor in many cases of polycystic ovary syndrome (PCOS). It results from resistance to the effects of insulin on glucose metabolism, which has been found to occur independently of obesity and to be related to hyperandrogenism. Insulin may directly stimulate androgen-responsive pilosebaceous units. Antidiabetic agents that improve insulin sensitivity lower insulin levels and consequently improve ovarian function and plasma androgens. Recent studies, in women with PCOS, provide data for the efficacy and safety of metformin for acne treatment, while it has been suggested that patients who might benefit from metformin treatment are those with PCOS, diabetes, or impaired glucose tolerance.

Metformin, a biguanide, is the most commonly used insulin sensitizer for the treatment of PCOS. It inhibits hepatic glucose production and increases peripheral insulin sensitivity but does not cause hypoglycemia.

Halborne et al. reported in 52 women with PCOS similar self-assessed improvement in mild acne with metformin 1,500 mg daily for 14 months compared to oral contraceptive 35 μg ethinyl estradiol plus 2 mg cyproterone acetate, with no changes in sebum excretion rates. Kolodziejczyk et al. showed that in 39 women with PCOS and fasting hyperinsulinemia, treatment with metformin 1,500 mg daily for 12 weeks resulted in a decline of insulin and free testosterone and an improvement of acne.

Another study by Bergstrom et al. in 188 women with PCOS showed that metformin (500–1,000 mg twice daily) for a 6-month period resulted in improvement in acne severity, testosterone level, insulin resistance, and menstrual irregularities. Ibanez et al. in a randomized open-label trial in 34 adolescent girls with hyperinsulinemic androgen excess evaluated ethinyl estradiol-cyproterone acetate (EE-CA) compared to a low-dose combination (PioFluMet) of pioglitazone (7.5 mg/day), flutamide (62.5 mg/day), and metformin (850 mg/day) for 6 months. EE-CA and PioFluMet were equally effective in improving acne (reduction of 0.8–1.1 in Leeds acne score after 6 months, $p \leq 0.001$).

Steroidogenic Enzyme Inhibitors

The skin is a steroidogenic organ that possesses all major enzyme systems for synthesizing androgens de novo from cholesterol and for locally converting circulating weaker androgens to more potent ones. The enzymes involved in cutaneous androgen metabolism, such as 5α-reductase type 1, steroid sulfatase, and 3-β hydroxysteroid dehydrogenase, may represent attractive targets for pharmacologic inhibition in acne treatment.

Blocking the Activation of Toll-Like Receptors (TLRs)

P. acnes has been shown to induce an increased expression of TLR-2, TLR-4, and matrix metalloproteinase-9 (MMP-9) by human keratinocytes and to stimulate keratinocyte proliferation. Blocking the activation of TLRs could therefore represent an attractive therapeutic target.

Targeting Peroxisome Proliferator-Activated Receptors (PPARs)

PPARs (α, δ, and γ subsets) are ligand-activated nuclear receptors that form heterodimers with retinoid X receptors and regulate the expression of target genes involved in many cellular functions including cell proliferation, differentiation, and immune/inflammation response. PPARs may be important in the regulation of human sebum production and the development of acne. Activation of PPARα and PPARγ by their ligands resulted in stimulation of lipid droplet accumulation in cultured immature sebocytes and sebum production was increased in patients. On the other hand, PPAR activators have shown

antiapoptotic, sebostatic, and anti-inflammatory effects in human skin. As increased sebum production is an important element in the pathogenesis of acne vulgaris, targeting PPAR isoforms to interfere selectively with sebum formation may have implications for the treatment of acne.

Future Perspectives at a Glance

- Insulin-sensitizing agents
- Selective inhibitors of key enzymes involved in cutaneous androgen metabolism
- Toll-like receptor antagonists
- Targeting PPARs

Acne Fulminans

Oral corticosteroids are the treatment regimen proposed in reported cases of acne fulminans. Patients may require prednisolone up to 1 mg/kg daily for the effective control of cutaneous, constitutional, and musculoskeletal symptoms. Oral corticosteroids should be gradually tapered after the disease has been controlled. Systemic isotretinoin has been used successfully in acne fulminans but, paradoxically, may precipitate acne fulminans. So, the addition of oral isotretinoin has been proposed after the acute inflammatory phase of the disease has been controlled with oral corticosteroids, with a gradual increase in isotretinoin dose. After 1 year of treatment, the risk of relapse is low and acne fulminans in general does not recur.

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Actinic Keratosis

2

Francisco M. Camacho-Martinez

Abbreviations

5-FU	5-fluorouracil
AK	Actinic keratoses
ALA	5-aminolevulinic acid
CIN or SIN	Squamous intraepithelial neoplasia
CO_2	Carbon dioxide
CPG	Computer pattern generator
DFS	Diclofenac sodium
HD-OCT	High-definition optical coherence tomography
IMG	Ingenol mebutate gel
IMIQ	Imiquimod
KIN	Keratinocytic intraepithelial neoplasia
LED	Light-emitting diodes
MAL	Methyl ester 5-aminolevulinic acid
PDT	Photodynamic therapy
PpIX	Photosensitiser protoporphyrin IX
RTCs	Randomised controlled trials
SCC	Squamous-cell carcinoma
UVR	Ultraviolet radiation
SORT	Strength of recommendation taxonomy
SPF	Sun protection factor

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Definition and Epidemiology

Actinic keratoses (AK) are common skin lesions in relation to disordered keratinocyte proliferation that are the result of cumulative ultraviolet radiation (UVR) from sun exposure. This chronic, long-term sun exposure results in mutagenic changes in epidermal keratinocytes and the development of various skin lesions ranging from actinic keratosis to invasive squamous-cell carcinomas. In consequence, currently we consider KA as "in situ" squamous-cell carcinoma (SCC) or a real "malignant neoplasm" from the very beginning. It should be considered a superficial squamous-cell carcinoma in the same form as there are superficial basal-cell carcinomas (Camacho 2014).

AK lesions may appear as rough, scaly spots or papules always on sun-exposed skin. The presence of certain clinical features such as large size, erythema, inflammation, induration, hyperkeratosis, ulceration or bleeding suggests risk of disease progression to invasive SCC. AK can be observed as a unique element or several elements over a field cancerization. In consequence, AK as an isolated element or as various elements, including the field of cancerization, will need different types of therapies.

AK appears on the skin of persons with phototype I to III who have received too much actinic radiations in a short time (acute AK) or during their lifetime (chronic AK) due to professional activity (e.g. sailors, farmers and drivers). Although it is almost certain that, sooner or later,

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_2, © Springer-Verlag Berlin Heidelberg 2015

100 % of these persons will present with AK, of the remaining people who had been exposed to the sun, it is unpredictable what percentage will develop AK.

AK is most frequent in sunny countries, e.g. Australia, part of the USA (such as California), southern Europe (e.g. Italy, France, Spain) and so on. Prevalence studies show clear differences depending on the country, being higher when closer to the equator. The prevalence in Australia is almost 60 % of population over the age of 40, in Italy of 1.4 % in persons with more of 45 years, in United Kingdom of 15.4 % in men of more than 40 years whereas in women of the same age was only of 5.9 % but this proportion increased till 34.1 % and 18.2 % respectively in patients with 70 years old (Guidelines ILDS 2015). In sum, despite its high prevalence large-scale records to estimate the exact incidence and prevalence in our environment have not been carried out.

Basic Concept of Pathogenesis

The natural history of actinic keratosis depends partly on environmental factors such as exposure to ultraviolet radiation, carcinogens and ionising radiation and partly on constitutional factors such as skin phototype, age, immune status or competence for DNA repair.

These neoplasms are extremely common on the sun-exposed skin of middle-aged and elderly fair-skinned individuals who live in sunny climates. It can be a consequence of chronic solar radiation, but occasionally they may also be due to exposure to x-radiation and to ultraviolet light from artificial sources. The last cause is very important because many persons, habitually young women, receive excessive amounts of this kind of radiation, from tanning beds.

But we go back to the concept of field cancerization since it would help us to understand the UVR aetiology of AK. Since the first explanation of Slaughter's concept of field cancerization in 1953, the knowledge of the mechanisms implicated in cancer after UVR exposure has progressively increased. Genetic alterations found in keratinocytes, mainly mutations in the TP53 gene, give rise to clonal units with a loss of cellular control. Additionally, molecular disturbance localised in the dermis may contribute to the development of skin cancer within field cancerization. These discoveries have allowed us to understand better how it is possible for a second skin tumour to appear, close to the primary one previously removed and localised in the same anatomical area.

The p53 chromosomal mutation, found in over 90 % of human cutaneous squamous-cell carcinomas, is also found in 50 % of AK, including renal transplant recipients – this may occur as an early step in transplant-associated skin carcinogenesis. Chronic UVB can produce molecular and genetic changes not only in the altered skin but also in all the photoexposed skin; in consequence, AK is currently considered as a "disease of field", not as an isolated lesion. UVB should modify the genetic material of keratinoblasts and fibroblasts, modifying the dermoepidermal interrelations and producing a clone of abnormal cells that, for some time, stay in the epidermis but, sooner or later and in unpredictable percentages, will go to the dermis as invaders. Excessive UV exposition also induces the expression of other tumor suppressor genes as $p14^{ARF}$, $p15^{ARF}$ and $p16^{ARF}$ in AK, SCC and peripheral tissues.

The UVB radiation is directly related to the presence of AK on skin phototypes I to III. The ozone layer in the stratosphere is a natural filter for UVB radiation, but as its thickness decreases, it allows more UVB to reach the earth's surface. Depletion of the ozone layer is another aetiological factor contributing to the incidence of AK.

There are other cocarcinogen factors that must be taken into account. For example, prior therapy with methotrexate might put patients treated with psoralen and UVA (PUVA) at risk of developing skin cancer.

Contact with environmental carcinogens has also been related to a higher risk to developing nonmelanoma skin cancer. Hydrocarbons act by direct contact, whereas arsenic is acquired by ingestion of contaminated water or alternative therapies. Ingestion of arsenic is associated with a high incidence of premalignant lesions, and its

effect can be potentiated by other factors such as sun exposure, smoking and pesticides.

Clinical Presentation

A dry and hyperpigmented photo-ageing skin that exhibits *dermatoheliosis* – previously named "chronic actinic degeneration" or "solar degeneration" – begins to develop multiple 1–2 mm rough lesions. They are circumscribed lesions that have irregular edges and are slightly elevated but frequently easier to visualise. They may be flesh coloured or rosy, erythematous with telangiectasias or deeply pigmented. Generally, the hyperkeratotic surface is formed by yellow or brown adherent scales, but when they are pulled up, they reveal some slight horny downward proliferation inside the follicular pores. The pull-up manoeuvre of the hyperkeratotic scales produces, in the majority of cases, small painful erosions and minimal haemorrhage.

Several years ago, we considered three types of AK in accordance with its quantity of hyperkeratosis: grade 1, easily seen and slightly palpable; grade 2, well developed and easily palpable; and grade 3, hyperkeratotic lesions. These different AK types were also nominated as KIN (keratinocytic intraepithelial neoplasia) by its similitude with the gynaecological CIN or SIN (squamous intraepithelial neoplasia) by its relation with SCC. This classification of three grades was not successful because the evolution of AK is not similar to CIN, not being obligated to pass.

Common locations for the lesion are the skin surfaces exposed to the sun such as the face, mainly the forehead, cheeks, nose and ears; back of the hands; forearms; and, occasionally, shoulders and scalp in men with premature baldness. The scalp is also the typical location of field cancerization. AKs on the face and the neck are thin, whereas those on the scalp, back of the hands or on the forearms are often thicker.

The normal course of development for AK is for hard horny proliferations known as "verrucous keratosis" to grow. In these circumstances, it is easier to display the progression to deep invasion. Although there are authors who have communicated that AK commonly undergoes spontaneous regression, there is no proof of this. Recently a review of natural history of AK has been published (Werner et al. 2013). According with this review, the actual risk of progression of single AK lesion to invasive SCC remains unclear (ranged from 0.0 % to 0.53 % per AK lesion per year). Although the rate of regression of single AK lesions was generally seen to be 20 % to 30 % with up to 63 % in one study, spontaneous regression of complete fields of AK were only seen in 0.0 % to 7.2 % of patients. One study assessed the rate of recurrences in AK fields after a complete regression and showed recurrences in 57 % of the observed fields (Guidelines ILDS 2015).

Diagnosis

Usually, the diagnosis of AK is possible on the basis of the clinical appearance. Sometimes biopsy may be performed. The cells of the stratum malpighii present a chaotic arrangement. Some of these cells present pleomorphism and anaplasia of their nuclei, and others present individual dyskeratosis with formation of corps ronds and grains. As the cytologic features of the neoplastic cells of AK are indistinguishable from those of thicker squamous-cell carcinomas, this justifies the theory of Ackerman that these two conditions, despite their different names, are really one and the same.

Microscopic study includes a wide spectrum of histological patterns, and even several patterns can coexist in the same lesion. These patterns range from hypertrophic form (warty) to other atrophic forms. The WHO describes six histological types of AK: hypertrophic, atrophic, bowenoid, acantholytic, pigmented and lichenoid. Additionally the pagetoid pattern has been described:

1. Hypertrophic, characterised by pronounced hyperkeratosis intermingled with areas of parakeratosis. The epidermis is thickened in some areas which shows irregular downward proliferation limited to the uppermost dermis. Atypia is minimal and exclusive of basal keratinocytes.

2. Atrophic, with slight hyperkeratosis and the epidermis on the whole is atrophic. The basal-cell layer shows atypical cells with large hyperchromatic nuclei that lie close together, and these cells may proliferate into the dermis as buds and duct-like structures.
3. Bowenoid, indistinguishable from that of Bowen's disease or carcinoma "in situ". Differential diagnosis might be made with "lumican" stain since it is positive in 91.8 % of Bowen's disease and negative in all AK.
4. Acantholytic or "Darier type", with intercellular clefts or lacunae as resulting from anaplastic changes in the lowermost epidermis that produce dyskeratotic cells without intercellular bridges. Within suprabasal clefts or lacunae, a few acantholytic cells may be observed. This form of AK was considered by Ackerman as a miniature type of pseudoglandular squamous-cell carcinoma and provided evidence to support his theory that AK and squamous-cell carcinoma were synonymous (Ackerman 1997). There is an acantholytic variety known as "epidermolytic AK" in which the acantholyses appear between normal and atypical keratinocytes.
5. Pigmented, with accumulation of the melanin within atypical basal keratinocytes and melanophages.
6. Lichenoid, with a dense band-like dermal infiltrate in the dermoepidermal interphase which damages the basal-cell layer producing degenerated basal cells known as "hyaline or colloid bodies".

Recently, new noninvasive evaluation techniques of skin cancer have evolved in the last years. In addition to dermatoscopy, new modalities of imaging include cross-polarised light and UV light photography, confocal reflectance microscopy and optical coherence tomography. With these tools precise diagnosis and monitoring of response to treatments in field cancerization and actinic keratosis are possible with no need of invasive biopsies. With dermatoscopy, a red pseudonetwork ("strawberry") pattern was significantly associated with AK (Zalaudek et al. 2012). Innovative high-definition optical coherence tomography (HD-OCT) demonstrates the following features in AK: disruption of the stratum corneum, architectural disarray, cellular/nuclear polymorphism in the stratum granulosum/stratum spinosum and bright irregular bundles in the superficial dermis. Reflectance confocal microscopy reveals characteristic features with good histological correlation: in the stratum corneum, corneocyte disruption is revealed as the presence of bright, highly refractile cells with polygonal morphology, whereas parakeratosis appears as round dark structures in the middle of the corneocytes; atypical keratinocytes are observed in the stratum granulosum and spinosum with dark nuclei and irregular shapes and sizes; the superficial dermis reveals varying degrees of solar elastosis, identified by its moderate–high brightness and a highly irregular reticulate pattern; and round blood vessels are observed crossing the dermal papillae.

Differential Diagnosis

It is possible that the following dermatoses have difficulties of diagnosis with AK: solar lentigo, basal-cell carcinoma, seborrheic keratosis and Bowen's disease. Really, the most problematic differential diagnosis is with solar lentigo since in many occasions both can coincide (Fig. 2.1a, b).

Solar Lentigo

Darkly and unevenly pigmented, inflamed, uniformly dark brown, macular, irregular outline, sharp margination, scalloped borders, occasionally with hypopigmented areas and light brown areas. Size from 0.5 to 2.0 cm; locations on the head and neck. Dermatoscopy shows linearly striated pigmented network that has been likened to a "fingerprint" pattern. Confocal features: variable presence of refractile particles/globules in the stratum corneum and inside the superficial epidermis; honeycomb and/or cobblestone epidermal pattern that are preserved; large, polymorphic and numerous dermal papillae; hyperrefractile papillary rings formed by round, uniform cells; and occasional large, bright cells

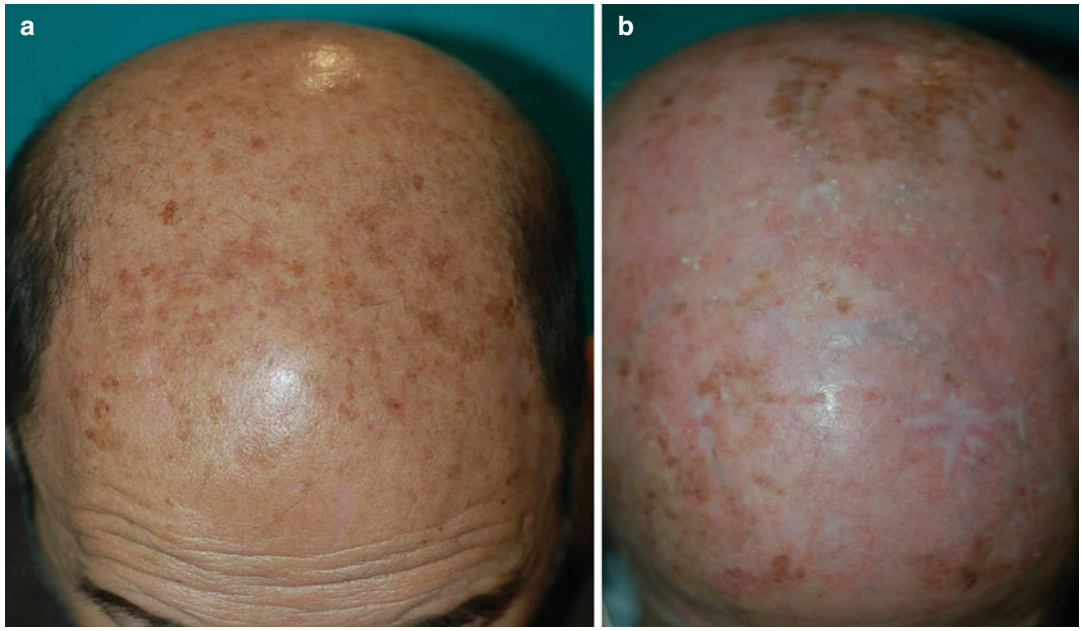

Fig. 2.1 (**a**) Solar lentigo. (**b**) Actinic keratoses. In this patient a scar can be observed. It is a consequence of squamous-cell carcinoma excised previously

in the dermis (melanophages) (Hirokawa and Lee 2011; Alsner et al. 2012).

Basal-Cell Carcinoma

Small telangiectatic vessels on its surface, pearly rolled border. Pigment and ulceration can be present. Dermatoscopy in nonpigmented forms: fine telangiectasias with subtle translucency, white streaks/white areas ("chrysalis" structures), translucency, milky-pink to red background, small ulceration and arborising vessels. In pigmented forms: island of pigment (blue-grey globules, blue-grey ovoid nests) and pigmented distribution pattern in maple-leaflike or spoke-wheel-like. Confocal features: elongated, monomorphic nuclei; nuclear polarisation along a single axis; and refractile stroma with frayed collagen bundles (gossamer), prominent inflammatory infiltrate, increased vascularisation and variable epidermal detachment (nucleated corneocytes, loss of the honeycombed pattern and nuclear pleomorphism of the keratinocytes) (Hirokawa and Lee 2011; Alsner et al. 2012).

Seborrheic Keratosis

Verrucous surface, soft and friable consistency and located on the trunk and occasionally in the face and scalp. Dermatoscopy: milia-like cysts, comedo-like openings and hairpin vessels. Confocal features: cerebriform-looking epidermal architecture, bright cysts often surrounded by a dark halo, bright cobblestone pattern in the stratum spinosum and poorly defined, bright polygonal cells in the upper dermis (melanophages) (Hirokawa and Lee 2011; Alsner et al. 2012).

Bowen's Disease (Intraepidermal Carcinoma)

Sharply demarcated, scaly, often hyperkeratotic, sometimes fissured macule, papule or plaque devoid of hairs; plaque may be composed of confluent reddish lenticular papules and nodules of variable size; tend to extend gradually with age in an annular or polycyclic pattern. Dermatoscopy features: dotted/glomerular vessels, diffuse

yellow opaque scales and microerosions are prevalent among intraepidermal carcinoma. Confocal features: disruption of the stratum corneum with evident parakeratosis; alteration of the epidermal pattern with severe keratinocyte detachment; and round, nucleated dyskeratotic cells present in the epidermis but never infiltrating the dermis (Zalaudek et al. 2012; Alsner et al. 2012).

General Principles of Treatment

AKs have the potential to spontaneously regress, remain stable or progress to nonmelanoma skin cancer. Given the high rates of regression and low rates of malignant transformation, some dermatologists think that not all AKs need to be treated. Others believe that AKs should be treated as a superficial squamous-cell carcinoma and in consequence must be removed using one of the several different methods of therapy selected by the dermatologists (Table 2.1).

Surgical Treatments

Radiosurgery

The original techniques in electrosurgery (electrodessication, electrocoagulation) after curettage have been replaced by machines that use radiofrequency waves. This enables AK to be removed easily under anaesthetics. It is the recommended technique for single or isolated AK (it allows to remove easily the AK after anesthesia, for which we used the Klein method) (Table 2.2).

Table 2.1 Treatment possibilities for actinic keratoses

(a) Surgical treatments
Radiosurgery
Cryosurgery
Dermabrasion
Laser
Surgical extirpation
(b) Medical treatments
5-fluorouracil
Imiquimod
Diclofenac
Ingenol mebutate
Medium-depth chemical peel
Oral retinoids
Photodynamic therapy (topical 5-aminolevulinic acid)
(c) Photoprotection

Cryosurgery

Currently liquid nitrogen freezing is the most commonly used method to destroy AK. Up to 98.8 % cure rate has been reported, but more recent data indicate smaller cure rates (Schmitt and Bordeaux 2013). It is an easy method that permits removal of AK without the need for anaesthesia. It is possible to use cryoprobes of different sizes. When the AK has developed fully, it is preferable to first perform curettage and then to use a cryoprobe. When the patient presents with multiple AKs, it is better to use cryospray in a centrifugal or paintbrush pattern. Consequently, the spray technique is the most adequate (gold standard) for field cancerization. Cryosurgery is undoubtedly the most used method based on ease; excellent cosmetic outcome results; grace, despite being painful; and efficiency, but does not allow histological study (Table 2.2).

Dermabrasion

Dermabrasion is a method that is useful to treating multiple AKs or field cancerization. Diamond fraises or wire brushes with a range between 800 and 33,000 rpm are used. It has the inconvenient in that the patient must stay in hospital at least 1 week. It is well known that only this technique treats AK successfully and provides long-term prophylaxis. As laser has become the most frequently used method of resurfacing, some believe that dermabrasion will soon be absent from the dermatologic tool box. Nevertheless dermabrasion remains an effective, economical and, some might argue, superior, resurfacing modality addressing many indications, one of them the treatment of actinic damage and AK (Hanke et al. 2013) (Table 2.2).

Laser

Carbon dioxide (CO_2) laser skin resurfacing is being used with increasing frequency in

Table 2.2 Treatments of actinic keratoses

Isolated (single). ≥ 1 and ≤ 5 palpable of visible AK lesion per field	Surgical techniques	Medical treatments	Photo-Protection
	Radiosurgery +++	5-fluorouracil +/–	+++
	Cryosurgery (cryoprobe) +	Imiquimod ++	
	Dermabrasion +/–	Diclofenac +/–	
	Laser ++ (CO_2)	Ingenol mebutate +/–	
	Surgical extirpation +++	Medium-depth chemical peel -	
		Oral retinoids -	
		Photodynamic therapy -	
Field cancerization. ≥ 6 distinguishable AK in one body region or field (multiple AK lesion), and contiguous areas of chronic actinic sun damage and hyperkeratosis	Radiosurgery +/–	5-fluorouracil ++	+++
	Cryosurgery (spray) +++	Imiquimod +	
	Dermabrasion +++	Diclofenac ++	
	Laser (laser-abrasion) ++	Ingenol mebutate +++	
	Surgical extirpation -	Medium-depth chemical peel +++	
		Oral retinoids +/–	
		Photodynamic therapy +++	

+++ Recommended
++ Acceptable
+ Occasionally
+/– Exceptionally
(–) Not recommended

dermatologic practice. The ultrapulse CO_2 laser, introduced in 1990, is an excellent method to remove keratoses; it is relatively easy to perform. The results are better, and the operative time for full-face resurfacing is markedly reduced when using computer pattern generator (CPG), a computer scanning device, in conjunction with the ultrapulse laser (Camacho 2005a). Full-face laser resurfacing is one of the treatment modalities that can treat whole surface areas, offering an effective and efficient treatment option that successfully reduces the number of actinic keratoses on diffusely damaged skin and may show a prophylactic benefit for preventing nonmelanoma skin cancers. Investigations with fractional technologies have demonstrated that treatment with ablative lasers is superior when compared with non-ablative fractional photothermolysis. However ablation of the epidermis is complicated by prolonged recovery time and higher risk of secondary effects. Recent studies with fractionated 1927 nm non-ablative thulium laser show a promising new therapeutic option for the treatment of actinic keratosis based on the clinical and histological findings as well as on the reported patient satisfaction and safety (Weiss et al. 2013).

Surgical Extirpation

This procedure should be only considered when the AK is a firm horny papule with the possibility

of invading deeper. The chosen technique must be governed by the location of the AK, but commonly it is sufficient to remove the neoplasm and then perform a direct suture (Table 2.2). When the AK is large, it may be useful to use a local flap to close the defect. Exceptionally, a graft will be necessary.

Medical Treatments

Should the clinician and patient agree to move forward with treatment, many options are available for the treatment of AK. AK therapies recently were classified having assigned a strength of recommendation taxonomy (SORT). A ratings include 5-fluorouracil, imiquimod, diclofenac, photodynamic therapy and cryotherapy (Carlson and Bordeaux 2011). Nevertheless it should be noted that further options exist for the treatment of AK, including oral retinoids, lasers, curettage and chemical peels, although the evidence behind these therapies is lacking or inconsistent. Recently, ingenol mebutate gel has been incorporated as a new topical treatment of AK.

5-Fluorouracil (5-FU)

This is the oldest medical treatment for the removal of AK, especially when the patient has multiple AKs. Topical 5-FU was approved for use in AK in any location. 5-FU is an antineoplastic antimetabolite, which interferes with the synthesis of DNA and RNA, provoking unbalanced cell growth and death. The usual regimen is twice daily application of a 5 % cream for 2–4 weeks; however, longer treatment (5–6 weeks) is preferred for a higher cure rate. Nevertheless since too many patients have discomforts with this technique, it is not used so often now (Fig. 2.2a–c). AK of the scalp and face might be used at 0.5 %, applying twice a day for 2–4 weeks, reaching an 82 % of complete clinical health rate. There are no differences between 5-FU at 1 % or 5 %. When 5-FU is associated to keratolytics as 10 % salicylic acid its efficacy and tolerance increase reaching cure rate of 90 % in 8 weeks of treatment that is maintained 1 year later (Schmitt and Bordeaux 2013). Askew et al. (2009) review 13 randomised controlled trials (RTCs) with 5-FU: one study compared different dosing regimens of 5 % 5-FU (twice daily for 3 weeks vs twice daily for 1 day per week for 12 weeks). Three studies compared 0.5 % 5-FU with placebo and one more compared 0.5 % 5-FU with 5-aminolevulinic acid (ALA) PDT, activated through either blue light or pulsed laser light. And the other 8 studies compared 5 % 5-FU with other treatments as imiquimod, cryotherapy,

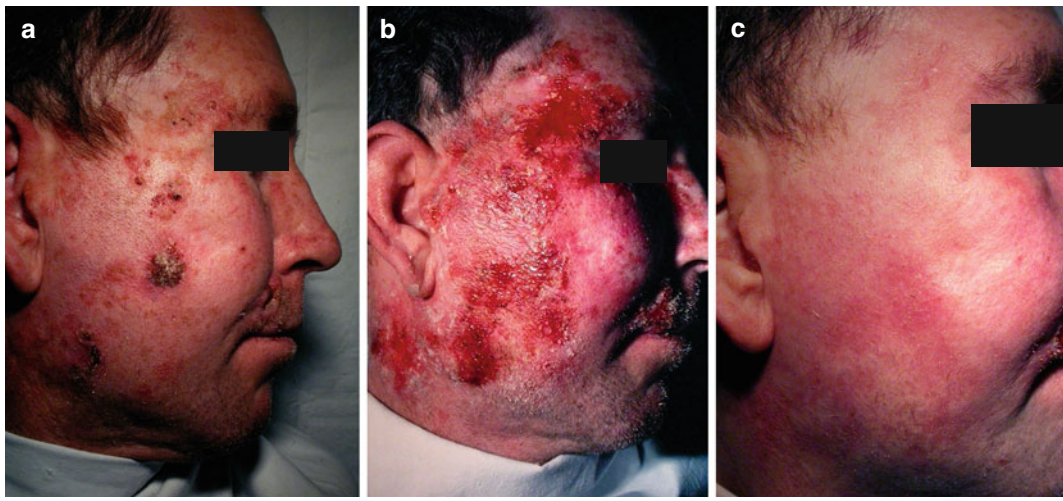

Fig. 2.2 AK treated with twice daily 5-FU 5 % cream. (**a**) Before treatment. (**b**) After 4 weeks of treatment. (**c**) One month after finishing the treatment

diclofenac sodium 3 % gel (DFS), full-face laser resurfacing, photodynamic therapy (PDT), 5 % 5-FU augmented with tretinoin 0.05 %, 30 % trichloroacetic acid peel, some of these combined, and lastly, the eighth compared with 0.5 % 5-FU once daily for 4 weeks (or until patient unable to tolerate). This systematic review provided valuable evidence to indicate that about one-half of patients using 5-FU for the treatment of AK lesions could expect complete clearance; that, overall, an 80 % reduction in lesion count could be expected; and that a 90 % reduction in total lesion count was likely. In sum, 5-FU that has been used in two different strengths is an extremely effective therapy for AK, typically only affects dysplastic areas of the skin, appears to be relatively well tolerated in practice, typically produces an excellent cosmetic reaction when used on the face, may be associated with a photosensitive reaction and needs to be continued for 4 weeks to obtain the full effect. A 8 weeks regimen with 0.5 % 5-FU associated to keratolytics as 10 % salicylic acid its efficacy and tolerance increase reaching cure rate of 90 %. As at 12 months 85.5 % of lesions did not recur, 0.5 % 5-FU demonstrated high sustained clinical efficacy, with high patient satisfaction (Stockfleth et al. 2011, 2012; Guidelines ILDS 2015).

Imiquimod (IMIQ)

Topical imiquimod, a modulator of the immune response which was originally approved for the treatment of anogenital warts, also was approved by the FDA in 2004 as therapy of actinic keratoses, including the field cancerization, and also may address subclinical disease. The usual regimen is once-daily treatment with 5 % IMIQ cream for 2–3 days per week for four (short treatment) to 16 weeks (long treatment), being effective in both schedules reaching complete clearance rate in 57.1 % and partial clearance rate in 72.1 %. Recurrence rates are 10 % during the first following year and 20 % during the two following years (Stockfleth et al. 2004).

A meta-analysis of four RCTs found that the odds of complete clearance of AK for patients using IMIQ are 20.76 times greater than for patients using placebo, and the recurrence rates at 12 months were 39 % in the IMIQ group and 59 % in the placebo group. When compared IMIQ with 5-FU have been found a higher average complete clearance rate with IMIQ treatment (70 % for IMIQ versus 52 % for 5-FU) suggesting that IMIQ is the topical election treatment of AK on the face and scalp. Another comparative study of 5 % 5-FU vs 5 % IMIQ vs cryotherapy demonstrated that at the 12-month follow-up, 81 % of patients treated with IMIQ have an excellent cosmetic outcome compared with just 4 and 5 % of those treated with 5-FU and cryotherapy, respectively (Krawtchenko et al. 2007).

A larger lesion diameter, specifically greater than 1 cm, and the presence of pain predict conventional treatment resistance. In these cases which have failed the standard therapy for AKs, combination treatment using topical IMIQ and 5-FU may be an effective alternative therapeutic strategy.

IMIQ may also be used at 2.5 and 3.75 % cream. Once-daily treatment with 3.75 % IMIQ cream for a 2-week period and once-daily treatment with 5 % IMIQ cream for 2–3 days per week for up to 16 weeks are both indicated for the treatment of multiple non-hyperkeratotic, non-hypertrophic AKs on the face and scalp and have a SORT rating of A (Swanson et al. 2010; Guidelines ILDS 2015).

Recently, a phase II dose-ranging study of topical resiquimod to treat AK was reported. Resiquimod, an agonist of type TOLL receptors, has greater immunologic effects than IMIQ with greater efficacy, but it may also have greater systemic and topical side effects (Szeimies et al. 2008). More studies with large follow-up are necessary.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug administered as 3.0 % diclofenac sodium and 2.5 % hyaluronic acid gel for the topical treatment of AK. A meta-analysis of three RCTs showed that diclofenac produced a complete resolution of all target lesions in 39.6 % of patients at 30 days posttreatment. Another meta-analysis of RCTs reported total and cumulative lesion number scores of 0 in 50 % of patients treated for 90 days and 33 % of those treated for 60 days. Dirschka et al. (2010) investigated the effect of

diclofenac in 65 patients with AK. Biopsy specimens were taken and stained with H&E and immunological markers. They demonstrated complete clinical resolution in 11 patients (16.9 %). A significant ($P=0.001$) downgrading of AK grade was observed. Complete histological resolution was achieved in 15 patients (23.1 %). The number of mitoses per high-power field was reduced significantly ($P=0.001$). The expression of anti-p53 antibody decreased significantly ($P=0.009$) as did the expression of anti-MiB-1 antibody ($P=0.021$). Their conclusion was that 3.0 % diclofenac in 2.5 % hyaluronic acid gel causes regression of signs of cancerous transformation after 3 months' therapy, erythema, pruritus, dry skin, dermatitis and scaling being its most common adverse effects. Nevertheless, 0.5 % 5-FU has superior sustained clinical efficacy with similar tolerability.

Ingenol Mebutate Gel (IMG)

Ingenol mebutate is a diterpene ester extracted and purified from an active fraction of the sap of the plant *Euphorbia peplus*, which has shown efficacy in the treatment of actinic keratoses and nonmelanoma skin cancer, and exerts its action by a dual mechanism, which includes specific cell necrosis and mitochondrial oedema secondary to a more specific response mediated by protein kinase C that allows the recruitment of immune effector cells in the lesion. It is effective against both AK and cancerization field. Treatment of AK with 0.015 % IMG on the face and/or scalp for 3 days and 0.05 % IMG on the trunk or extremities for 2 days achieved high clearance rates (Martin and Swanson 2013; Lebwohl et al. 2012). The local inflammatory responses are typically mild to moderate and tend to resolve by the second week of the end of treatment. The main advantage of ingenol mebutate gel is that it provides a short treatment of only 2 or 3 days. The short-term treatment regimen and tolerability profile make this topical treatment a useful addition to therapies for AK. The safety and efficacy of IMG for the treatment of AK were evaluated in four multicenter randomised, vehicle-controlled, double-blind studies. In the two studies of AK of the face or scalp, 547 patients were randomised to 0.015 % IMG ($n=277$) or vehicle gel ($n=270$) that was self-applied once daily for three consecutive days to the 25 cm^2 treatment field. In the two studies of AK on the trunk or extremities, 458 patients were randomised, 226 to 0.050 % IMG and 232 to vehicle, in both cases applied daily for 2 days (Gupta and Paquet 2013). Efficacy results were pooled for the four studies. The proportion of patients who achieved complete and partial clearance on the face or scalp was significantly higher with IMG than with vehicle (42.2–63.9 vs 3.7–7.4, respectively; $P=0.001$). Efficacy analysis by anatomic location demonstrated higher rates of complete and partial clearances on the face than on the scalp. In the studies on the trunk or extremities, results for complete and partial clearances also demonstrated significantly higher with IMG than with vehicle (34.1–49.1 vs 4.7–6.9, respectively; $P=0.001$) (Table 2.2). Adverse effects in all groups were pain, pruritus and irritation, always in relation to the drug concentration (Martin and Swanson 2013). IMG has been approved by the European Medicines Agency (EMA) for the treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. It should be applied once daily to the affected area for three consecutive days (Guidelines ILDS 2015).

Medium-Depth Chemical Peel

It is an excellent treatment for multiple AK. The medium-depth chemical peel may be achieved both with Jessner's solution and 35 % trichloroacetic acid. The patient treated with medium-deep chemical peel should be checked annually or every 1.5 years for reappearance of AK and retreatment as appropriated. Seventy per cent trichloroacetic acid instead of radiosurgery for individual AK can be used, and then anaesthesia is not necessary. Today, with the topical treatments previously explained, this technique is less used (Camacho 2005b).

Oral Retinoids

Topical tretinoin alone is only partially effective in the treatment of AK even after 1 year of daily applications. Oral retinoids as isotretinoin (13-cis-retinoic acid) and acitretin have an

antitumor effect being useful both as prophylaxis and in therapy. A combination of low-dose oral isotretinoin and topical 5-FU was found effective in drastically reducing the number of AK and preventing the appearance of new ones. Nevertheless, this treatment is reserved to cases of recent field cancerization (Sander et al. 1997).

Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) using topical 5-aminolevulinic acid (ALA) or its methyl ester (MAL) as photosensitiser has been demonstrated useful in the treatment of various superficial cutaneous malignant neoplasms such as superficial basal-cell carcinomas, Bowen's disease and AK. The mechanism of action of the ALA, when it is applied topically on the skin, is dependent upon the accumulation of the endogenous photosensitiser protoporphyrin IX (PpIX) in epidermal cells of the lesion. Then, the PpIX is activated by the application of light, resulting in a tissue-specific phototoxic effect. There are several topical preparations of ALA, solution, nanoemulsion and adhesive patch, and also MAL cream. Different light sources, including light-emitting diodes (LED), intense pulsed light and lasers, have proven to be effective, red light ($\lambda = 630 \pm 10$ nm) being the most used. Clinical trials have shown a complete response rate of 86–89 % for mild and moderate AKs at the 3-month follow-up, decreasing to 68 % at the 12-month. PDT is suggested for AK especially if they are multiple and/or in the context of field cancerization, at sites of poor healing or where the cosmetic result is important. Size larger than 10 mm, histological severity, acral location and occurrence in organ transplant recipients are markers of poor response to PDT. Pain during illumination is the most important adverse effect, the size of the lesion and the facial location being the most reliable predictors and cold and nerve blocks the most effective measures to control it. The use of less powerful light sources, such as daylight or ambulatory devices (Ambulight®), has shown similar efficacy to conventional PDT with less pain. Compared to other treatments, PDT is the second most effective treatment after 5-FU in AKs, but better tolerated and more satisfactory for patients. Several methods to promote penetration of the photosensitiser, such as microneedling or fractional laser, or the combination of PDT with other treatments, such as imiquimod or diclofenac, apparently improve its efficacy. PDT currently has enough resources to effectively treat AK, specially in the context of field cancerization (Table 2.2).

Photoprotection

Photoprotection must always be recommended because ultraviolet radiation (UVR) exposure leads to harmful acute and chronic effects on the human skin. Acute effects of UVR include erythema, pigment darkening, delayed tanning, epidermal hyperplasia, free radial formation and vitamin D synthesis. Chronic effects of UVR include photo-ageing, immunosuppression, photocarcinogenesis and exacerbation of photodermatoses. In relation to photocarcinogenesis, UVR induces DNA mutations and malignant transformations, and the immunosuppressive properties of UVR concurrently impair host immune system recognition of damaged malignant cells. The relationship between UVR exposure and the development of skin cancer, including basal cell carcinoma, superficial and invasive squamous cell, lentigo maligna melanoma, and actinic keratosis are related to cumulative sun exposure.

In the past, the Federal Drug Administration recommended that sunscreens had a sun protection factor (SPF) of 15 to block the erythema response in persons with phototypes I to III. Years after, several studies have demonstrated that an SPF of no less than 30 is necessary to prevent immunosuppression and therefore sun avoidance is highly recommended. Broad-spectrum sunscreens (SPF 30) should be applied to all exposed skin before sun exposure. The application of an adequate quantity of sunscreen (2 mg/cm^2), clothes, and hats must be recommended (Lecha 2014). Three points must be considered to prevent sunburn and its consequences: habits, avoiding sun from 11 a.m. to 4 p.m.; sun protection with clothes, hats and glasses; and

sunscreen well distributed on the skin, especially on the face and scalp. While there are controversies involving sunscreen ingredients, formulations, and side effects, based on current data, the risk-benefit ratio indicates that it is appropriate to include the use of sunscreen as an important component of Photoprotection strategy (Table 2.2).

To all the patients with dermatoheliosis, whether with AK or not, 30 mg of β-carotene in the morning is recommended. Other systemic photoprotective agents such as *polypodium leucotomos*, afamelanotide, other carotinoids as lycopene, lutein, and zeaxanthin, polyphenols, nonsteroideal antinflammatory drugs, and antioxidants as vitamin C and E can be suggested (Wener et al. 2015). These vitamins, topically and orally, work synergistically to reduce oxidative stress. Simultaneous topical application of both AOs better protects against UV-induced erythema, sunburn cell formation and thymine dimer formation than when vitamin C alone is applied.

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Adamantiades-Behçet Disease

3

Christos C. Zouboulis

Key Points

- Rare disease with a worldwide distribution but strongly varying prevalence; certain ethnic groups are mainly affected.
- A genetically determined disorder with a probable environmental triggering factor.
- Multisystem occurrence, with oral aphthous ulcers, genital ulcers, papulopustules, erythema nodosum-like lesions, uveitis, and arthropathy as most common signs.
- Inflammatory disease representing a neutrophilic vascular reaction or vasculitis.
- Diagnosis is defined by new clinical criteria.
- Chronic relapsing progressive course and potentially poor prognosis (especially in males with systemic presenting signs; mortality, 0–6 %).

Definition and Epidemiology

Adamantiades-Behçet disease is a multisystem inflammatory disease of unknown etiology, classified as systemic vasculitis involving all types and sizes of blood vessels and characterized clinically by recurrent oral aphthous and genital ulcers, skin lesions, and iridocyclitis/posterior uveitis, occasionally accompanied by arthritis and vascular, gastrointestinal, neurologic, or other manifestations (McCarty et al. 2003; Suzuki Kurokawa and Suzuki 2004).

Historical Aspects

The disease is named after Benediktos Adamantiades, a Greek ophthalmologist, and Hulûsi Behçet, a Turkish dermatologist, who, in 1931 and 1937, respectively, described patients with the characteristic clinical complex insisting for a single clinical entity (Zouboulis and Keitel 2002).

Epidemiology

Adamantiades-Behçet disease presents a worldwide occurrence with varying prevalence, being endemic in the eastern and central Asian and the eastern Mediterranean countries (along the so-called Silk Road) and rare in northern European countries, central and southern Africa, the American continent, and Australia (Zouboulis

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_3, © Springer-Verlag Berlin Heidelberg 2015

et al. 2003c). A prevalence of 80–420 patients per 100,000 inhabitants has been reported in Turkey (Azizlerli et al. 2003), whereas only 1.5 to 7.5:100,000 in southern Europe and 0.12 to 1.18:100,000) in Northern Europe and the United States (Zouboulis et al. 2003c). Its annual incidence is low; 0.75–1.0 new cases per 100,000 inhabitants were assessed in Japan (1990) and Germany (2005) (Altenburg et al. 2006).

Adamantiades-Behçet disease most often affects patients in their 20s and 30s; however, early and late onsets (first year of life to 72 years) have been reported. Both genders are equally affected; a male predominance is still observed in Arab populations, whereas female predominance is evident in Korea, China, some northern European countries, and the United States.

Etiology and Pathogenesis

The etiology of the disease remains unknown, although genetic factors, infectious agents, environmental pollution, immunologic mechanisms, and endothelial and clotting factors have been implicated and studied intensively (Zouboulis and May 2003; Hirohata and Kikutchi 2003). The endemic occurrence along the historical Silk Road, the major involvement of certain ethnic groups (mostly of Turkmen and Mongol descent), and associated immunogenetic data support the hypothesis that the disease followed the migration of these old nomadic tribes. On the other hand, the wide variation of the disease prevalence in the same ethnic group in association with different geographic areas of residence indicates an additional environmental triggering factor. Therefore, transfer of genetic material and/or of an unknown exogenous agent may have been responsible for the expansion of the disease.

There is no specific mode of Mendelian transmission in Adamantiades-Behçet disease (Zouboulis and May 2003; Hirohata and Kikutchi 2003). Familial occurrence with regional differences has been reported. A significant association exists between the disease and human leukocyte antigen (HLA)-B_{51} in Japan, the Middle East, and the Mediterranean countries (de Menthon et al. 2009). The allele also seems to be associated with a more severe prognosis (Zouboulis et al. 2003a). Its exact role in the disease mechanism is still unknown; however, it may be involved in the disease development through specific antigen presentation, molecular mimicry with microbial antigens, or participation in linkage disequilibrium with a presently unknown susceptibility gene (Fietta 2005; Durrani and Papaliodis 2008). Among the 24 currently described alleles, HLA-B5101 and B_{5108} have most frequently been associated with Adamantiades-Behçet disease (Zierhut et al. 2003). Shared amino acid residues (defining the Bw4 epitope) are crucial for antigen binding and natural killer cell interactions (Remmers et al. 2010), and Bw_4 was also reported to contribute to the severity of the disease (Papoutsis et al. 2010). Genes possibly associated with the disease have been localized on chromosome six in the region between the tumor necrosis factor gene and HLA-B or HLA-C genes, including the major histocompatibility complex class I chain A gene (A6 allele) and genes for heat shock proteins (Hirohata and Kikutchi 2003; Fietta 2005; Zierhut et al. 2003; Escudier et al. 2006).

Adamantiades-Behçet disease is not considered contagious, as no horizontal transmission has ever been reported. However, viral and bacterial infections have been implicated in initiating immunopathologic pathways, leading to the onset of the disease (Zouboulis and May 2003; Hirohata and Kikutchi 2003).

Immunologic mechanisms are considered to play a major role in the pathogenesis of Adamantiades-Behçet disease (Zouboulis and May 2003; Hirohata and Kikutchi 2003; Zierhut et al. 2003; Escudier et al. 2006). The disease has currently been classified among the autoinflammatory disorders (Gül 2005), which are caused by primary dysfunction of the innate immune system.

Clinical Presentation

Adamantiades-Behçet disease is a chronic, recurrent, multisystem, and, occasionally, life-threatening disorder (McCarty et al. 2003;

Altenburg et al. 2006). Recurrent oral aphthous ulcers, recurrent genital ulcers, skin manifestations, ocular lesions, and arthritis/arthropathy are the most frequent clinical manifestations. Vascular, gastrointestinal, neurologic, psychiatric, pulmonary, renal, and cardiac manifestations, epididymitis, and other findings can also occur. The clinical picture usually develops within a few months after the presenting sign; both an acute multisystem presentation and long-term development of the disease over years are possible.

Approach to the Patient

Diagnosis of Adamantiades-Behçet disease is based on clinical signs, as pathognomonic laboratory test or histologic characteristics are absent. There are several sets of diagnostic criteria, the most popular of them being the criteria of the International Study Group (International Study Group for Behçet's Disease 1990) and those of the Behçet Disease Research Committee of Japan (Kaneko et al. 1999). However, there have been several problems with these criteria, including their performance in selectivity and specificity, so that both of them have currently been revised (International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) et al. 2013) (Table 3.1).

Table 3.1 Revised international criteria for Behçet's disease (International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) et al. 2013)

Symptom	Points
Ocular lesions (recurrent)	2
Oral aphthosis (recurrent)	2
Genital aphthosis (recurrent)	2
Skin lesions (recurrent)	1
Central nervous system	1
Vascular manifestations	1
Positive pathergy test[a]	1

Scoring: score ≥4 indicates Adamantiades-Behçet disease

[a]Though the main scoring system does not include pathergy test, where pathergy testing is conducted, a positive result may be included for one extra point

Mucocutaneous Lesions

Recurrent oral aphthous and genital ulcers are the most frequently observed mucosal manifestations. Oral aphthous ulcers are the presenting sign in more than 80 % of the cases (McCarty et al. 2003; Altenburg et al. 2006). Although recurrent aphthous stomatitis is a common disorder, only a few patients progress to Adamantiades-Behçet disease, and it is not possible to determine in whom or when the transition may occur (Oh et al. 2009). Typically, lesions are multiple, painful, 1–3 cm in diameter, and sharply margined with a fibrin-coated base and surrounding erythema (Fig. 3.1). Oral aphthous ulcers usually heal without scarring (92 %). Genital ulcers may not recur as often and usually heal with a characteristic scar (64–88 %; Fig. 3.2). Spontaneous healing of aphthae occurs within 4 days to 1 month; genital ulcers may persist longer. Large oral ulcerations can also be associated with problems such as pharyngeal involvement, dysphagia, and dyspnea or fistulae involving the pharynx, larynx, trachea, or esophagus. Genital ulcers can occur on the penis, scrotum, vagina, labia, and urethra, and also in the anal, perineal, and inguinal regions.

Skin lesions that should be accepted as diagnostically relevant in Adamantiades-Behçet disease should be confined to pustular vasculitic lesions (including pathergy lesions), erythema nodosum-like lesions, Sweet-like lesions, pyoderma gangrenosum-like lesions, and palpable purpuric lesions of necrotizing venulitis (Fig. 3.3). All of these lesions are characterized in their early stages by a neutrophilic vascular reaction (Jorizzo et al. 1995). Acneiform lesions or follicle-based pustules should not be considered relevant.

Systemic Lesions

Ocular involvement is the major cause of morbidity in patients with Adamantiades-Behçet disease. The most diagnostically relevant lesion is posterior uveitis (also called *retinal vasculitis*), which can lead to blindness (Fig. 3.4). Other

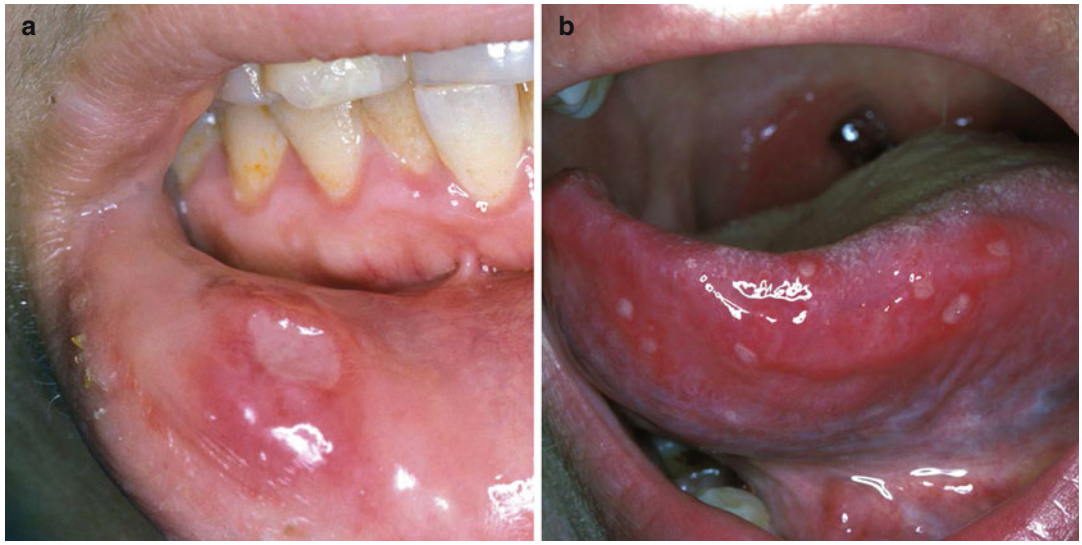

Fig. 3.1 Single (**a**) and multiple (**b**) oral aphthous ulcers (**a** From Altenburg et al. (2006), with permission)

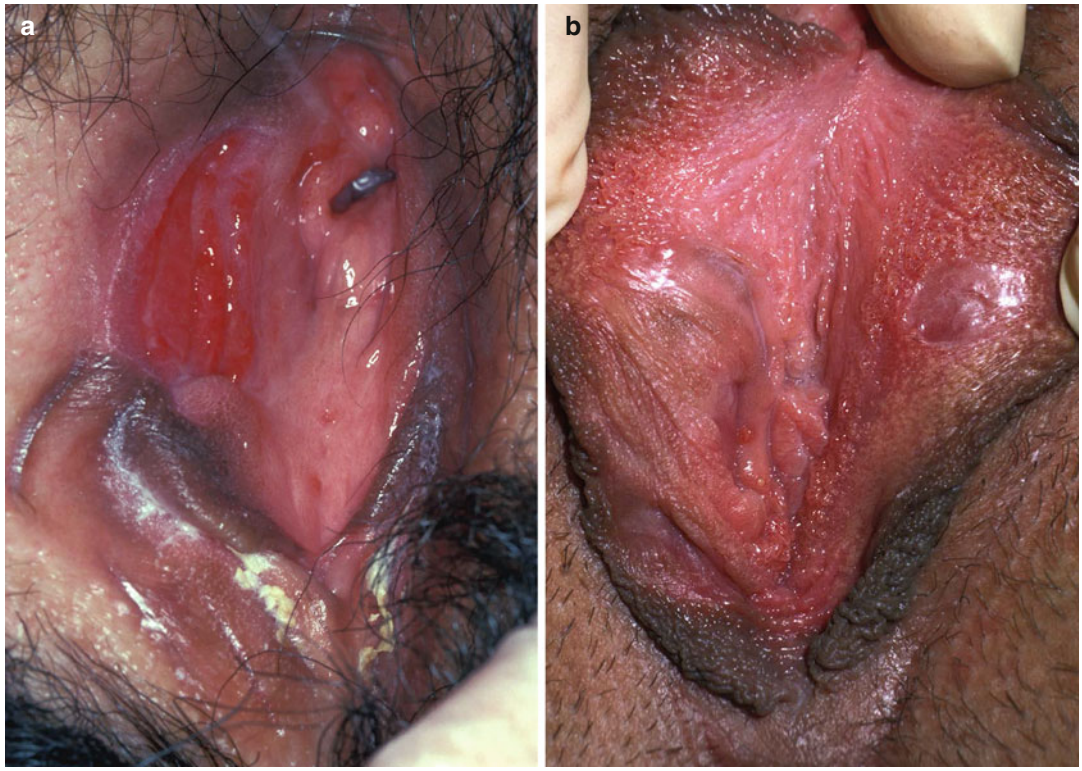

Fig. 3.2 Genital ulcer (**a**) healing with a demarcated flat scar (**b**)

ocular lesions include anterior uveitis, hypopyon (pus in the anterior chamber of the eye, which is now—due to early treatment—uncommon), and secondary complications such as cataract, glaucoma, and neovascular lesions (Krause 2005). Retinal inflammation can lead to vascular occlusion

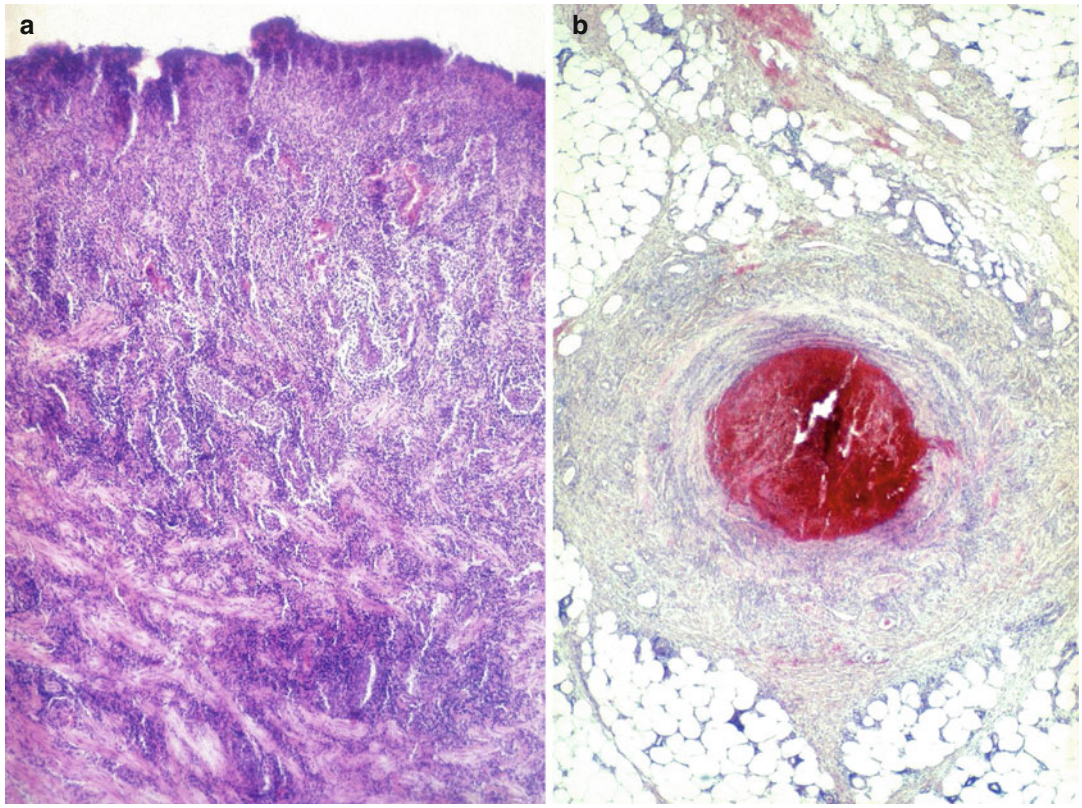

Fig. 3.3 (**a**) Abundant mixed inflammatory infiltrate dominated by neutrophils in an oral ulcer of Adamantiades-Behçet disease. (**b**) Vessel thrombosis in an erythema nodosum-like lesion

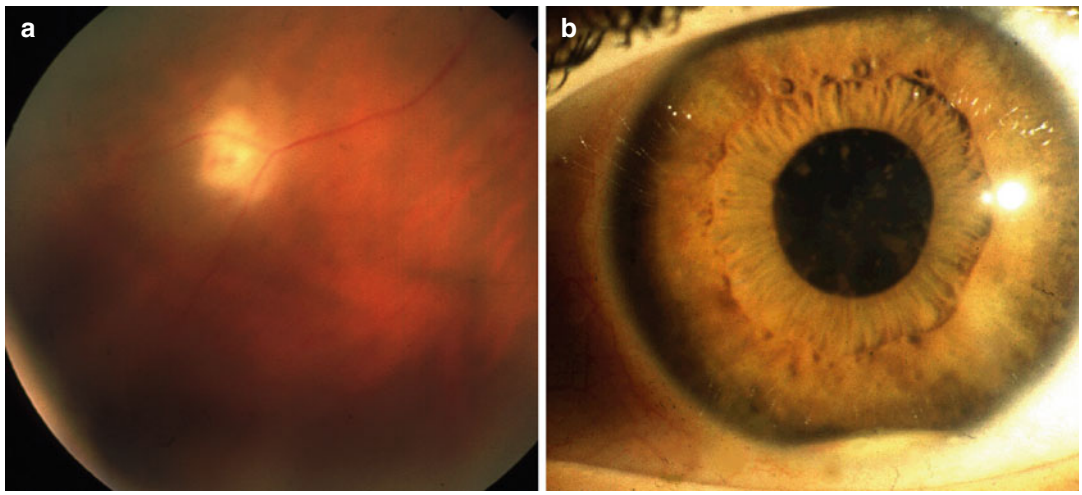

Fig. 3.4 (**a**) Posterior uveitis. (**b**) Hypopyon iritis (From Altenburg et al. (2006), with permission)

and, ultimately, tractional retinal detachment. Severe vitreous involvement, chronic cystoid macular edema, and possible—presumably also vasculitic—involvement of the optic nerve can result in vision loss. Recurrent vasculitic changes can ultimately lead to ischemic optic nerve atrophy.

The characteristic arthritis is a nonerosive, asymmetric, sterile, seronegative oligoarthritis; however, symmetric polyarticular involvement is common. Joint manifestations frequently occur first in one knee or ankle and then the other as migratory monoarthritis, then in both joints simultaneously, and finally affecting nearly all joints. An HLA-B27-positive, erosive sacroiliitis has to be excluded.

Systemic vascular involvement can be significant and includes venous occlusions and varices, arterial occlusions, and aneurysms, often being migratory. Cases of large-vein thrombosis (inferior vena cava, cranial venous sinuses) or large-artery aneurysms are potentially fatal (McCarty et al. 2003; Altenburg et al. 2006). Arterial involvement is rather rare and usually presents in the form of thromboses and, less often, of aneurysms, resulting from multicentric arteritis. Pulmonary artery aneurysms are the principal feature of pulmonary involvement in Adamantiades-Behçet disease, occasionally resulting in coughing and hemoptysis. Cardiac involvement can include myocarditis, coronary arteritis, endocarditis, and valvular disease. A wide spectrum of renal manifestations can occur, varying from minimal change disease to proliferative glomerulonephritis and rapidly progressive crescentic glomerulonephritis. Immune complex deposition is thought to be responsible for the underlying pathogenesis in some cases of glomerulonephritis. Gastrointestinal complaints can be a symptom for aphthae throughout the gastrointestinal tract and can rarely result in perforation and peritonitis (0.5 %). Inflammatory bowel disease has to be excluded. Sterile prostatitis and epididymitis can be present in male patients without genital ulcers.

Significant neurologic manifestations occur in approximately 10 % of patients and may be delayed in onset. Meningoencephalitis, cerebral venous sinus thrombosis, benign intracranial hypertension, cranial nerve palsies, brainstem lesions, and pyramidal or extrapyramidal lesions have been described. Poor prognosis is associated with a progressive course, relapses after treatment, repeated attacks, and cerebellar symptoms or parenchymal disease. Neurologic manifestations usually present with severe headache. Further symptoms include gait disturbance, dysarthria, vertigo, and diplopia as well as hyperreflexia, epileptic seizures, hemiplegia, ataxia, or a positive Babinski reflex. Psychiatric symptoms, such as depression, insomnia, or memory impairment, are also signs of neurologic involvement.

Histopathology

Characteristic histopathologic features of Adamantiades-Behçet disease are vasculitis and thrombosis (Fig. 3.3). Biopsies from early mucocutaneous lesions show a neutrophilic vascular reaction with endothelial swelling, extravasation of erythrocytes, and leukocytoclasia or a fully developed leukocytoclastic vasculitis with fibrinoid necrosis of blood vessel walls (McCarty et al. 2003; Altenburg et al. 2006). Although there are reports of lesions that consist primarily of a lymphocytic perivasculitis, most of these lesions are likely older. The neutrophilic vascular reaction should be considered the predominant histopathologic finding (Jorizzo et al. 1995). Aneurysms can also develop in large arteries as a result of vasculitis of the vasa vasorum with penetration of the lamina elastica.

Special Tests

Pathergy Test

A positive pathergy test (hyperreactivity reaction) manifests within 48 h as an erythematous papule (>2 mm) or pustule at the site of a skin needle prick or after intracutaneous injection of 0.1-ml isotonic salt solution using a 20-gauge needle without prior disinfection of the injection site. The skin prick is generally placed at an angle of 45° 3–5 mm intracutaneously on the volar forearm. Erythema without infiltration is considered a negative finding. Provoked oral aphthae and genital ulcers after injection or injury (such as chorioretinitis in the corneal region of the eye after photocoagulation of the ocular fundus region) can also be considered as positive pathergy

phenomenon. Broader pathergy phenomena also include the occurrence of aneurysms around vascular anastomoses as well as local recurrence of ulcers after resection of affected bowel segments. Although a positive pathergy reaction is a sign of Adamantiades-Behçet disease, it is not pathognomonic, as it can also occur in patients with pyoderma gangrenosum, rheumatoid arthritis, Crohn disease, and genital herpes infection.

Radiologic Findings

Scintigraphic evidence of arthritis is found in 50 % of the patients (Altenburg et al. 2006). Cranial magnetic resonance imaging allows documentation of hypodense or atrophic changes in the brain. Electroencephalographic detection of diffuse α waves is considered a positive finding. Vascular lesions can be detected by angiography

Differential Diagnosis (Table 3.2)

Table 3.2 Differential diagnosis of Adamantiades-Behçet disease

Oculocutaneous/mucocutaneous syndromes
Erythema multiforme exudativum and variants, including Stevens-Johnson syndrome
Vogt-Koyanagi-Harada syndrome
Reiter disease
Bullous autoimmune diseases: pemphigus vulgaris, cicatricial mucous membrane pemphigoid, epidermolysis bullosa acquisita
Viral infections (herpes, coxsackie, echo)
Syphilis
Articulomucocutaneous syndromes
Systemic lupus erythematosus
MAGIC syndrome (*m*outh *a*nd *g*enital ulcers with *i*nflamed *c*artilage)
Yersiniosis
Arthropathic psoriasis
Gastrointestinal/mucocutaneous syndromes
Ulcerative colitis, Crohn disease
Tuberculosis
Bowel-associated dermatitis-arthritis syndrome
Aphthae
Recurrent aphthous stomatitis (RAS)
Cyclic neutropenia
Herpes simplex infection
Genital ulcers
Ulcus vulvae acutum (Lipschütz ulcer)
Herpes simplex infection
Sexually transmitted infections
Uveitis
Other forms of uveitis
Arthritis
Ankylosing spondylitis
Juvenile rheumatoid arthritis
Central nervous system manifestation
Multiple sclerosis
Neuro-Sweet disease
Lung manifestation
Sarcoidosis

Adapted from Altenburg et al. (2006)

Clinical Course and Prognosis

The clinical course of Adamantiades-Behçet disease is variable. There can be a delay of up to several years before the diagnosis is made, and this may influence the prognosis. Mucocutaneous and joint manifestations usually occur first. Recurrent erythema nodosum and $HLAB_{51}$ positivity are risk factors for the development of superficial thrombophlebitis and vision loss (Zouboulis et al. 2003a, b; Sakamoto et al. 1995), and superficial thrombophlebitis, ocular lesions, and male gender are risk factors for the development of systemic vessel involvement (Zouboulis et al. 2003a, b; Coskun et al. 2005). A severe course, including blindness, meningoencephalitis, hemoptysis, intestinal perforation, and severe arthritis, occurs in approximately 10 % of patients. Blindness can often be prevented with early aggressive therapy of posterior uveitis. Lethal outcome has been seen in 0–6 % of affected patients in different ethnic groups. Central nervous system and pulmonary and large vessel involvement, as well as bowel perforation, are the major life-threatening complications; death may also result as a complication of immunosuppressive therapy. Markers of severe prognosis include HLA-B_{51} positivity, male gender, and early development of systemic signs (Zouboulis et al. 2003a). Onset in childhood

does not necessarily predict a poor prognosis. Spontaneous remissions of certain or all manifestations of the disease have been observed. Ophthalmic and neurologic sequelae are leading causes of morbidity, followed by severe vascular and gastrointestinal manifestations, and their effects on morbidity may be cumulative.

General Principles of Treatment

The choice of treatment for patients with Adamantiades-Behçet disease depends on the site and severity of the clinical manifestations of the disease. Recurrent aphthae are most often treated with palliative agents, such as mild diet, avoidance of irritating agents, and potent topical glucocorticoids and local anesthetics (Zouboulis 2003a; Alpsoy 2005); lately topical hyaluronic acid 0.2 % gel 2×/day over 30 days was found effective (Table 3.3) (Altenburg et al. 2007). For the topical treatment of genital ulcers and skin lesions, corticosteroid and antiseptic creams can be applied for up to 7 days. Painful genital ulcerations can be managed by topical anesthetics in cream. Corticosteroid injections (triamcinolone acetonide, 0.1–0.5 ml/lesion) can be helpful in recalcitrant ulcerations. They can also be beneficial on panuveitis and cystoid macular edema as a single intravitreal injection (triamcinolone acetonide 4 mg) (Atmaca et al. 2007; Tuncer et al. 2007).

Patients with mucocutaneous lesions resistant to topical treatment, those with systemic involvement, and patients with markers of poor prognosis are candidates for systemic treatment (Zouboulis 2003a; Pipitone et al. 2006; Hatemi et al. 2009). Several compounds have been found effective in randomized, double-blind, placebo-controlled trials (Mat et al. 2006; Matsuda et al. 2003; Davatchi et al. 2009; Yurdakul et al. 2001; Aktulga et al. 1980; Sharquie et al. 2002; Yazici et al. 1990; Alpsoy et al. 2002; Davies et al. 1998) (Table 3.4). Additional treatments have been successful in studies with a lower grade of evidence (Suzuki Kurokawa and Suzuki 2004; Zouboulis 2003a; Kiliç et al. 2009; Hamuryudan et al. 1998; Masuda et al. 1989; Ozyazgan et al. 1992; BenEzra et al. 1988; Melikoglu et al. 2005; Davies et al. 1988; Moral et al. 1995; Sfikakis et al. 2007; Nanke et al. 2008; Zouboulis and Orfanos 1998; Krause and Altenburg 2008; Guillaume-Czitrom et al. 2007; Zouboulis 2003b) (Table 3.5). Oral and intravenous prednisolone can be combined with other immunosuppressants, colchicine, dapsone, sulfasalazine, or interferon-α. A synergistic effect with cyclosporin A has been described in patients with ocular involvement. Prednisolone is one of the few medications that can be used

Table 3.3 Topical treatment of oral aphthous ulcers

Mild diet
Avoidance of hard, spicy, or salty nutrients and irritating chemicals, such as toasted bread, nuts, oranges, lemons, tomatoes, spices (pepper, paprika, curry), alcohol- or CO_2-holding drinks, mouthwashes, toothpastes containing sodium lauryl sulfate[a]
Topical treatment of the aphthous oral ulcers includes:
Caustic solutions (silver nitrate, 1–2 %; tinctura myrrha, 5–10 % weight/volume; H_2O_2, 0.5 %; methyl violet, 0.5 %) 1–2×/day
Antiseptic and anti-inflammatory preparations (amlexanox, 5 % in oral paste[a]; triclosan, 0.1 % mouthwash solution and in toothpastes[a]; amyloglucosidase- and glucose oxidase-containing toothpastes[a]; hexetidine, 1 %, chlorhexidine, 1–2 % mouthwash solutions; benzydamine; chamomile extracts) 3 % diclofenac in 2.5 % hyaluronic acid[a]; hyaluronic acid 0.2 % gel; tetracycline mouthwash (as glycerine solution 250 mg/5 mL glycerine) 2 min 4–6×/day[a] (caveat: pregnancy); doxymycine in isobutyl cyanoacrylate[a]
Corticosteroids (triamcinolone mucosal ointment, dexamethasone mucosal paste, betamethasone pastilles) 4×/day or during the night (ointment/paste) or intrafocal infiltrations with triamcinolone suspension 0.1–0.5 mL per lesion
Anesthetics (lidocaine, 2–5 %; mepivacaine, 1.5 %; tetracaine, 0.5 %–1 % gels or mucosal ointments) 2–3×/day (caveat: allergy)
5-Aminosalicylic acid (5 % cream) 3×/day (reduces the duration of lesions and the pain intensity)
Cyclosporin A, 500-mg solution for mouthwash 3×/day (effective as topical immunosuppressive drug)
Sucralfate suspension, 5 mL × 4/day[a] (for oral aphthous and genital ulcers)
A close association of smoking with a decrease of recurrences of oral aphthous ulcers has been described

[a]Small, randomized, double-blind, placebo-controlled trial against placebo

Table 3.4 Systemic treatment of Adamantiades-Behçet disease

Drug	Dose	Indication
Methylprednisolone	40 mg/every 3 weeks IM	Erythema nodosum (but not orogenital ulcers)
Rebamipide	300 mg/day PO (caveat: pregnancy, lactation)	Oral ulcers
Colchicine	1–2 mg/day PO (caveat: pregnancy, lactation—induces oligozoospermia)	Oral aphthous ulcers, genital ulcers, folliculitis, erythema nodosum
	1.5 mg/day	Erythema nodosum, arthritis, genital ulcers (oral ulcers in females)
		Ineffective
Dapsone	100 mg/day PO (caveat: pregnancy, lactation—methemoglobin increase: ascorbic acid, 500 mg/day)	Oral ulcers, genital ulcers, skin lesions, pathergy test
Azathioprine	2.5 mg/kg/day (caveat: pregnancy, lactation, severe liver disease, bone marrow depression, severe infection, children)	Recent onset ocular disease
Interferon-α 2a	6×10^6 IU/3×/week SC (caveat: pregnancy, lactation—induces psychotic signs, psoriasis, myopathy)	Oral ulcers, genital ulcers, papulopustular lesions
Interferon-α	1,000 and 2,000 IU/day PO	Ineffective
Thalidomide	100 mg/day or 300 mg/day (caveat: pregnancy, lactation—induces polyneuropathy: minimized at 25 mg/day)	Oral ulcers, genital ulcers, papulopustular lesions
Cyclosporin A	10 mg/kg/day PO (against colchicine, 1 mg/day PO) (caveat: lactation, renal insufficiency—induces pathologic central nervous system findings)	Ocular manifestations, oral ulcers, skin lesions, genital ulcers
	5 mg/kg/day PO (against cyclophosphamide pulses)	Visual acuity
	5 mg/d PO (against conventional treatment)	Ocular attacks
Etanercept	25 mg/2×/week PO (caveat: pregnancy, lactation)	Oral ulcers, nodular lesions, papulopustular lesions (not pathergy test)
Acyclovir	5 × 800 mg for 1 week +2 × 400 mg/day for 11 week	Ineffective
Azapropazone	900 mg/day over 3 weeks PO	Arthritis

Evidence grade A—randomized, double-blind, placebo-controlled trial (RCT) against placebo except otherwise mentioned

Table 3.5 Systemic treatment of Adamantiades-Behçet's disease

Drug	Dose	Indication
Corticosteroids	5–60 mg/day prednisolone equivalent PO	Active disease
	100–1,000 mg/day IV over 1–3 days (alone or in combinations) (can induce diabetes or psychosis)	Acute exacerbation (partic. uveitis, neurological manifestations)
Indomethacin	100 mg/day PO	Mucocutaneous lesions, arthritis
Pentoxifylline	300 mg × 1–3/day PO	Oral ulcers (partic. in children)
Oxpentifylline	400 mg × 3/day PO	
Irsogladine	2–4 mg/day PO	Recurrent aphthous ulcers
Cyclosporin A	3–6 mg/kg/day PO (serum levels: 100–150 ng/ml) (caveat: lactation, renal insufficiency – induces pathologic CNS findings)	Uveitis, mucocutaneous signs, thrombophlebitis, acute hearing loss
Tacrolimus	0.05–0.2 mg/kg/day PO (serum levels: 15–25 ng/ml)	Refractory uveitis
Interferon-α	9×10^6 IU × 3/week/3–9×10^6 IU × 5/week SC (3 10^6 IU × 3/week maintenance dose) (caveat: pregnancy, lactation – induces psychotic signs, psoriasis, myopathy)	Ocular lesions, long-term visual prognosis, arthritis, vascular lesions
	1.5–3 × 10^6 IU × 3/week according to body weight	Corticodependent uveitis in children

(continued)

Table 3.5 (continued)

Drug	Dose	Indication
Cyclophosphamide	1 g/month IV bolus (caveat: hemorrhagic cystitis: mesna 200 mg)	Uveitis, neurologic manifestations
Chlorambucil	0.1 mg/day PO (2 mg/day maintenance dose) (caveat: cumulative toxicity)	Neurologic manifestations, uveitis, thrombosis, mucocutaneous lesions
Methotrexate	7.5–20 mg/1× week PO (caveat: pregnancy, lactation, severe bone marrow depression, liver dysfunction, acute infections, gastrointestinal ulcers, kidney insufficiency)	Severe mucocutaneous lesions, arthritis, progressive psychosis, or dementia
Infliximab	5 mg/kg IV days 1, 7, 14, and 28 or days 1, 14/1, 30/1, and 45 (caveat: pregnancy, lactation)	Acute uveitis, refractory posterior uveitis, neurologic manifestations, intestinal involvement
Adalimumab		Refractory ocular lesions
Sulfasalazine	1.5–3 g/day PO	gastrointestinal ulcers
Thalidomide	2 mg/kg/day PO; increased to 3 mg/kg/day if necessary or decreased to 1–0.5 mg/kg/day according to the response (caveat: neurotoxicity)	Intestinal involvement (in children)

Evidence grade B—well-conducted open clinical trial

during pregnancy. Colchicine can be combined with immunosuppressants and interferon-α. A rapid relapse often occurs after discontinuing cyclosporin A, interferon-α, dapsone, or infliximab (Hamuryudan et al. 1998; BenEzra et al. 1988; Davies et al. 1988).

Prevention

- Patients with severe or progressive recurrent aphthous stomatitis should be followed up for years as potential candidates for Adamantiades-Behçet disease, particularly those patients with familial occurrence of the disease.
- Patients with suspected Adamantiades-Behçet disease should be referred early for specialist advice.
- Male patients with systemic involvement as a presenting sign and/or an early age of onset should be treated systemically because of the poor prognosis.

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Alopecia Areata

4

Markus Böhm

Key Points

- Alopecia areata is a chronic and often relapsing non-fibrosing inflammatory skin disorder of the hair follicles.
- High-potency topical corticosteroids, e.g. clobetasol propionate, remain the mainstay of all therapeutic options for treatment of alopecia areata on the scalp.
- Topical immunotherapy with 2,3-diphenylcyclopropenone or squaric acid dibutylester is recommended for patients with alopecia areata of the scalp not resolving spontaneously within 1 year or for those not responding to topical corticosteroids.
- Intralesional injection of corticosteroids, e.g. triamcinolone acetonide, should be reserved for therapy-resistant patchy hair loss of the scalp and cosmetically sensitive sites such as the eyebrows.
- Other treatment options with limited level of evidence include topical dithranol, minoxidil, aroma oils and laser therapy.
- Systemic treatment with corticosteroids may be considered for those patients suffering from severe psychological distress and from acute bursts of the disease on the scalp.
- There is only limited evidence for the efficacy of other immunosuppressants (methotrexate, ciclosporin, sulfasalazine).
- Treatment should be individualized and depends on the extent of disease, age and individual level of psychological distress and social impairment.
- Supportive measures (counselling, wigs and other hairpieces, psychotherapy and patient support groups) are important cornerstones in the treatment of patients with alopecia areata.

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Definition and Epidemiology

Alopecia areata is a chronic inflammatory skin disorder of the hair follicles with a lifetime incidence of 1–2 %. It affects both women and men equally. The disease most often starts in young adults with children frequently affected. The disease has a sudden onset of patchy areas of hair loss that can occur on the scalp or elsewhere on the body. The individual extent of psychological distress in patients with the disease is often underestimated and frequently leads to severe psychological distress and social impairment.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_4, © Springer-Verlag Berlin Heidelberg 2015

Basic Concepts of Pathogenesis

Alopecia areata is considered a CD8+T-cell-mediated, organ-specific autoimmune disease with several genetic factors contributing to the disease origin (about 20 % of affected patients have a positive family history for the disease). Several loci/regions with genome-wide significance have been reported to confer susceptibility to the disease. They include the histocompatibility leukocyte antigen and the cytokine genes of interleukin (IL)-13, IL-2/21 and IL-2 receptor alpha as well as genes implicated in the regulation of immune responses, i.e. cytotoxic T-lymphocyte-associated antigen 4, cytomegalovirus UL16-binding protein and C-type lectin domain family 16, member A. Several of these susceptibility genes have been associated with other autoimmune diseases. Accordingly, alopecia areata may also be a dermatological sign of an underlying autoimmune polyglandular disease. The pathogenetic concept of alopecia areata in which hair follicles lose their immune privilege is mirrored by histopathology in which a bee swarm-like lymphocytic infiltrate of variable extent is seen around the growing hair bulbs (bee swarm). This inflammation leads to increased numbers of catagen hairs and finally to dystrophic, miniaturized hairs. Notably, hair follicles are not destroyed during the course of the disease and retain their capacity for regrowth even in long-standing alopecia areata.

Clinical Presentation

The disease typically starts with a sudden onset of a single round or oval patch or multiple patches of hair loss that may coalesce into larger areas of alopecia. During the course of the disease, alopecia areata may progress to complete loss of all terminal hair follicles. The scalp is often the initial and only site of involvement, but any other areas of the body including the beard, eyebrows and eyelashes may be affected. Traditionally, alopecia areata is distinguished into limited disease, i.e. *unifocal* or *multifocal* alopecia areata and extensive disease, i.e. complete loss of the scalp hair (*alopecia totalis*) or complete loss of hairs of the total body (*alopecia universalis*). *Ophiasis* describes a band-like pattern of hair loss on the occipital scalp (Figs. 4.1, 4.2, 4.3 and 4.4). *Diffuse alopecia areata* describes a rare form of alopecia areata in which no patchy areas of hair loss are present. This form commonly progresses to alopecia totalis. The extent of hair loss on the scalp can be more precisely assessed by the so-called SALT (severity of alopecia areata tool). This quantification tool has been shown to be useful for monitoring the efficacy of the chosen therapy against alopecia areata. In addition to the changes of the hairy areas of the body, about 10–20 % of the patients with alopecia areata have structural nail abnormalities including pits and other forms of nail dystrophy (e.g. "sand paper nails") (Fig. 4.5).

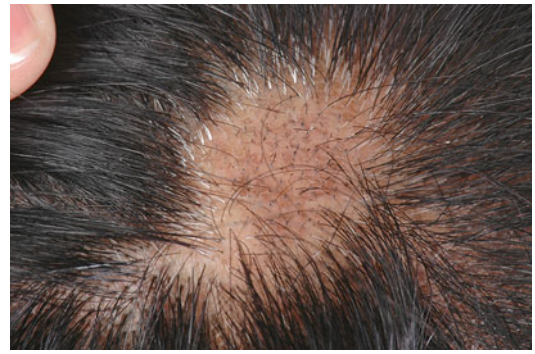

Fig. 4.1 Classical patch of alopecia areata on the scalp. Note exclamation mark hairs

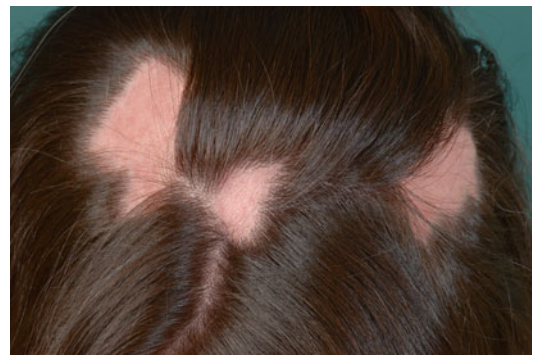

Fig. 4.2 Multifocal alopecia areata of the scalp

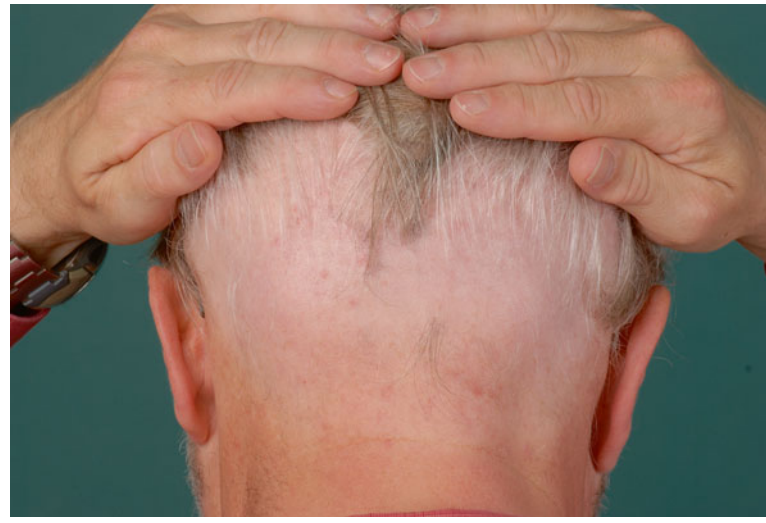

Fig. 4.3 Ophiasis type of alopecia areata

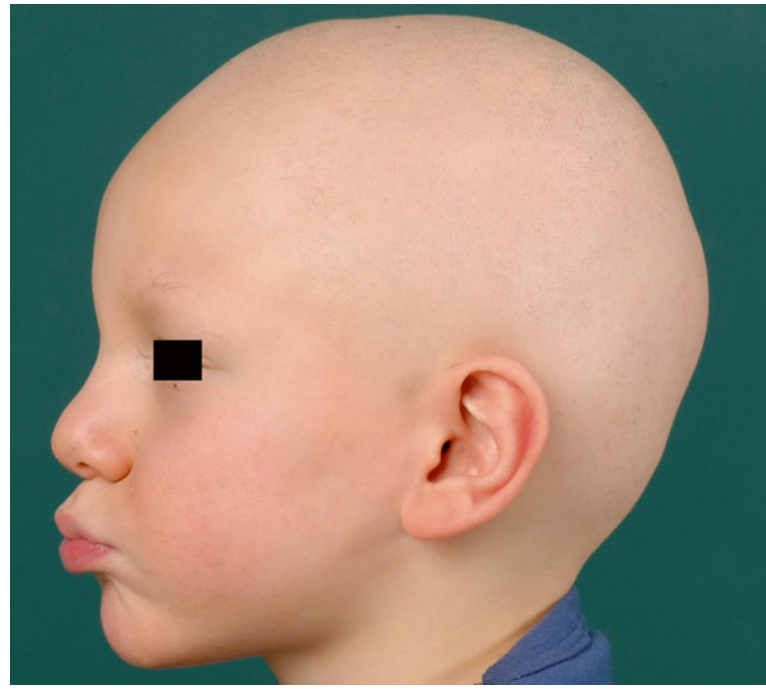

Fig. 4.4 Alopecia areata totalis. Note also almost full absence of eyebrows and eyelashes

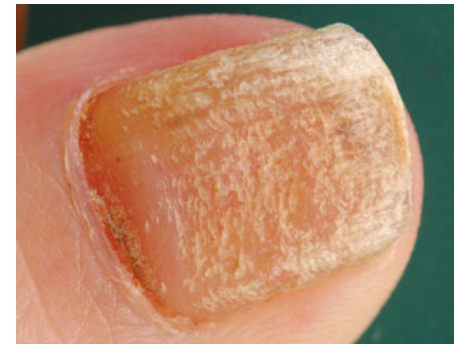

Fig. 4.5 Typical changes of alopecia areata on the nail plate

Differential Diagnosis

Alopecia areata is a clinical diagnosis that rarely requires the need for an excisional skin biopsy. The typical patchy configuration of the hair loss together with the presence of exclamation mark hairs and the lack of fibrosis are indicative for the diagnosis. Patchy forms of hair loss, however, can also be found in the following:

- *Tinea capitis*. Inflammation is present on the scalp (erythema, scales, yellow crusts, scutula). Depending on the type of fungus, Wood light gives also a greenish fluorescence (*Microsporon*). KOH examination followed by fungal microscopy and cultures is positive. Children are most often affected.
- *Trichotillomania.* Here, the hair loss in the affected areas is often incomplete with multiple broken hairs of varying length. The epilation test ("pull test") at the margins of the lesions is negative. Children are most commonly affected and indicate an underlying psychological problem.
- *Fibrosing (cicatricial) alopecia*, e.g. chronic discoid lupus erythematosus (CDLE) and lichen planopilaris show fibrosis and signs of inflammation depending on the stage of the disease. CDLE of the scalp presents with irregular footstep-like patches of erythema and hyperkeratosis. Lichen planopilaris shows perifollicular erythema, hyperkeratosis and the paintbrush sign (bundles of residual hairs surrounded by fibrotic skin). To definitely exclude such forms of fibrosing alopecia, an excisional skin biopsy of the scalp may be necessary.

Diffuse alopecia areata must be differentiated from other forms of diffuse alopecia which include the following:

- *Syphilis* can rarely affect the scalp hair either as a patchy form of alopecia or as diffuse alopecia. Serologic testing easily excludes this differential diagnosis.
- *Loose anagen hair syndrome* occurs in children between the age of 2 and 5 years often with blond hair. Patients have typically short and dull hairs. Parents notice the sudden onset of a diffuse effluvium in which hairs can be easily pulled out without pain. The trichogram reveals almost exclusively anagen hairs.
- *Telogen and anagen effluvium* may mimic diffuse alopecia areata. In both conditions, the pathognomonic exclamation mark hairs of alopecia are not present. Careful exploration of the patient's history will usually identify a causative drug responsible for anagen effluvium.

General Principles of Treatment

Alopecia should never be considered a cosmetic problem but a disease that can severely affect the quality of life of an affected individual. Quality of life can be easily assessed, e.g. by a visual analogue scale. It does not only provide a simple proxy for the psychological distress of the patient but also an outcome measurement for the success of any therapy. Importantly, the individual extent of psychological distress and the resulting social impairment in patients with the disease is often underestimated by physicians. Professional counselling and supportive measures (e.g. wigs) of patients with alopecia areata including the offer of psychological intervention or contact to patient support groups are essential cornerstones in the state-of-the-art management of individuals with alopecia areata.

All patients should be encouraged that spontaneous resolution may occur even in long-standing and extensive alopecia areata due to the fact that hair follicles are not destroyed. As spontaneous resolution occurs in up to 80 % of patients with limited patchy hair loss and <1 year duration of the disease, *no treatment* remains a therapeutic option especially in young children. Notably, most patients with alopecia areata will not be satisfied with *therapia nulla* and request medical treatment. It should be further pointed out that the general course of the disease is unpredictable. Notably, its sustained remission is rare in patients with extensive alopecia areata. Prognostic factors indicating a prolonged course of the disease are early age of onset, coexisting atopic dermatitis and extensive disease, e.g. alopecia totalis or universalis.

The various forms of topical and systemic therapies should be briefly explained to all patients with alopecia areata. As only few randomized controlled trials have been published, the efficacy of all existing therapies must be interpreted in the light of the high rate of spontaneous resolution of the disease and the risk-benefit ratio of each treatment modality. It should be noted, moreover, that only very limited information exists on the long-term outcome of all presently available therapies for alopecia areata.

Topical Therapy

A variety of topical treatments exist for alopecia areata. Among them, topical high-potency corticosteroid formulations have the highest level of therapeutic evidence based on a randomized controlled trial. In addition, several controlled trials (often retrospective with a self-controlled design) highlight the relative efficacy of topical immunotherapy. All other topical treatments did either not fulfil the review criteria for inclusion into the most recent Cochrane's review or have yielded conflicting results with regard to efficacy.

Topical Corticosteroids

High-potency corticosteroids are frequently used in patients with alopecia areata and can be considered the mainstay therapy of this disease. They act by reducing the inflammatory infiltrate in the hair bulb and possibly promote spontaneous resolution. They are most useful for all limited forms of the disease (unifocal and multifocal alopecia areata) involving the scalp. The strongest evidence comes from a randomized controlled trial in patients with moderate to severe alopecia areata in which 0.05 % clobetasol propionate foam was given twice daily against the vehicle for 12 weeks and found to significantly promote hair regrowth. Other formulations of 0.05 % clobetasol propionate (cream, solution) may be administered accordingly with possibly similar effects. In patients suffering from alopecia areata totalis or universalis, 0.05 % clobetasol propionate under an occlusive dressing may further promote hair growth of the scalp. It can be applied overnight on six out of seven nights for 6 months and may promote long-term hair growth. No evidence for systemic absorption was noted under this treatment in adult patients. A well-known side effect of topical high-potency corticosteroids on the scalp is folliculitis. Upon extended treatment, skin atrophy will also occur. There are no data on the safety and efficacy of high-potency corticosteroids in children with alopecia areata.

Topical Immunotherapy

Topical immunotherapy (also known as contact immunotherapy) has an established role in the treatment of corticosteroid-refractory, prolonged and extensive disease (alopecia areata totalis and universalis) for many years. The precise mode of action of this therapy is still unclear, but the general therapeutic principle resides in the induction of a type IV allergic reaction to an epicutaneously administered allergen. During subsequent challenges with the antigen, a low-grade allergic contact dermatitis is elicited which alters the extent and nature of the perifollicular infiltrate. There are no randomized controlled trials of this treatment, but extensive experience over the last 30 years and a number of large observational studies with a self-controlled design (half-head method) support the efficacy of this therapy for alopecia areata. It is important to note that topical immunotherapy is tricky and time-consuming, both for the patient and for the treating dermatologist.

The commonly used allergens 2,3-dephenylcyclopropenone (DCP) and squaric acid dibutylester (SADBE) have probably the same therapeutic efficacy, but DCP is more suitable since it is more stable in solution. Therapy starts with sensitization of one half of the scalp with 2 % DCP in acetone. After 2 days, this solution is removed by washing. Two weeks after sensitization, the previously sensitized scalp area is challenged weekly with increasing DCP concentrations (0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.75, 1 and 2 %) until

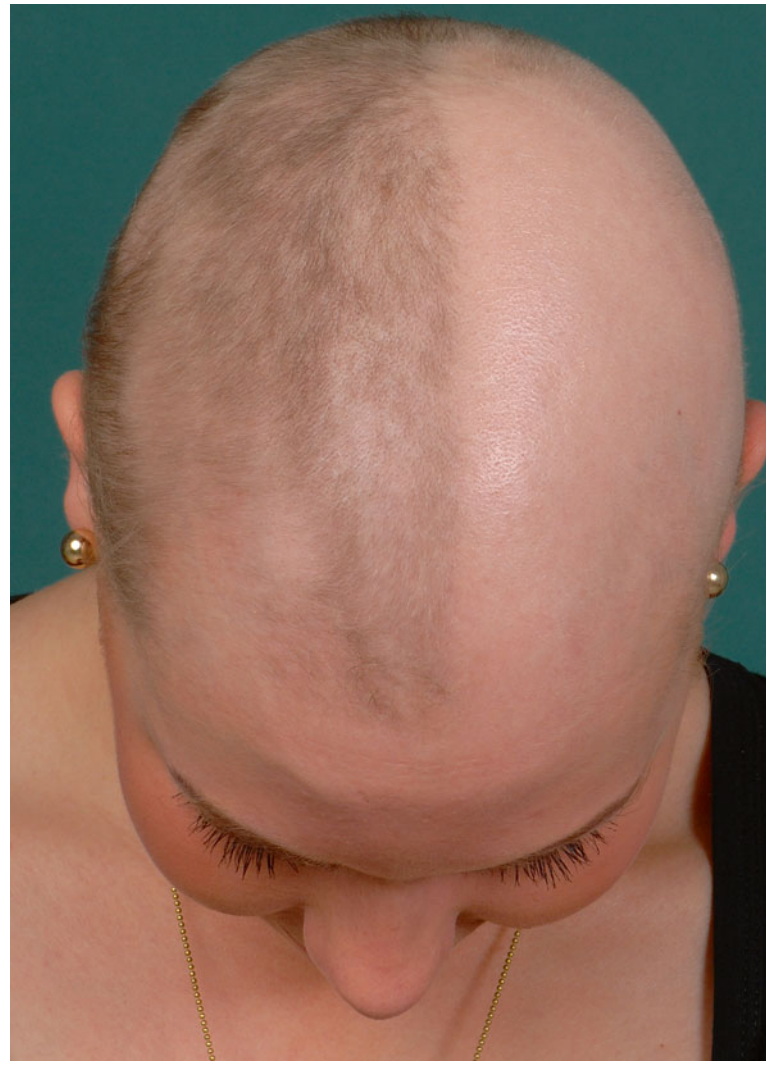

Fig. 4.6 Regrowth of hairs under DCP immunotherapy on the right side of the scalp

an eczematous reaction consisting of erythema and pruritus for 2 days has been reached. Most patients develop the first eczematous reaction after applying a median concentration of 0.2 %. When the appropriate DCP concentration has been found, this dose is applied in weekly intervals to the aforementioned area until regrowth is detected (Fig. 4.6). Then, the solution is applied to the whole scalp to promote hair growth on both sides of the head. If no hair growth is observed after unilateral application of the allergen for total length of 1 year, topical immunotherapy is considered ineffective and should be discontinued. Once complete or cosmetically acceptable regrowth of scalp hair has been achieved, DCP should be best tapered off by prolonging the application intervals of DCP to 2 weeks, to 3 weeks and then to 4 weeks. In case of recurrence of hair loss, topical immunotherapy can be restarted in weekly intervals. Around 5 % of all patients treated with DCP are anergic and thus will not respond to this treatment. Here, DCP must be discontinued and SADBE can be tried as an alternative allergen. Prognostic factors for an unfavourable prognosis for DCP are extensive scalp involvement and long disease duration. Patients and treating physicians should also be aware that relapses frequently occur after cessation of the treatment.

The most commonly encountered adverse effect of topical immunotherapy is high-grade allergic contact eczema (blisters and bullae) which is not intended but can easily be controlled with topical class-II corticosteroids and a pause of allergen exposure for 1 week upon which it is reapplied in a lesser concentration. Careful titration of the allergen dose is thus essential to avoid this complication. Moreover, special care should be taken to not contaminate other regions of the body (face, hands) with the allergen. Accordingly, all patients should be requested to wear a wig or protective hat for 2 days after the allergen-containing solution has been applied to avoid contact eczema and elicitation of photoallergy in skin areas other than the scalp. Many patients further develop occipital and/or cervical lymphadenopathy during the treatment period. Additional side effects include urticaria, angioedema of the eyelids (upon high-grade allergic dermatitis) and pigmentary changes (both hypopigmentation and hyperpigmentation). Induction or exacerbation of vitiligo has been noted in several case reports. However, long-term side effects have not been reported albeit topical immunotherapy has been used for more than 30 years.

Importantly, it is should be noted that topical immunotherapy is an unlicensed treatment as it uses non-pharmacological-grade allergens. All patients need to be informed about the nature of the treatment, possible side effects and alternative treatments. All should give signed consent to the therapy. Furthermore, DCP- and SADBE-containing solutions must be stored in the dark and should be handled only with gloves during application onto the patients' scalp to avoid sensitization. Upon pregnancy, topical immunotherapy should be discontinued as no data on safety are available. Notably, topical immunotherapy may also be administered to children with alopecia areata.

Intralesional Corticosteroids

Injection of depot corticosteroids into patches of alopecia areata has long been performed by practitioners and may result in prolonged hair growth. Triamcinolone acetonide (5–10 mg/ml) and hydrocortisone acetate (25 mg/ml) are commonly used. The corticosteroids (0.05–0.1 ml) are injected with a needle into the upper subcutis or by a needleless device. Multiple injections, e.g. every 1–2 weeks, can be performed. Regrowth of hairs can be expected in >60 % of the treated patients. Since injection of corticosteroids is painful, this treatment is most suitable for single hairless patches or for a limited number of lesions, especially those located on cosmetically sensitive sites like the eyebrows. Skin atrophy is a common adverse effect, and physicians must be aware that injections of depot corticosteroids have also the risk for anaphylactic reactions, increased intraocular pressure and cataract. For children, intralesional injection of corticosteroids is not a suitable treatment option.

Other Topical Treatments

Minoxidil

Topical minoxidil solution (5 % for men and 2 % for women) is an effective and approved treatment for androgenetic alopecia. Its mode of action remains unclear, but induction of distinct growth factors is believed to play a role. Conflicting data have been reported regarding the efficacy of minoxidil in alopecia areata. While it is ineffective in alopecia areata totalis and universalis, it may be useful in limited disease (unifocal or multifocal alopecia areata) as a second-line treatment. It may also be used to prevent relapses. It should be applied twice daily (2 % for women; 5 % for men) and may also be used for regions not suitable for topical corticosteroids (e.g. beard and eyebrows).

Dithranol

Irritants such as dithranol may modulate the extent and composition of the inflammatory infiltrate around the hair follicles and thus may promote hair growth in alopecia areata. There is evidence from several case reports and uncontrolled trials that topical anthralin once sufficiently applied to induce irritant dermatitis may be beneficial to some patients. Dithranol is

applied daily in increasing concentrations (0.1–1.0 %) in short-term applications (not more than 20 min) and then washed off. It can be considered as a second-line treatment of alopecia areata and is suitable also for children.

Aromatherapy

Daily massage of essential aroma oils from lavender, thyme, rosemary and cedarwood for 2 min into the scalp skin has been reported to induce hair growth on alopecia areata. This form of therapy may also be combined with other treatment options, e.g. topical minoxidil or aromatherapy, and can also be used in children.

Laser Therapy

Preliminary data suggests that lasers may induce some hair growth in patches of alopecia areata. In one study, an infrared diode laser was used; in the other, a 308 nm excimer laser. In the latter study, laser treatment was performed twice weekly for 12 weeks.

Systemic Treatments

Corticosteroids

Since alopecia areata is an immune-mediated inflammatory disease, systemic corticosteroids appear to be a reasonable therapeutic approach to halt disease progression. However, there are no randomized controlled trials, and evidence for efficacy in alopecia areata is confined mostly to case reports and smaller case series. Perhaps systemic corticosteroids are best justified in patients suffering from extensive psychological distress together with an acute burst of the disease (positive pull test in all regions of the scalp) and resistance to previously applied topical corticosteroids. Prolonged therapy with systemic corticosteroids will lead to significant side effects, and upon cessation of the therapy, patients frequently experience relapses limiting the usefulness of this treatment in alopecia areata.

Oral prednisolone can be given at a starting dose of 40 mg per os followed by a tapering period over 6 weeks. Alternatively, dexamethasone (5 mg) twice weekly or prednisolone (200–300 mg) once monthly can be given. More invasive treatment protocols consist of intravenous pulse therapy with 250 mg methylprednisolone for 3 days or intravenous 2 g prednisolone. We have good experience with monthly intravenous pulses of dexamethasone (100 mg per day) for 3 consecutive days (100 mg per day). Six cycles of this therapy can be done to halt disease progress and promote hair regrowth. Side effects under this regimen are often minimal. Importantly, patients should be monitored under intravenous pulse therapy with corticosteroids.

Other Systemic Therapies

Based on the immune-mediated nature of alopecia areata, several other immunosuppressive or immunomodulating agents have been tried and reported in the past, all of which do not fulfil the criteria for a higher level of therapeutic evidence. While topical tacrolimus is ineffective in alopecia areata, oral ciclosporin was shown to induce hair regrowth in some patients with alopecia areata. Data from uncontrolled trials also suggested some therapeutic effect of sulfasalazine. A more recent study revealed some partial and complete responses in patients with alopecia treated with 15–25 mg methotrexate per week with our without prednisolone (10–20 mg per day). Notably, none of these agents is approved for alopecia areata but can lead to a number of adverse effects. Thus, these agents cannot be generally recommended for the routine therapeutic management of alopecia areata patients.

Phototherapy

In the past, all types of psoralen plus ultraviolet A (PUVA) treatment (oral and topical) have been assessed in patients with alopecia areata. None of these studies however were controlled. Due to uncertainty of the efficacy of PUVA in alopecia areata, its potential adverse effects (especially in systemic PUVA) and the long-term safety concerns PUVA of therapy cannot be currently recommended.

Supportive Measures

As pointed out above, life quality of patients with alopecia areata is often severely affected. Psychological profiling has shown that patients with alopecia areata experience more depressive, hysterical and anxiety feelings and may be more in conflict with their social environment. In light of this disease-associated psychological distress and social impairment, counselling and, if desired, psychological intervention including hypnotherapy are considered important supportive measures to optimally treat patients with alopecia areata. Many patients will further profit from the use of wigs, integrated systems, hairpieces, headscarves, hats and false eyelashes or permanent to better cope with the burden of the disease. Information on patient support groups should be offered to all patients suffering from a chronic course of the disease.

Guidelines for Treatment

Guidelines for the management of alopecia areata have been published by the British Association of Dermatologists in 2012. Accordingly, topical corticosteroids (level evidence 2+) and topical immunotherapy (level of evidence 2++) have the highest level of evidence followed by topical minoxidil (level of evidence 2–). All other therapies of alopecia areata as outlined above were classified as level 3 of evidence.

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Androgenetic Alopecia

5

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Abbreviations

AGA	Androgenetic alopecia
DHEA	Dehydroepiandrosterone
DTH	Dihydrotestosterone
EBM	Evidence-based medicine
PHL	Pattern hair loss

Key Points

- Androgenetic alopecia is the most common hair loss disorder.
- The hair loss is genetically determined, androgen induced, age dependent, and with sex-dependent differences in incidence, pattern, and severity.
- Due to the frequency and often significant impairment of life quality perceived by affected individuals, competent diagnosis and treatment are important.
- The diagnosis is established by history taking and clinical inspection, including dermoscopy, where a patterned, non-scarring, progressive alopecia with diversity of hair shaft diameters is observed.
- A systematic literature review revealed excellent evidence levels for the therapeutic use of topical minoxidil and oral finasteride. The limited success rate of evidence-based treatments points to a more important complexity of the problem. One must remain open-minded for the possibility of a multitude of cause relationships underlying hair loss, including seasonality of hair growth and shedding, hormonal factors, nutrition, inflammatory phenomena and scarring, and ageing.
- Finally, the influence of the prescribing physician should be kept in mind, since inspiring confidence versus scepticism and fear clearly impacts the outcome of treatment.

Definition and Epidemiology

Androgenetic alopecia (AGA), also referred to as male-pattern hair loss or common baldness in men and as female-pattern hair loss in women, is the most common hair loss disorder, affecting both men and women.

The hair loss is genetically determined, androgen induced, age dependent, and with sex-dependent differences in incidence, pattern, and severity.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_5, © Springer-Verlag Berlin Heidelberg 2015

It is assumed that the genetically predisposed hair follicles are the target for androgen-stimulated hair follicle miniaturisation, leading to gradual replacement of large, pigmented hairs (terminal hairs) by barely visible, depigmented hairs (vellus hairs) in affected areas. The result is a progressive decline in visible scalp hair density.

First signs often occur in adolescence, but may be observed as early as in childhood. The condition affects at least 50 % of men by the age of 50 years and up to 70 % of all males in later life. Estimates of its prevalence in women have varied widely, though recent studies claim that six per cent of women aged under 50 years are affected, increasing to a proportion of 30–40 % of women aged 70 years and over (Norwood 2001).

While male-pattern hair loss is characterised by its typical bitemporal recession of hair and balding vertex, female-pattern hair loss is set apart by its rather diffuse thinning of the crown and a usually intact frontal hairline.

Due to the frequency and the often significant impairment of life quality perceived by affected individuals, hair loss cures have been experimented on for centuries. What is remarkable about their history is that despite the more recent genuine advances in effective medical treatments, hair cosmetics, surgical procedures, and phony hair loss solutions continue to be marketed today with an amazing success. Therefore, competent diagnosis and treatment are particularly important in dealing with AGA.

Basic Concepts of Pathogenesis

Do not believe everything you hear on hair. Exactly as the fixation on treating hair loss is not a new phenomenon, age-old myths regarding hair growth and shedding continue to exist up to this day. In dealing with the fear or complaint of hair loss, it is important to weed out these myths from the facts: wearing hats causes hair loss, frequent washing and blow drying can lead to hair loss, hairstyling products and dyes cause hair loss, brushing your hair can make it stronger and more resistant to hair loss, or cutting your hair will make it grow back thicker.

While the popular or layman's myths are usually easy to dismiss, the physician's myths root deeper in the conception of primary care physicians. Adding to the patient's concern about hair loss may be prior frustrating experiences with physicians, who tend to trivialise complaints of hair loss or even to dismiss them completely. This attitude on the part of physicians may result from lack of knowledge or from misconceptions regarding hair loss in women. Among the most prevalent among physician's myths standing in the way to successful management of hair loss are the following:

The majority of women complaining of hair loss are suffering of imaginary hair loss. Fact is that with the appropriate methods for early diagnosis, a diagnosis of AGA can usually be made, and the appropriate therapy can be initiated. Only a minority of women complaining of hair loss suffer of imaginary hair loss. In these cases, we are dealing with hypochondrial disease and body dysmorphic disorder. More frequently we are dealing with adjustment disorders to a true hair loss disorder, and the best way to alleviate the emotional distress caused by a hair disorder is to eliminate the hair disease that is causing the problem.

Losing 100 strands of hair per day is normal. Fact is that the number of hair loss per day is dependent on the amount of hairs on the scalp and on a number of internal and external factors. The hair follicle is subject to constant turnover in the course of perpetual cycles through phases of proliferation, involution, and resting, with regeneration in the successive hair cycle. Cyclic hair growth activity occurs in a random mosaic pattern, so that on average, the amount of new scalp hair formation matches the amount that is shed, thereby maintaining a consistent covering. Each follicle possesses its own individual control mechanism over the evolution and triggering of the successive phases of the hair growing cycle, though systemic factors, such as the hormonal system, cytokines, and growth factors, as well as external factors linked to the environment, toxins, deficiencies of nutrients, vitamins, and energy, have influence. In AGA, hair loss results from a progressive shortening of the proliferation phase of the hair cycle without synchronisation, so that significant hair loss can result with a

relatively small number of hairs shed per day, while seasonal effects may result in partial synchronisation phenomena with temporary increase of hair shedding.

The most frequent disorder associated with hair loss in women is iron deficiency. Fact is that several studies have evaluated the relationship between decreased serum ferritin levels and hair loss and have resulted in opposing conclusions. A critical appraisal of available data points to the fact that iron deficiency is probably overestimated as a single cause of hair loss in women.

The first-line therapy for female AGA is anti-androgens. Since AGA is recognised as an androgen-induced loss of hair, at least in men, anti-androgens have been the first-line of treatment for AGA in women. Fact is that the observation that female AGA may develop in the absence of circulating androgens and that female AGA does not respond to anti-androgen treatment, unless there is a hyperandrogenic state, points to the fact that other, androgen-independent pathomechanisms underlie the condition in women and that therefore anti-androgen treatment has so far been overestimated.

Hair loss in men cannot be stopped or helped. In the past, this was true, and the history of treatments for hair loss is one of charlatanry and quackery. In a survey of 508 men, when topical minoxidil and oral finasteride were available for the treatment of androgenetic alopecia, we found that 27 % of balding men denied the use of hair growth-promoting agents because they did not believe in their efficacy (Trüeb et al. 2001). Fact is that today, with the advances in science and technology, and our understanding of hair growth and disorders, effective treatments have become available for the prevention of hair loss and recovery of hair. Hair loss medications and hair transplantation are effective means to help hair loss sufferers restore hair or improve the appearance of hair.

Evidence-Based Medicine

Evidence-based medicine (EBM) aims for the ideal that healthcare professionals should make conscientious, explicit, and judicious use of the best available evidence gained from the scientific method to clinical decision-making.

It seeks to assess the strength of the evidence of risks and benefits of diagnostic tests and treatments, using techniques from science, engineering, and statistics, such as the systematic review of medical literature, meta-analysis, risk-benefit analysis, and randomised controlled trials.

As *EBM guidelines* on hair disorders are rare, a European consensus group was recently constituted to develop guidelines for both diagnostic evaluation and treatment of AGA. The conclusions resulted in guidelines for diagnostic evaluation in androgenetic alopecia in men, women, and adolescents and in guidelines for the treatment of androgenetic alopecia in women and in men, both recently published in the European dermatologic literature (Blume-Peytavi et al. 2011; Blumeyer et al. 2011).

Clinical Presentation

AGA is diagnosed by history taking and a clinical hair and scalp inspection, including dermoscopy, where a patterned, non-scarring, progressive alopecia with diversity of hair shaft diameters is observed.

History taking is of paramount importance in assessing hair loss. By careful and systematic questioning, it is possible to assess the factors pertinent to differential diagnosis and particular lines of further investigation. It is advisable never to accept anything for true, neither from the patient nor from the referring physician, which is not clearly recognisable as such, that is to say, carefully to avoid precipitancy and prejudice and to comprise nothing more in one's judgement than what is presented to the mind so clearly and distinctly as to exclude all grounds of doubt.

A detailed *family history* relating to hair loss is pertinent to the diagnosis of genetic disorders.

The *personal history* encompasses on date of onset of the hair loss problem; periodicity of hair loss; rate of progression; previous investigations and treatments; present and past health status; medications, including hormonal treatments (oral

contraceptive, replacement therapy); dietary behaviour; associated symptoms relating to the condition of the scalp; and hair care habits.

The *medical history* should focus on most frequent causes of hair loss, especially in women: iron deficiency, thyroid disorder, and lupus erythematosus. Risk factors for iron deficiency are heavy menstrual bleeding (>80 ml per month), use of an IUD, history of iron deficiency anaemia, and insufficient dietary iron intake. Finally, a history should be taken of stressful life events, UV exposure, cigarette smoking, alcohol abuse and malnutrition, drug abuse, and sexual risk behaviour (syphilis, HIV infection).

The skin and hair are gratifying for diagnosis. One has but to look, and recognise, since everything to be named is in full view. Looking would seem to be the simplest of diagnostic skills, and yet its simplicity lures one into neglect. To reach the level of artistry, looking must be a skilful active undertaking. The skill comes in making sense out of what is seen, and it comes in the quest for the underlying cause, once the disorder has been named. The first look is best made without prejudices of former diagnoses and without bias of laboratory data. In many instances, a specific diagnosis is made in a fraction of a second if it is a simple matter of recognition. The informed look is the one most practised by dermatologists; it comes from knowledge, experience, and visual memory. Where the diagnosis does not come from a glance, the diagnostic tests come in, i.e. the dermatological techniques of examination and the laboratory evaluation.

By definition, alopecia is the acquired condition of recognisable hair loss. When examining the scalp, the distribution of hair loss (pattern recognition), the presence and characteristics of associated skin and nail lesions, and the presence of inflammation and scarring should be noted. Part widths should be measured and all abnormalities noted.

The *pull test* is an easy test to perform and to repeat, with the aim to roughly judge active hair shedding. Approximately 50 hairs are grasped by the thumb, index, and middle fingers. While the hairs are tugged away, the test is positive when >10 % of the grasped hair can be pulled out. Naturally, the test is influenced by the condition of hair with respect to shampooing, so that this must be taken into consideration. The test is performed in different scalp areas. In patients with active AGA, the pull test is positive only in the affected area, while a diffusely positive pull test requires further diagnostic evaluation to exclude telogen effluvium or diffuse alopecia areata.

Dermoscopy of the scalp or trichoscopy is a noninvasive diagnostic tool that permits recognition of morphologic structures not visible to the naked eye. Dermatologists involved in the management of hair and scalp disorders have discovered dermoscopy to be useful in their daily clinical practice. Ultimately, examination of the scalp by dermoscopy can reassure patients that they have received a thorough scalp examination, since patients with hair loss are very distressed and often feel that they are not properly examined. Using trichoscopy, signature patterns are seen in a range of scalp and hair conditions.

Trichoscopic features of AGA are diversity of hair shaft diameter, peripilar sign, and empty follicles. Originally Tosti et al. (2007) suggested that diversity of hair shaft diameter >20 % is diagnostic of female AGA. We found that trichoscopy is a valuable and superior method to the trichogram for diagnosis of female AGA, especially in early cases, with the highest yield irrespective of the suggested cut-off of 20 % diversity of hair shaft (Galliker et al. 2012). More recently, Rakowska et al. (2009) proposed more sophisticated diagnostic criteria for diagnosis of pattern hair loss (PHL) in women based on trichoscopic imaging. Major criteria are (1) ratio of more than four empty follicles in four images (at 70-fold magnification) in the frontal area, (2) lower average thickness in the frontal area compared to the occiput, and (3) more than 10 % of thin hairs (<0.03 mm in diameter) in the frontal area. Minor criteria were (1) increased frontal to occipital ratio of single-hair pilosebaceous units, (2) vellus hairs, and (3) peripilar signs. Fulfilment of two major criteria or of one major and two minor criteria allows diagnosis of PHL in women with a 98 % specificity.

The *trichogram* is a semi-invasive technique for hair analysis on the basis of the hair growth

cycle. It involves the forceful plucking of 50–100 hairs with a forceps from specific sites of the scalp. A major objective of trichogram measurements is to evaluate and count the status of individual hair roots and to establish the ratio of anagen to telogen roots. It is particularly useful to exclude diffuse telogen effluvium or in individual cases where loose anagen hair or dystrophic anagen effluvium is suspected.

In requesting *laboratory tests*, clinical suspicion is the determinant, and knowledge of clinical dermatology is prerequisite for combining medical sense with economic sense. The greater the number of different tests done, the greater the risk of getting false-positive or irrelevant leads. Therefore, laboratory testing must be kept sharply focused.

General Principles of Treatment

The aim of treatment is to increase hair coverage of the scalp and to retard progression of hair thinning. With respect to the treatment of male and female AGA, the European consensus group (Blumeyer et al. 2011) conducted a systematic literature review in Medline, Embase, and Cochrane databases until August 2008. One thousand three hundred seventy publications were found, 51 added by hand search. Eighty-five publications fulfilled the following inclusion criteria for the guideline: prospective study with a number of patients ≥20 (no minimal patient number required in twin studies), age ≥12 years, and with confirmed diagnosis of AGA (diagnosis either clinically or by further diagnostic evaluations, e.g. trichogram, TrichoScan, biopsy). The objective outcome measure of efficacy described for drug therapy was mean change from baseline hair count in target area or measurement of hair growth/loss in target area by global photography.

The guideline revealed excellent evidence levels for the therapeutic use of topical minoxidil (2 and 5 %) in men and in women and for 1 mg oral finasteride in men (Figs. 5.1a, b and 5.2a, b), low evidence levels for hormonal treatments, and insufficient or lacking evidence to the broad panel of miscellaneous treatments available claiming to be efficient too.

Minoxidil promotes hair growth through increasing the duration of anagen. It causes hair follicles at rest to grow and enlarges suboptimal follicles. While minoxidil was developed for the treatment of hypertension, and this feature of the drug's action is best understood, its mechanism of action on hair growth is poorly understood. Minoxidil is a potassium-channel opener and vasodilatator and has been reported to stimulate the production of VEGF in cultured dermal papilla cells. There is evidence that this effect is mediated by adenosine and sulfonylurea receptors, which are well-known target receptors for adenosine-triphosphate-sensitive potassium-channel openers. Topical solutions of 2 and 5 % minoxidil are available for the treatment of AGA in men and women.

Finasteride is a competitive inhibitor of type 2 5α-reductase and inhibits the conversion of testosterone to dihydrotestosterone (DHT). The rationale for the use of finasteride to treat AGA in men is based on the absence of AGA in men with congenital deficiency of type 2 5α-reductase and the presence of increased 5α-reductase activity and DHT levels in balding scalp.

While oral finasteride has unanimously been shown to be effective in the treatment of hair loss in men, its efficacy in women remains controversial. Due to teratogenicity for the male fetus, oral finasteride is contraindicated for use in premenopausal women. Differences in response of women to oral finasteride have led to the suggestion that not all types of female AGA have the same pathophysiology, i.e. a distinction should be made between alopecia with early (premenopausal) or late (postmenopausal) onset and with or without hyperandrogenemia. Up to date no predictive factor for response to finasteride treatment has been identified in women with female AGA.

Oestrogens and anti-androgens are traditionally used in women with AGA, although no controlled studies have been done with systemic oestrogens, and topical 17α-estradiol (alfatradiol) and anti-androgens have proven to be ineffective. Nevertheless, when a combination of oestrogen and a progestin is prescribed for oral contraception or hormonal replacement therapy in women with AGA, care should be taken to select a

Fig. 5.1 Successful treatment of male androgenetic alopecia in a 45-year-old male with 1 mg oral finasteride and 5 % topical minoxidil lotion twice daily, (**a**) before and (**b**) after 18 months of treatment

progestin with no androgenic activity, e.g. norethisterone, levonorgestrel, and tibolone. Women with this condition should also avoid androgens and their precursors as well, such as dehydroepiandrosterone (DHEA), since these may exacerbate hair loss.

As a general rule, topical minoxidil 2 % solution twice daily or topical minoxidil 5 % solution 1 ml once daily represents the first-line treatment for female AGA, irrespective of age. Increase of hair growth is evident within 8 weeks of treatment and generally peaks by 12–16 weeks. Response to treatment should be assessed at 6 months. If successful, treatment needs to be continued to maintain efficacy. In case of treatment failure, topical minoxidil 5 % solution twice daily may be tried, and in postmenopausal women without a family or personal history of breast cancer, 5 mg oral finasteride once daily may be considered.

One milligram oral finasteride once daily is the first-line treatment for male AGA in men between 18 and 40 years of age with mild to moderate AGA while topical 2 % or 5 % minoxidil solution twice daily (in children under 12 years once daily) is recommended for the treatment of premature alopecia and the treatment of AGA in men over 40 years who have retained some hair. The younger subjects experience better efficacy of topical minoxidil than the older subjects, although clear treatment effects are noted also in the older age group. Males show an inverse relationship between the effect of topical minoxidil and duration of balding: males with duration of balding <5 years show a significantly better effect than those with duration of balding >21 years. The diameter of vertex balding in men shows an inverse relationship with efficacy of topical minoxidil: males with <5 cm diameter vertex balding area show a better effect of

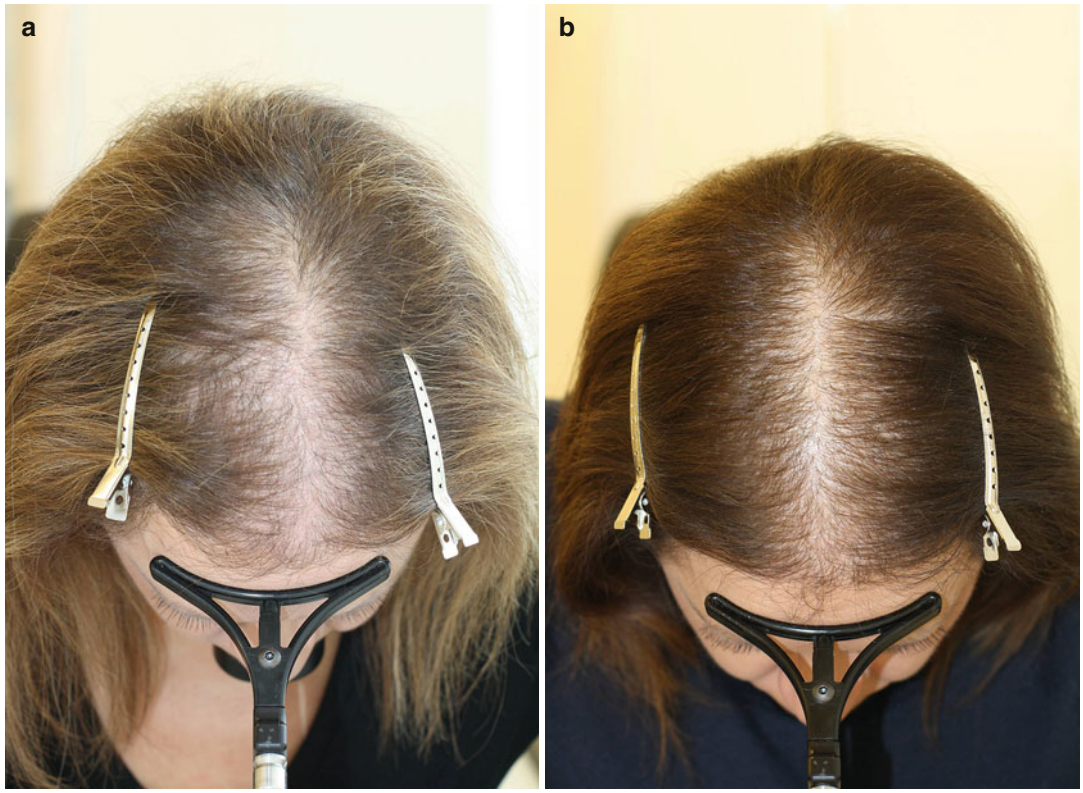

Fig. 5.2 Successful treatment of female androgenetic alopecia in a 51-year-old female with 5 % topical minoxidil lotion twice daily and oral supplementation therapy with L-cystine, medicinal yeast, and pantothenic acid, (**a**) before and (**b**) after 6 months of treatment

treatment than subjects with diameters >15 cm. Finally, duration of hair loss less than 1 year compared with more than 10 years at onset of treatment results in a significantly more effective treatment with topical minoxidil with respect to stabilisation of alopecia and new hair growth. Oral finasteride retains its efficacy in men over 40 years of age, though to a lesser degree and with a higher frequency of sexual adverse effects compared to men between 18 and 40 years. Again, response to treatment for both topical minoxidil and oral finasteride should be assessed at 6 months, although in some men response to finasteride may not become evident until 12 months. If successful, treatment needs to be continued to maintain efficacy, though finasteride may be tapered in the ageing male, due to decrease of efficacy and increase of sexual adverse events. For greater efficacy, the combination of topical 5 % minoxidil solution 1 ml twice daily and oral finasteride 1 mg daily may be considered.

Ultimately, surgery, specifically follicular unit transplantation (FUT), can be considered in male and female patients with unsatisfactory results of 1 year pharmacological treatment and sufficient occipital donor hair. In males, the combination of FUT with 1 mg oral finasteride daily is recommended to achieve more sustained results.

Beyond Evidence-Based Medicine

Although EBM is becoming regarded as the gold standard for clinical practice, there are a number of limitations of its use. EBM guidelines do not remove the problem of extrapolation to different populations or longer timeframes. Even if several top-quality studies are available, questions

always remain about how far, and to which populations, their results may be generalised. Certain groups have been historically under-researched, such as racial minorities and people with many comorbid diseases, and thus the literature is sparse in areas that do not allow for generalising. EBM applies to groups of people, but this does not preclude clinicians from using their personal experience in deciding how to treat each patient. Ex cathedra statements by the medical expert are considered to be the least valid form of evidence. Nevertheless, knowledge gained from clinical research does not directly answer the primary clinical question of what is best for the patient at hand and suggests that EBM should not discount the value of clinical experience. Good medical practice means integrating individual clinical expertise with the best available external clinical evidence from EBM.

Finally, one must remain open-minded for the possibility of a multitude of cause relationships underlying hair loss, including seasonality of hair growth and shedding, hormonal factors, nutrition, and medications; especially in the elderly the problems of comorbidities and multimorbidity must be taken into account.

Ultimately, combination treatments with topical minoxidil, oral finasteride, nutritional supplements, scalp surgery, and appropriate hair care may act synergistic to enhance hair growth (Fig. 5.3a, b). The scientific rationale for such an approach is given, but there is a need for clinical studies to establish increase in efficacy of combination regimes and adjuvant treatments.

At length, the influence of the prescribing physician should be kept in mind, since inspiring confidence versus scepticism and fear clearly impacts the outcome of treatment. Treatment

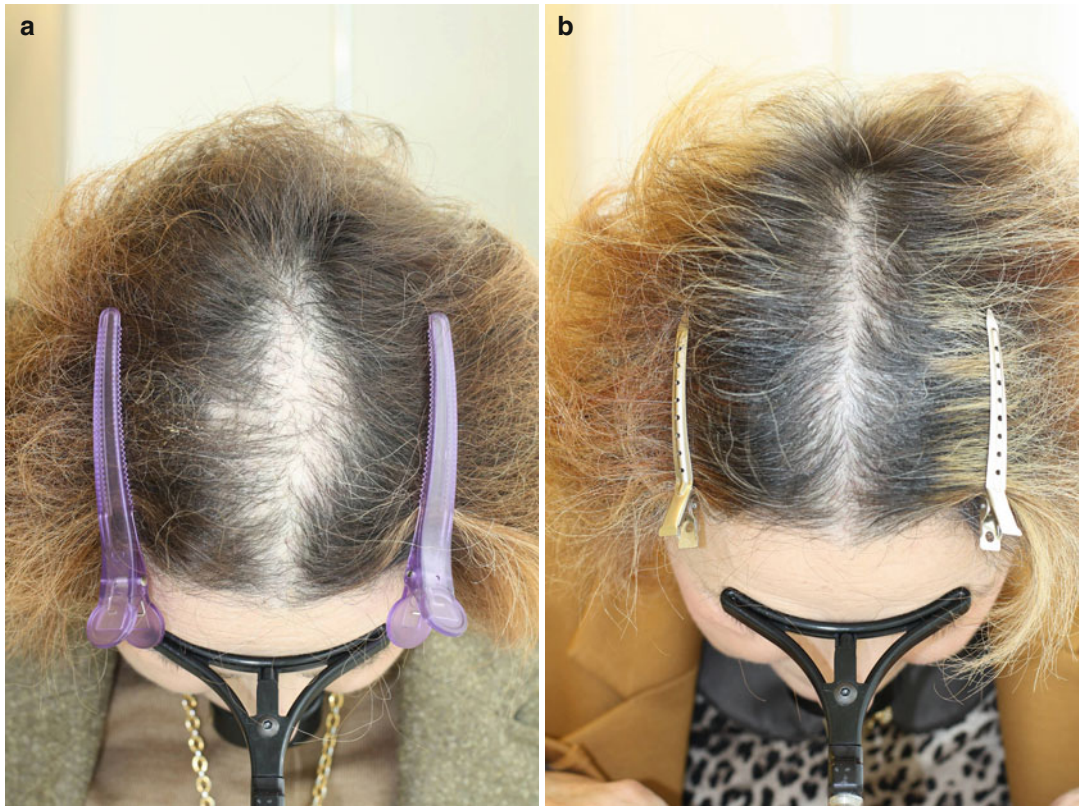

Fig. 5.3 Successful treatment of cicatricial-pattern hair loss in a 64-year-old female with 0.5 mg oral dutasteride, topical 5 % minoxidil, and 0.2 % triamcinolone acetonide, (**a**) before and (**b**) 3 months after autologous hair transplantation

success relies on patient compliance that, on its part, relies on comprehension of treatment benefit, confidence, and motivation. The overall goal is to gain short-term compliance as a prerequisite to long-term adherence to treatment.

A positive physician-patient relationship and regular follow-up visits are the most important factors in determining the degree of patient compliance. Only treatments that are effective in circumstances they are required should be recommended. Dosage regimen should be simplified by selecting different treatment or using a preparation that needs fewer doses during the day, e.g. 5 % topical minoxidil once daily instead of 2 % topical minoxidil twice daily for the treatment of female AGA. Treatments with lower levels of side effects or fewer concerns for long-term risks should be selected; possible side effects should be discussed with the patient, together with advice on minimising or coping with side effects. Ultimately, regular follow-up for reassurance on drug safety and treatment benefits is important, typically at 3, 6, and 12 months and yearly thereafter.

Global photographic assessment was successfully established as a standard method for objectively monitoring hair growth in the course of the minoxidil and finasteride trials. Since its introduction the technique has proven to be essential for follow-up of hair loss patients undergoing long-term treatment in daily clinical practice as well. For clinical study purposes the method is used in tandem with the phototrichogram technique. The former reflects the overall clinical changes in the patient over time in a standardised manner, while the latter yields a quantitative measure of the hair number (*n*), hair density (*n*/cm^2), ratio of anagen to telogen phase hairs (%), hair thickness (μm), and linear hair growth rate (mm/day) within a defined area of the scalp. For daily clinical practice, a combination of global photography with trichoscopic examination and photography is recommended.

Patients should be aware of seasonal fluctuations in hair growth and shedding, at times complicating the assessment of pharmacological effects. Awareness of these fluctuations is prerequisite to providing the correct cause and prognosis to the patient, ensuring patient adherence.

In the recent past some issues have arisen concerning the long-term safety of oral finasteride for the treatment of male AGA, e.g. sexual dysfunction, fertility problems, prostate cancer, and depression. For the time being, probably the best way in dealing with them, apart from a detailed patient information and follow-up visits, is to refrain from prescribing finasteride to patients with a personal history of depression, sexual dysfunction, or fertility problems. When fertility is an issue, one may consider performing a sperm count before and during treatment. Finally, PSA levels should be performed in all men 45 years and above, before and after initiating therapy and thereafter on twice yearly basis. The level should drop by ca. 50 % upon initiation of therapy, and in case of an increase >0.4 ng/ml per year, the prostate should be evaluated.

Cicatricial-Pattern Hair Loss

The limited success rate of the treatment of AGA with the available hair growth-promoting agents means that further pathogenic pathways may be taken into account. On histologic examination of scalp biopsies, the miniaturisation of terminal hairs is frequently associated with perifollicular lymphocytic infiltration and eventually fibrosis. The significance of these findings has remained controversial. However, morphometric studies in patients with AGA treated with minoxidil showed that a lesser percentage of those with microinflammation had regrowth in response to treatment, in comparison to those patients without inflammation and fibrosis. Moreover, inflammatory scarring alopecias with a pattern distribution have recently been described, underlining the fact that a subset of patients seemingly suffering of AGA show true signs of follicular inflammation and fibrosis. Finally, in 2005 Olsen acknowledged the existence of clinically significant inflammatory phenomena and fibrosis in AGA and proposed the term “cicatricial-pattern hair loss”. More recently, Kossard (2010) suggested that this unusual alopecia may hold the key to understanding the complex relationship of

pattern alopecia, sex-related differences, and triggers for autoimmune follicular destruction.

Senescent Alopecia

Ageing of the hair is characterised by a reduction in the duration of hair growth and diameter of hair shafts and a prolongation of the interval separating the loss of a hair in telogen and the emergence of a replacement hair in anagen. These phenomena resemble those observed in the course of AGA, though microarray analyses have demonstrated different gene expression profiles in senescent and AGA, suggesting that they represent different entities. In AGA, genes required for anagen onset, hair shaft differentiation, and anagen maintenance are downregulated, while genes for catagen and telogen induction and maintenance are upregulated. In senescent alopecia, genes involved in mitochondrial function are downregulated, while oxidative stress and inflammatory response genes are upregulated. Nevertheless, dermal papilla cells derived from AGA grow slower in vitro than normal dermal papilla cells, and this loss of proliferative capacity is associated with expression of markers of oxidative stress and DNA damage suggesting that dermal papilla cells in AGA are particularly sensitive to environmental stress. In contrast to AGA expression of 5α-reductase and response to treatment with 5α-reductase, inhibitors are decreased in senescent alopecia. Both commonalities and differences between AGA and senescent alopecia have implication for therapy.

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Aphthous Stomatitis

6

George Laskaris

Definition and Epidemiology

Recurrent aphthous stomatitis (RAS) or recurrent aphthous ulcers (RAU) are painful oral ulcerations that characteristically recur at intervals ranging from days to months or even years. They represent the most common lesion of the oral mucosa with an overall prevalence, ranging from 15 to 30 %. Females are more commonly affected than males, and although they may begin at any age, they usually start during the second and third decades of life. Familial occurrence is common, and about 30–40 % of the patients with RAS have another affected family member.

Basic Concepts of Pathogenesis

Although RAS is one of the oldest oral diseases known from the time of Hippocrates (460–370 B.C.), its aetiology still remains unclear. Many predisposing factors have been incriminated such as genetics, trauma, food hypersensitivities, stress, infections [*Streptococcus sanguis and S. mitis*, *Helicobacter pylori*, *Herpes simplex virus-1* (*HSV-1*), *Varicella-zoster virus* (*VZV*), *Cytomegalovirus*], systemic diseases (Adamantiadis-Behçet's disease), gastrointestinal disorders (Crohn's disease, ulcerative colitis, coeliac disease), nutritional deficiencies, cyclic neutropenia, blood deficiencies, Sweet's syndrome, human immunodeficiency virus infection (HIV), hormonal changes, immunological disorders and others. Although these predisposing factors may play a role in the developments of RAS, the disease is idiopathic and its aetiology remains unknown. Accumulated data supports the concept that the pathophysiology is immunologically mediated and that the cell-mediated immune response is dysregulated. In addition, several reports show a negative association between RAS and smoking.

Clinical Presentation

The main clinical features of RAS are the recurrence of painful oral ulcerations at intervals ranging from days to weeks or even months. The prodromal stage is variable and is usually characterized by discomfort and occasionally erythema of 1–3 days duration. This stage is soon followed by a painful oral ulcer.

The lesions are usually confined to movable non-keratinized or poorly keratinized oral mucosa, e.g. the buccal mucosa, the labial mucosa, tongue, floor of the mouth, soft palate and uvula. Occasionally the attached gingiva and the hard palate may also be involved. The lesions

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_6, © Springer-Verlag Berlin Heidelberg 2015

usually begin in childhood or adolescence and have a slight predilection for females. Clinicians should keep in mind that RAS may be associated with the following systemic disorders:

- Adamantiadis-Behçet's disease
- Sweet's syndrome
- PFAPA syndrome
- MAGIC syndrome
- Crohn's disease
- Ulcerative colitis
- Coeliac disease
- HIV infection
- Malabsorption syndromes
- Haematinic deficiencies (vitamins B1, B2, B6, B12, folic acid, iron, zinc)
- Neutropenias

Based on clinical criteria, recurrent aphthae are classified into three forms: *minor*, *major* and *herpetiform ulcers*.

Minor RAS

This is the most common form of the disease. It is clinically characterized by a shallow oval and painful ulcer 2–6 mm in diameter (Fig. 6.1). The ulcer is covered by a yellow-white necrotic membrane and is surrounded by an erythematous halo. Ulcers may be single or multiple (Ball et al. 1997; Chavan et al. 2012; Haeyrinen-Immonen et al. 1994; Laskaris 1999, 2012); they persist for 6–10 days, heal with no evidence of scarring and recur usually at 1–5-month intervals.

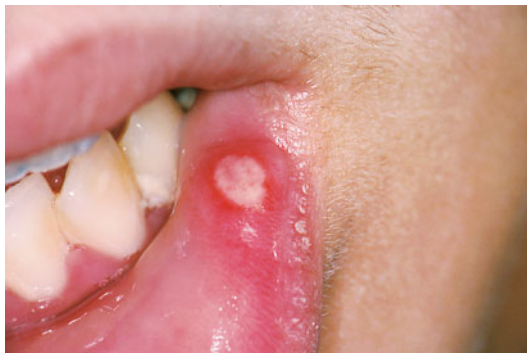


Fig. 6.1 Minor aphthous ulcer

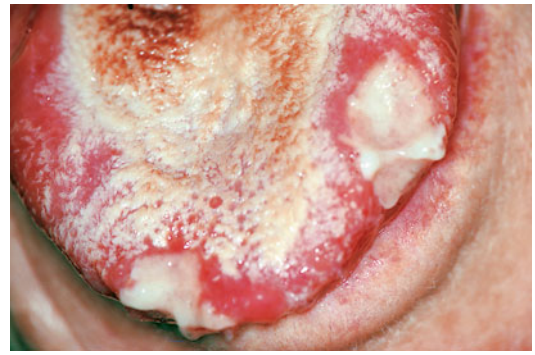


Fig. 6.2 Major aphthous ulcers

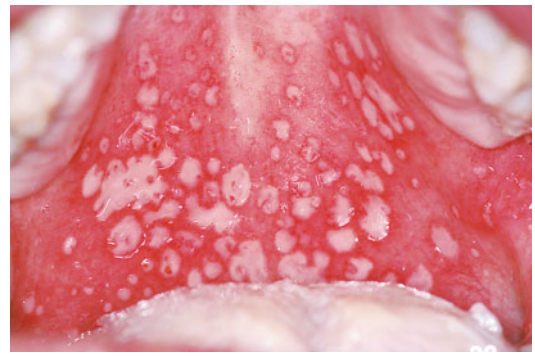


Fig. 6.3 Herpetiform ulcers

Major RAS

This is much less commonly encountered and represents the severe form of RAS. The ulcers are deep, extremely painful and 1–2 cm in diameter, and their number varies from one to three (Fig. 6.2). They last approximately 3–6 weeks and occasionally leave a scar on healing and often recur at 1–3-month intervals.

Herpetiform Ulcers

These belong to the least common variety of RAS. The lesions present as multiple (10–100 or more), shallow ulcers, 1–3 mm in diameter, and characteristically tend to occur in clusters (Fig. 6.3). The ulcers persist for 1–2 weeks, often recur over a period of 1–3 years and are more commonly seen in females. The onset is at an older age than the other forms of RAS.

Table 6.1 The differential diagnosis of aphthous stomatitis

Traumatic ulcer	History, clinical features, histopathological examination
Primary and secondary herpetic stomatitis	History, clinical features, serum viral antibody tests, viral cultures
Hand, foot and mouth disease	Clinical evaluation, viral cultures
Herpangina	Clinical evaluation, viral cultures
Erythema multiforme	Clinical features, histopathological examination
Pemphigus	Clinical features, histopathological examination, direct and indirect immunofluorescence
Mucous membrane pemphigoid	Clinical features, histopathological examination, direct and indirect immunofluorescence tests
Primary and secondary syphilis	Clinical evaluation, microbiology, serological tests
Adamantiadis-Behçet's disease	Clinical features, histopathological examination, HLA antigens
Crohn's disease	Clinical evaluation, histopathological examination
Ulcerative colitis	Clinical evaluation, histopathological examination
Coeliac disease	Clinical evaluation, histopathological and immunological examination
Cyclic neutropenia	Clinical evaluation, repeated determination of neutrophils in the peripheral blood

Diagnosis

The diagnosis of all three forms of aphthous stomatitis is based exclusively on clinical criteria, as there is no specific diagnostic test, unless there is an underlying systemic disease.

Differential Diagnosis

See Table 6.1.

General Principles of Treatment

- It is important in managing RAS to rule out aphthous-like ulcers associated with systemic diseases. The great majority of patients with RAS are healthy individuals without a history or signs of a systemic disease.
- Successful therapy for RAS requires a correct diagnosis and control of the contributing aetiological factors.
- The treatment of RAS depends on the frequency, the number and the size of the ulcers.
- A wide spectrum of therapeutic regimes or agents have been suggested, but the management of RAS is unsatisfactory, as there is no cure and all attempts are palliative.
- The goal of treatment should be (a) elimination of pain and discomfort, (b) shortening of the course, (c) extension of the time between recurrence and (d) avoidance of recurrence (see table 6.2).

Recommended Therapies

Control of Possible Contributing Aetiological Factors

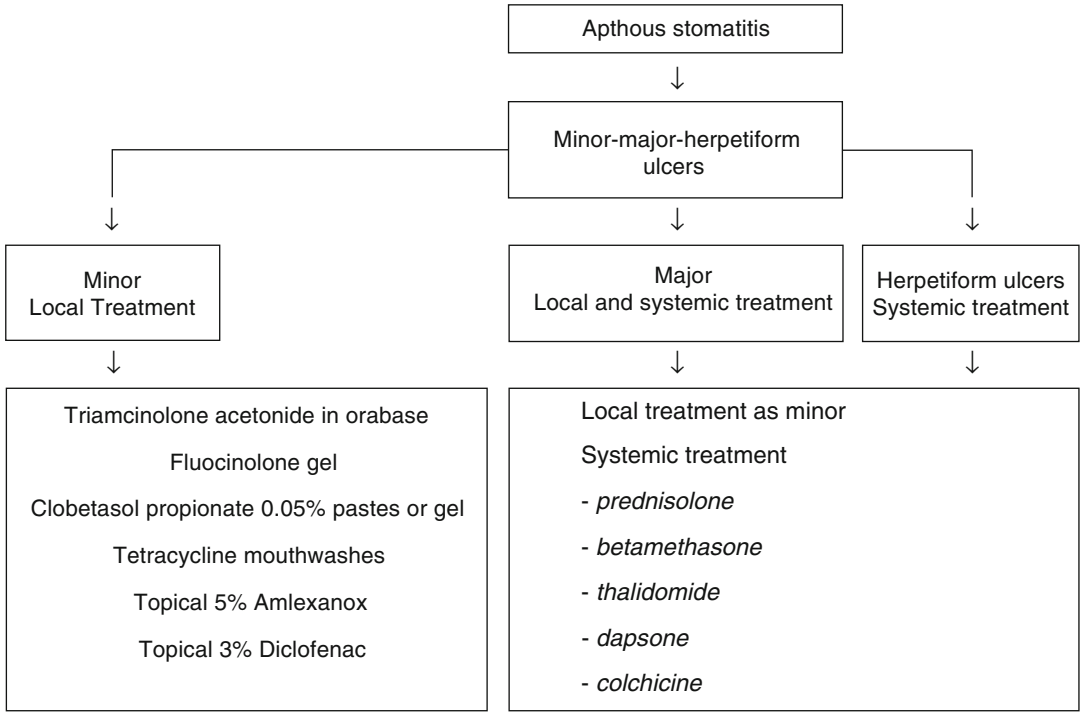
Patients should be encouraged to keep a food diary in an attempt to identify a potential precipitating link with the onset of aphthous ulcers. Patients should avoid minor trauma of the oral mucosa. Stress and female sex hormonal changes should also be controlled. A gluten-free diet may be useful in controlling lesions even in the absence of coeliac disease.

Topical Measures

Topical medications may reduce pain and shorten the course, but they do not prevent recurrence.

Topical anaesthetics such as 2 % viscous lidocaine, benzocaine and benzydamine hydrochloride may reduce pain only for a short time. Recently, 5 % amlexanox oral paste and 3 % diclofenac in 2.5 % hyaluronan have also been used to reduce pain. Topical tetracyclines have been used with partial success. A 250-mg capsule is dissolved in 30 mL of water. Then 5 mL of the solution is used to rinse the lesion four to six times a day. This is repeated for 3–5 days. Many other anti-inflammatory and antimicrobial agents (e.g. chlorhexidine) have also been used with unsatisfactory results. The best of the topical treatments is 0.1 % triamcinolone acetonide in an

Table 6.2 Proposal treatment of aphthous stomatitis



oral adhesive base (Orabase) or fluocinonide gel (Lidex gel) or clobetasol propionate gel 0.05 % (Temovate) applied to the ulcer three to four times a day for 4–6 days. Intralesional injection of triamcinolone acetonide retard or betamethasone dipropionate and sodium phosphate retard may be successfully used only in major aphthous ulcers.

Systemic Measures

Systemic corticosteroids (prednisolone, betamethasone) in an average dose of 20–30 mg or 2–3 mg, respectively, for 4–8 days is very helpful for major ulcers or herpetiform ulcers. In cases of repeated episodes and when new ulcers occur before the previous ones have healed, systemic medications may prove useful in preventing new lesions.

In my experience 20 mg prednisolone or 2 mg betamethasone for 10–15 days and then an injection of betamethasone dipropionate and sodium phosphate retard every 2 weeks for a period of 2 months may significantly increase the time intervals between recurrence. Long-term systemic corticosteroid is contraindicated because of its side effects.

In severe cases with a high recurrence rate and in HIV-infected patients, thalidomide 100–300 mg/day for 2–3 months may result in complete remission of the ulcers for a long time. However, teratogenesis and polyneuropathy preclude the routine use of thalidomide.

Clinicians should know that safe prophylaxis of RAS recurrence for a long time is not available. Conclusively, until RAS aetiology is discovered, treatment will remain partially effective.

Alternative and Experimental Treatments

In severe cases, many other systemic medications have been used with ambiguous results. These include the following:

- Dapsone 25–50 mg/day for several weeks
- Levamisole hydrochloride
- Azathioprine
- Colchicine
- Interferon-α
- Cyclosporine
- Pentoxifylline
- Clofazimine
- Acyclovir
- Etretinate

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Atopic Dermatitis

7

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Abbreviations

AD	Atopic dermatitis
ASIT	Allergen-specific immunotherapy
BB-UVB	Broadband ultraviolet B
CsA	Cyclosporine A
EASI	Eczema area and severity index
EH	Eczema herpeticum
EM	Eczema molluscatum
FTU	Fingertip unit
MMF	Mycophenolate mofetil
MTX	Methotrexate
nbUVB	Narrowband UVB
SCORAD	Scoring of atopic dermatitis
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
UV	Ultraviolet irradiation

Key Points

- Atopic dermatitis (AD) is an inflammatory, pruritic, chronic, or chronic relapsing skin disease.
- The hallmarks of atopic dermatitis are a chronic, itching, and relapsing skin inflammation, a disturbance of epidermal-barrier function that culminates in dry skin, and IgE-mediated sensitization to food and environmental allergens.
- Because the skin-barrier dysfunction, dry skin, and chronic inflammation are features of AD, short-term and long-term management plans have to be carried out.
- The long-term management should emphasize prevention, intensified skin care, the control of chronic inflammation, and reduction of bacterial colonization.
- The basic therapy is represented by basic rules the patient has to follow in order to counteract every day the disturbed barrier function.
- The patient has to be carefully educated to:
  - Cleansing and bathing
  - Application of emollients
  - Avoidance of irritants and identification and addressing of specific trigger factors
  - Antimicrobial treatment

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_7,

- The new *proactive* approaches (low weekly dose/application of topical corticosteroids/topical calcineurin inhibitors (TCS/TCI) for a long period) aim to control the residuals of the disease and to prevent new flares. These approaches have been shown to be safe and effective, to reduce the use of the pharmacological treatment, and to improve the quality of life of patients.
- Many patients achieve very good results from artificial UV (ultraviolet) radiation, mainly UVA1 and narrowband UVB as well as *heliotherapy and balneophototherapy*.
- *Cyclosporine A* is an immunosuppressant drug licensed in many European countries for treatment of AD. Despite its well-proved efficacy, its side effects limit its use, especially in long-term treatment.
- *Systemic steroids* are commonly used, but they present a largely unfavorable risk/benefit ratio for the treatment of this disease.
- Pruritus in AD has a multifactorial and complex etiopathogenesis. Despite that antihistamines have been used for decades, in attempt to relieve pruritus, surprisingly there are no conclusive data concerning the real efficacy of oral antihistamines in the treatment of pruritus in AD.

Definition and Epidemiology

Atopic dermatitis (AD), also called atopic eczema, neurodermitis (in German-speaking countries), or endogenous eczema, is an inflammatory, pruritic, chronic, or chronic relapsing skin disease. It is one of the most common skin diseases affecting up to 30 % of children and 1–3 % of adults in Europe. The prevalence of AD has doubled or tripled in industrialized countries during the past decennia, and its incidence is still increasing.

This disorder can represent the first step in the development of other atopic diseases including allergic oculo-rhinitis, asthma, and other allergic diseases.

The lower prevalence of AD in rural as compared with urban areas suggests a link to the "hygiene hypothesis," which supposes that the absence of exposure to infectious agents at early age increases the susceptibility to allergic diseases.

The hallmarks of atopic dermatitis are a chronic, itching, and relapsing skin inflammation, a disturbance of epidermal-barrier function that culminates in dry skin, and IgE-mediated sensitization to environmental and food allergens.

It is clinically characterized by a heterogeneous spectrum of clinical manifestations, varying with age. Clinical and laboratory criteria have been introduced for the definition. The most commonly used are the Hanifin and Rajka criteria.

Basic Concepts of Pathogenesis

Atopic dermatitis is a very complex genetic disease that is the result of gene–gene and gene–environment interactions. Research in the last decades has led to change the view in genomic and immunologic mechanisms that drive cutaneous inflammation. They have highlighted the critical role of the epidermal-barrier function and the immune system.

The genetic influence is important as shown by the higher concordance rate for AD among monozygotic twins (about 80 %) than dizygotic twins (about 20 %).

Characteristic features of pathophysiology have to be considered in a personalized or stratified approach to a patient suffering from AD. They are the following:

- Th2 immune response in the initiation phase with consequent increased IgE production. It precedes a chronic phase in which Th0 cells (cells that share some activities of both Th1 and Th2 cells) and Th1 cells are predominant.
- Abnormal skin-barrier function that causes "dry" skin. It is the result of epidermal-barrier components (filaggrin mutation, protease inhibitor deficiency, etc.) and/or abnormal lipid metabolism.

- Microbial colonization with pathogenic organisms, such as *Staphylococcus aureus* and *Malassezia furfur*.
- Strong psychosomatic factors that influence the autonomic nervous system and an increased production of inflammatory mediators.
- Pruritus that induces scratching that, as a vicious circle, increases pruritus.

A new picture of the pathogenesis of AD has emerged recently, and it is possible to highlight three phases (Fig. 7.1).

The first phase, the *nonatopic form* of AD (when sensitization is not occurred yet) is the result of genetically determined epidermal-barrier dysfunction and the effect of environmental factors.

Subsequently, many patients (60–80 %) become sensitized as a consequence of the interaction between the genetic predisposition for IgE-mediated sensitization, the allergen exposition, and *Staphylococcus aureus* enterotoxin products (*atopic form of AD*).

In a last phase, which can occur also in early life, the release of structural proteins due to tissue damage by scratching and molecular mimicry with *Staphylococcus aureus* proteins triggers an IgE response to self-proteins (*autoreactivity*). The presence of auto-IgE has been shown to be associated to a worse prognosis (higher severity and higher risk of becoming chronic).

Clinical Presentation

Atopic dermatitis is an itching and inflammatory disorder that, starting often in early age, can present a chronic or chronic relapsing course.

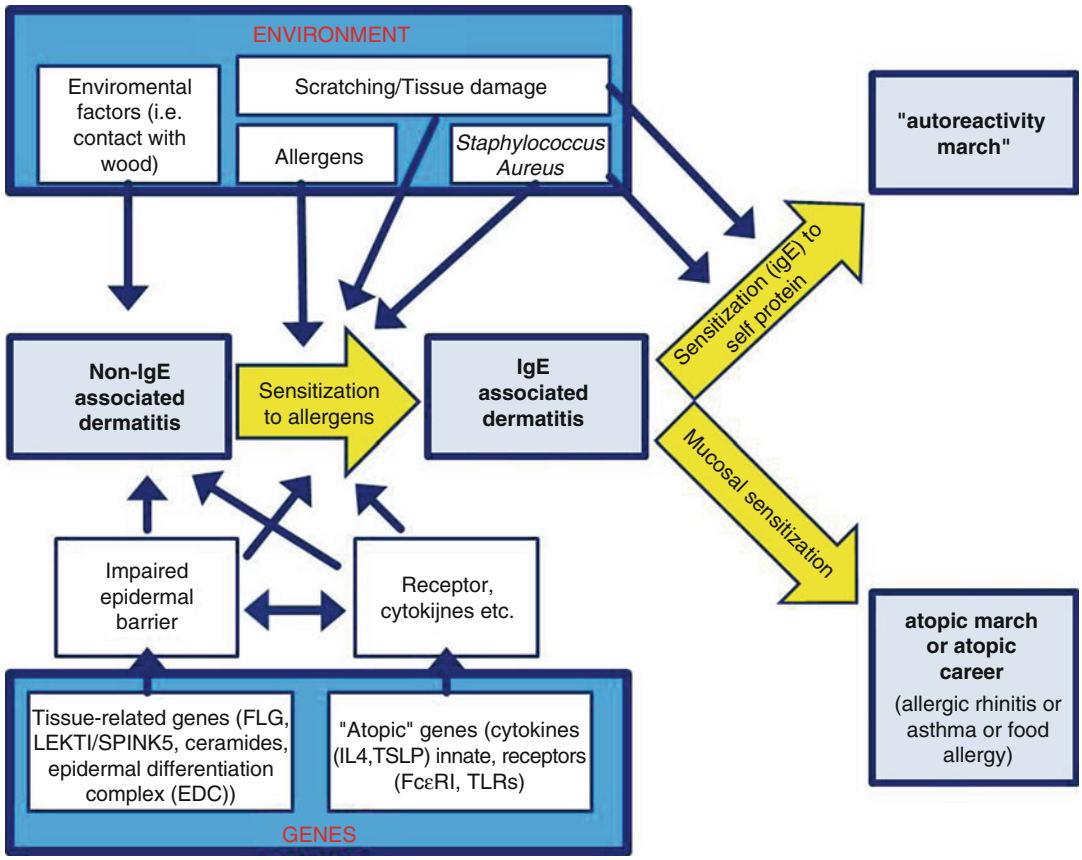


Fig. 7.1 Pathogenesis course of AD (From Bieber (2008, 2011))

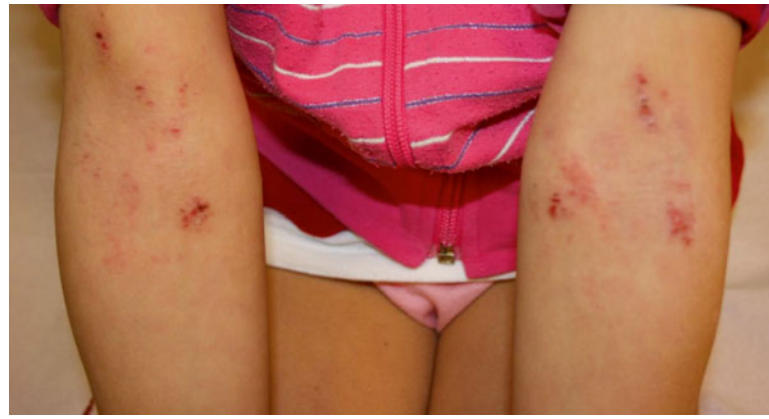


Fig. 7.2 Atopic dermatitis involving antecubital flexures

AD may be divided in four phases: infantile, childhood, adolescent/adult, and senile phases.

The infant phase usually starts during the third month, and it is characterized by red scaling areas on the cheek and chin, sparing the perioral and paranasal regions. Moreover, the eczema lesions can affect the arms, legs, and trunk. Scratching, which frequently starts a few weeks later, causes crusted erosions. The nappy area is usually spared.

Exudative lesions typical of the infant phase are not common in the childhood phase.

In the latter, lesions involve flexures, the nape, and the dorsal aspects of the limbs, and they are characterized by lichenification and depigmentation (Fig. 7.2).

AD, in adolescence and adulthood, is characterized by lichenified eczematous plaques affecting flexures, hand and/or foot, face (typical around the eyes), and neck (Fig. 7.3).

Lastly, an AD may occur in the elderly. Manifestations similar to adult AD, such as eczematous dermatitis involving the face and neck, trunk, and extensor and flexure sites of extremities, and atypical ones, as diffuse eczema, xerosis, and nummular eczema, have been described.

In each stage, the presence of pruritus all day long causes sleep loss and substantially impairs the patient's quality of life.

Despite that part of children have a spontaneous remission before adolescence, in a lot of cases, the dermatitis becomes a lifelong chronic disease and persists up to adulthood and elderly, often with intermittent periods of remission.

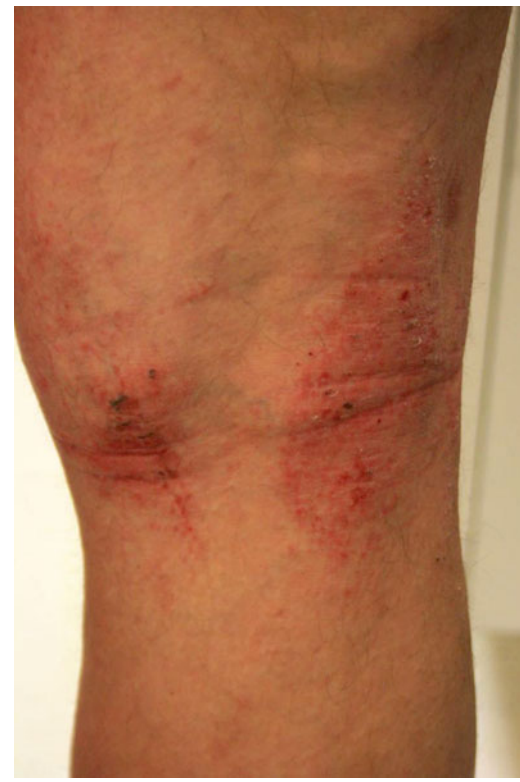


Fig. 7.3 Atopic dermatitis in adulthood involving popliteal flexures

According to the classification of Wuthrich, it is possible to distinguish five subgroups based on the age of onset: previous to 2 years (the so-called early-onset AD) (60 % of cases), between 2 and 6 years, between 6 and 14 years, between 14 and 20 years, and later than 20 years (the so-called late onset).

The early onset is characterized by an increased risk of development of high levels of total and specific IgE (also known as *atopic march* or *atopic career*). The presence of high level of IgE is connected to the risk for AD of becoming chronic.

On the basis of the presence of IgE, one classification distinguishes an IgE-associated form of AD (called "extrinsic" AD) from a non-IgE-associated form (called "nonatopic" or "intrinsic" or "atopiform" AD). This division might imply that extrinsic and intrinsic forms are two different diseases. As seen previously, the absence of IgE-mediated sensitization may be only a transient factor, and there is a need to reconcile these divergent hypotheses and to better describe the two "forms" and the different courses. In fact, a few patients with "intrinsic" AD will never produce high level of IgE, and they will not develop the atopic march. In these patients, allergen avoidance does not make sense. On the other hand, it is important to recognize which patients become sensitized (extrinsic AD) because they will benefit from allergen avoidance.

Moreover, as reported in a recent paper by Garmhausen et al. (2013), the dermatitis is often chronic, and it is possible to individualize five most common groups according to the onset and course of AD. These five groups, which cover the 85 % of the clinical course of AD, differentiate each other for the onset (one group for each of the five Wuthrich's groups) and for some clinical characteristics (i.e., the development of IgE is higher in those with early onset). It is worthy to know that in these five groups, the disease persists up to the adulthood with a chronic course.

Several criteria have been established in the diagnoses of AD. Since there are no laboratory tests available to confirm the diagnosis, this is made clinically. For the heterogeneous clinical presentations and courses, it becomes very important to individualize some candidate biomarkers, characterized by the potential use for screening patients, to prevent and to recognize the disease, to perform the prognosis, and to better manage the disease.

The Hanifin and Rajka criteria published in 1980 represent an important tool in performing the diagnosis (Table 7.1). To fulfill the criteria, the patient must have three or more of the major and three or more of the minor criteria.

Rarely a biopsy can be necessary. The histologic features of acute eczematous patches are spongiosis pattern and a prominent perivascular infiltrate of lymphocytes, monocyte macrophages, and some eosinophils in the dermis. In subacute and chronic lichenified plaques, the spongiosis is milder, the epidermis is thickened, and its upper layer is hypertrophied.

The presence of atopy can be confirmed by serum testing (i.e., radioallergosorbent test or RAST) or by intracutaneous challenge, looking for allergen-specific IgE antibodies to:

- House dust mite
- Pollen (tree, grass, weed)
- Animal dander (cat, dog)
- Molds
- Food (apple, peanuts, etc.)

Table 7.1 Hanifin and Rajka criteria

Major criteria
Pruritus
Flexural lichenification
Chronically relapsing course
A personal or family history of atopy
Minor criteria
Xerosis
Ichthyosis
Immediate skin test reactivity
Elevated serum IgE
Early age of onset
Tendency for developing cutaneous infections
Tendency for developing nonspecific hand or foot dermatitis
Dennie–Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/erythema
Pityriasis alba
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
The influence of emotional factors
White dermographism/delayed blanch

Presently, the level of total IgE can allow us to help distinguish "intrinsic" AD from "extrinsic."

After establishing the diagnosis of AE, the severity of the disease has to be determined. The classical method is the "scoring of atopic dermatitis" (SCORAD) developed by the European Task Force on Atopic Dermatitis. The patient-oriented SCORAD (PO-SCORAD) is a new patient-assessment scale in atopic dermatitis validated in Europe that has demonstrated a good correlation with SCORAD.

AD with an objective SCORAD higher than 40 is generally regarded as "severe," whereas below 20 can be regarded as "mild."

Differential Diagnosis

Due to the heterogeneous manifestations, a lot of diseases have to be distinguished from AD at different ages. The main differential diagnoses are reported in Table 7.2.

General Principles of Treatment

As a result of the skin-barrier dysfunction, dry skin and chronic inflammation are features of AD, and short- and long-term management has to be carried out. The long-term management should emphasize prevention, intensified skin care, the control of chronic inflammation, and reduction of bacterial colonization.

Correct skin care programs and allergen avoidance strategies should be beneficial in infants and children before and after the diagnosis of IgE-mediated sensitization.

Early and proactive pharmacological intervention can control the skin inflammation, prevent new flares, and reduce the *S. aureus* colonization.

According to the European guidelines published recently (Ring et al. 2012a, b), some therapeutical proposals are summarized in Fig. 7.4.

It is possible to classify the therapeutical proposal in three main groups: basic therapy, topical therapy, and phototherapy/systemic therapy.

Basic Therapy

The basic therapy is represented by basic rules the patient has to follow in order to contrast every day the disturbed barrier function. The skin must be cleaned gently and carefully in order to get rid of crusts and mechanically eliminate bacterial contaminants.

The duration of the bath is suggested short (5 min) and daily. The use of bath oils has to be preferred in order to avoid epidermal dehydration.

Topical emollients for restoring the stratum corneum are preferentially applied directly after a bath or a shower when the skin is still slightly humid. Their long-term use is highly suggested, except on inflamed acute patches because it is poorly tolerated. It is better to treat the inflamed skin with pharmacological medication first.

The amount required is usually high, and the cost may restrict their use (only in a few countries they are reimbursed). The high-quality emollients (i.e., sterile and low in contact allergens) are suggested, but sometimes their higher cost may reduce the patient's compliance. A better knowledge of the AD pathogenesis may help to develop new specific topical agents versus barrier defects (i.e., mutation or filaggrin).

Glycerol, urea plus sodium chloride, and white petrolatum with liquid paraffin in equal parts are very effective. Glycerol seems to be better tolerated than urea plus sodium chloride.

Preventive use of emollients containing allergens such as peanuts may increase the risk of skin sensitization and allergy.

As reported in the European guidelines, there is consistent evidence of short- and long-term steroid-sparing effect by a regular use of emollients. Furthermore, their use has an important role in the persistence of remission obtained with topical corticosteroids/topical calcineurin inhibitors.

Elimination of Trigger Factors

Numerous environmental factors can irritate the skin of patients with AD that is usually more sensitive than healthy controls. Sometimes these factors can trigger eczema flares.

Table 7.2 AD differential diagnoses

Type of disease	Diagnosis	Differentiating features	Age	Notes
Inflammatory	Seborrhoeic eczema	Seborrhoeic areas	Infantile AD	Sometimes the diagnosis is challenging
		No excoriated lesions on the extremities		
	Allergic contact dermatitis	No improvement with appropriate treatment	Childhood, adolescence/ adulthood, elderly	
		Patch test positive		
	Irritant contact dermatitis	No improvement with appropriate treatment		
		Carefully anamnesis		
	Photocontact and photoallergic dermatitis	Photodistribution	Childhood, adolescence/ adulthood, elderly	
		Photopatch test positive		
	Lichen simplex chronicus (LSC)	Clinical presentation Circumscribed, limited to single area	Childhood, adolescence/ adulthood, elderly	LSC can be a consequence of an AD patch
	Psoriasis	Sharply demarcated, scaly, biopsy, carefully anamnesis	All the ages	The differential diagnosis between psoriasis and AD severe at the hands can be very challenging
	Xerotic eczema	No history of AD, clinical presentation (diffuse xerosis)	Elderly	
	Erythroderma	Carefully anamnesis. Clinical presentation		AD can be a cause of erythroderma
	Nodular prurigo (NP)	Carefully anamnesis. Clinical presentation (nodular lesions mainly at the arms and legs)	Adulthood, elderly	Atopy history can be present in patient with NP
Infectious	Dermatomycosis	Carefully anamnesis	Children, adulthood, elderly	
		KOH examination		
	Scabies	Interdigital or genital burrow	All the ages	Lesions involving the face can be present in the infants
Immunological or infiltrative	Cutaneous T-cell lymphoma (CTCL)	Clinical presentation, histology	Adulthood, elderly	
	Wiskott–Aldrich syndrome (WAS)	Thrombocytopenia	Infant, childhood	The clinical findings of WAS are almost indistinguishable from AD
	Hyper-IgE syndrome	γ-Globulin, boys	Infant, childhood	
	Severe combined immunodeficiency (SCID)	Clinical presentation: pyoderma and candidiasis	Infant	

(continued)

Table 7.2 (continued)

Type of disease	Diagnosis	Differentiating features	Age	Notes
Genetic	Netherton's syndrome	Bamboo hairs	Infant	SPINK5 (serine protease inhibitor Kazal-type 5)/LEKTI (lymphoepithelial Kazal-type-related inhibitor) is involved also in AD
	Acrodermatitis enteropathica	Clinical examination (periorificial area distal extremities)	Infant	
	Ataxia, telangiectasia (AT)	Ataxia, telangiectasia, pigmentation abnormalities	Infant	AD was noted in two patients with AT
	Ectodermal dysplasia	Anhidrosis, dental or hair abnormalities	Infant	
	Phenylketonuria	Pyogenic infections, laboratory phenylalanine	Infant	

Modified from Beltrani et al.

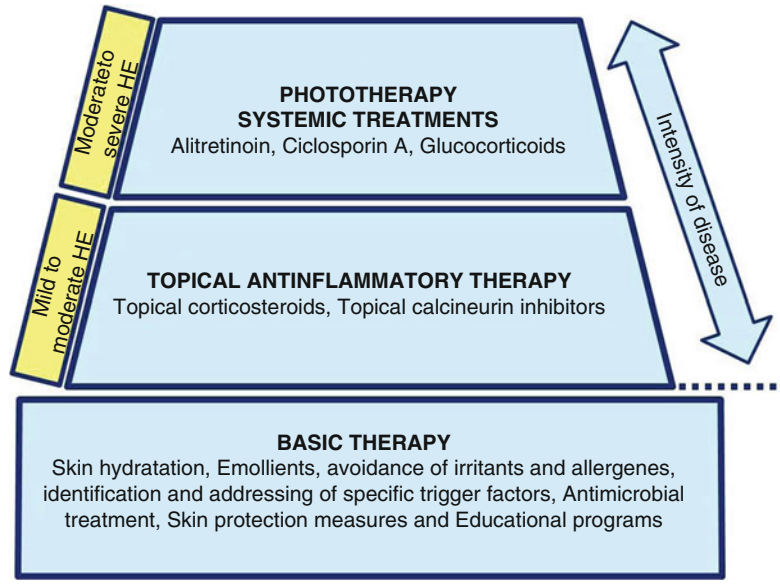


Fig. 7.4 Stepwise management of patients with AD

They can be physical (i.e., wool, irritating synthetic fibers, occlusive clothing, prolonged hot showers, high or low temperature, low humidity, indoor and outdoor environments, and smoking exposure), chemical (acids, bleaches, use of nickel-releasing jewelers, solvents, soaps, perfumes, makeup, and water), or biological (microbes). It is important to educate the patients to identify and avoid the individual trigger factors. Thus, adequate skin care and hygiene procedures at home and at job place have to be discussed with the patient.

Allergen Avoidance

Regarding the aeroallergens, the most important in atopy are the following:

- House dust
- House dust mite
- Pollen (tree/grass/weed)
- Animal dander (cat/dog)
- Mold

It is generally believed that they should be avoided because they have been shown to elicit eczematous skin lesions. Especially patients who will develop sensitization will benefit from avoidance strategies.

Particularly, house dust mite avoidance strategies have been proved to have positive effects on the course of the disease. House dust mites live in a complex ecosystem consisting of air humidity, temperature, and organic materials. Contacts with these allergens can be prevented with the use of dust mite-proof (Gore-tex) covers for mattresses and pillows, wet-mopping floors, and avoiding rugs (especially in bedrooms).

In spring- and summertime, pollen exposure as well as dusty ambient may exacerbate AE; thus, pollen avoidance measures have to be recommended.

Lastly, in selected highly sensitized patients, an allergen-specific immunotherapy (ASIT) may have positive therapeutic implications in AD and its associated allergic respiratory diseases. The best evidence so far is available for ASIT with house dust mite allergens.

Among food allergens, several studies have emphasized the etiological role of food allergens in AD exacerbation in infancy. Common implicated food allergens are cow's milk, hen's egg, wheat, soy, tree nuts, peanuts, fish, and apple.

It is accepted that the importance of food allergens rapidly decreases with increasing age.

The role of diet and food allergy/intolerance in AD management is still controversial. Patients with moderate to severe AD can benefit from a diet eliminating those foods that have elicitated clinical early or late reactions upon controlled oral provocation tests.

Antimicrobial Treatment

The high rate of cutaneous *Staphylococcus aureus* colonization (up to 90 % in moderate to severe eczema) characterizes the AD lesions.

In general, improving eczema with anti-inflammatory regimens (i.e., topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and ultraviolet irradiation (UV)) decreases staphylococcus colonization. Anyway, patients can benefit from combination of corticosteroids and antimicrobial treatment, i.e., antiseptics such as triclosan or chlorhexidine, or from the addition of antiseptic to the bathing waters (i.e., natriumhypochlorit).

The use of silver-coated and silk textiles has been introduced recently in the management of AD. They can reduce *S. aureus* colonization and eczema severity.

It is worth to remember that the European Guidelines do not suggest the use of topical antibiotics for long periods due to the risk of sensitizations and increasing resistances. It is important to check in daily practice the possible superinfections of the lesions by bacteria (*S. aureus*), virus (molluscum, herpes), and fungi and to treat them immediately.

Educational Programs

Stress, anxiety, and depression can represent trigger factors because they may reduce the threshold for pruritus. Similarly, pruritus dramatically affects the patients' quality of life and represents a significant trigger for anxiety and depression. To reduce the scratch behavior, the help of psychologist and/or educational programs can be useful.

Psychosomatic counseling in AD can include psychotherapeutic approaches and behavioral therapy techniques.

Educational programs, also known as training programs, or "eczema schools" have been successfully developed in many countries as an adjunct to conventional therapy in children and adults.

Educational programs aim to improve the adherence in eczema management, the itch/scratching cognition, and the clinical and psychological condition.

The nurse-led programs want to achieve a more effective use of topical pharmacological and non-pharmacological therapies, sparing doctor's time.

The evaluation of all these factors is a prerequisite for long-term management of the disease in order to achieve longer phases of remission or total clearance of symptoms.

Basic Therapy at a Glance

The basic therapy is represented by basic rules the patient has to follow in order to contrast every day the disturbed barrier function.

The patient has to be carefully educated properly to:

- Cleansing and bathing (daily, short, and with the use of bath oils)
- Application of emollients (at least once a day, directly after a bath or a shower when the skin is still slightly humid)
- Avoidance of irritants (chemical, physical, and biological) and aero- and food allergens
- Identification and addressing of specific trigger factors
- Antimicrobial treatment
- Attend educational programs

The evaluation of all these factors is a prerequisite for long-term management of the disease in order to achieve longer phases of remission or total clearance of symptoms.

Topical Anti-inflammatory Therapy

Before corticosteroids were introduced in the late 1950s, coal tar ointment was the most frequently used therapy.

Nowadays, topical corticosteroids (TCS) and, recently, topical calcineurin inhibitors (TCI) have replaced the previous medication.

In a correct management program, proper strength, dosage, and application have to be taken into consideration.

Previously anti-inflammatory topical therapy was suggested to be used only to lesional skin. Their use had been stopped or tapered down when the visible lesions were cleared. In the last years, this *reactive* approach (Fig. 7.5a) has been combined with the *proactive* approach (Fig. 7.5b), which is

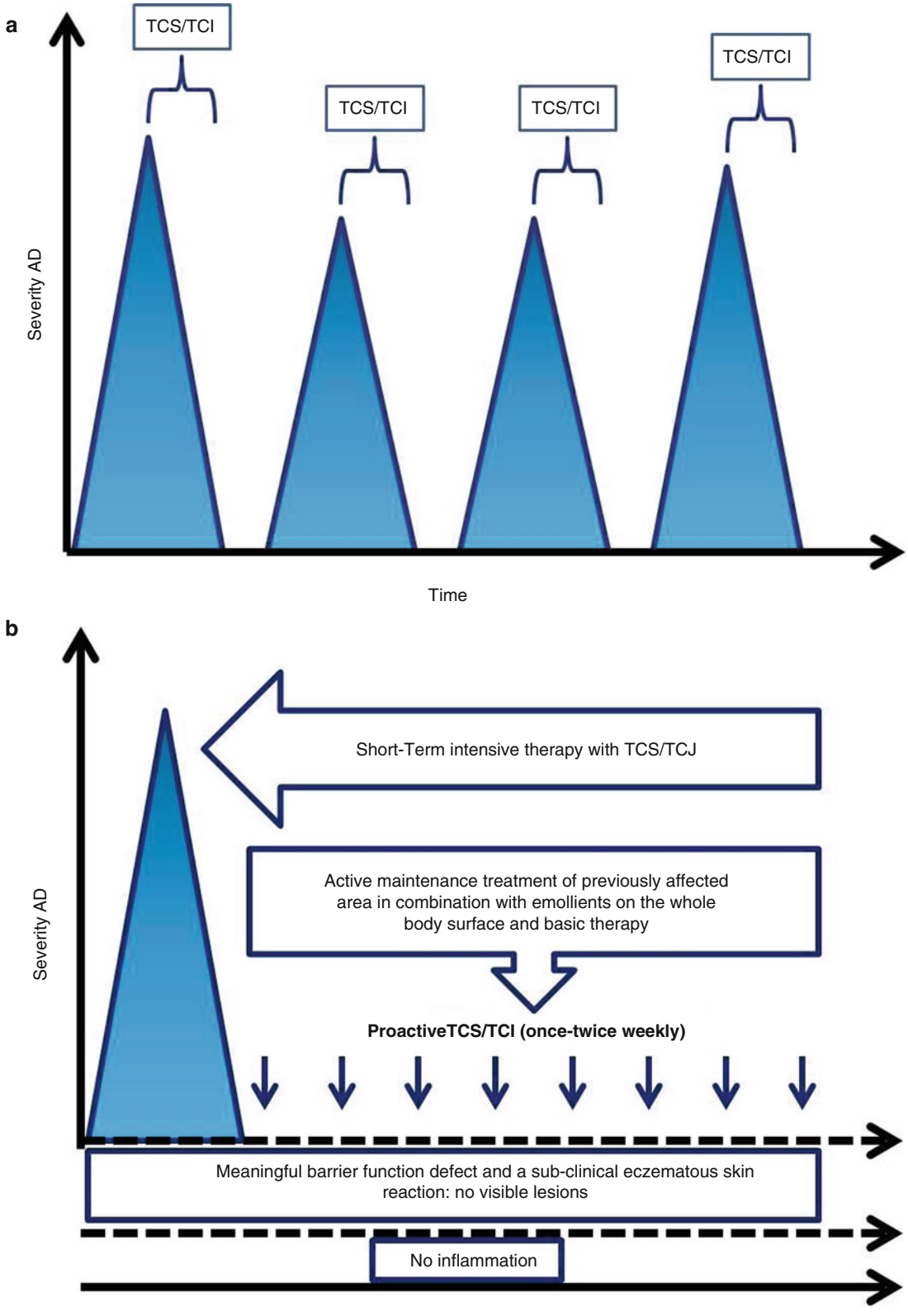


Fig. 7.5 (**a**) Reactive approach. (**b**) Proactive approach

defined as a predefined, long-term, low-dose treatment with anti-inflammatory drugs that have to be applied to the previously affected areas.

The use of emollients on the entire body and basic therapy remain the basis with whom the reactive and proactive anti-inflammatory treatments are going to be combined. The emollient should be applied first, about 15 min before the topical anti-inflammatory treatments. Patients with acute and erosive lesions sometimes do not tolerate standard topical application. In these cases, wet wraps should be used. They are also protective to persistent scratching, and they decrease the itch by cooling the skin.

Topical Corticosteroids

Topical corticosteroids (TCS) are a first-line anti-inflammatory treatment in AD.

They can be applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flares). A large variety of topical steroids are available. The potency of these corticosteroids ranges from mild to very potent. In addition, the vehicle may differ, which is of limited influence on therapeutic efficacy. Most steroid preparations are available as lotion, cream, fatty cream, and ointment. It is worthy to remember that the corticosteroid concentration and its efficacy may be different when the preparation changes. For example, fluticasone propionate 0.005 % ointment is considered a potent corticosteroid, while fluticasone propionate 0.05 % cream is a moderately potent corticosteroid. Another analogous example can be made with mometasone: in this case, the concentration of the active principle is the same.

An overview is given in Table 7.3.

To prevent tachyphylaxis, side effects, and rebound phenomena, it is suggested to use a potent steroid in a short term, followed by a less potent preparation. Tachyphylaxis is the phenomenon that a given therapy loses efficacy during continuous treatment.

In the first weeks, TCS can be used once or twice daily in combination with basic therapy. Then, they should be used once/twice a week as maintenance (*proactive therapy*) for a long period, and during the other days the patients continue with only emollients.

The patient should be instructed to not stop the treatment too early and to be educated in the correct use of TCS for a long period. In fact, with subclinical to mild disease activity, a small amount of topical corticosteroids from once to thrice weekly (considering a monthly amount in the mean range of 15 g in infants, 30 g in children, and up to 60–90 g in adolescents/adults), together with a correct use of emollients, generally allows a good and long-term maintenance therapy.

The application amount of topical anti-inflammatory therapy should follow the fingertip unit (FTU) rule. An FTU corresponds to the amount of topical corticosteroid measured from the distal skin crease to the tip of the index finger (approximately 0.5 g); this amount should cover two adult palm areas.

Topical Calcineurin Inhibitor (TCI)

Tacrolimus ointment and pimecrolimus cream are macrolide-type inflammatory cytokine inhibitors licensed for topical eczema treatment. They have a mechanism of action similar to cyclosporine A (CsA). Differently from the latter, they are effective in the topical treatment of AD due to their relative small size.

They are available in two different formulations of tacrolimus ointment: 0.03 and 0.1 %. In Europe, the first is licensed for children over the age of 2 years, and the latter over 16. There is only one formulation of pimecrolimus: 1 % cream, licensed for older than 2.

The anti-inflammatory efficacy of 0.1 % tacrolimus ointment is similar to a corticosteroid with intermediate activity, which is more active than 1.0 % pimecrolimus cream.

TCI are highly effective against pruritus. In contrast to TCS, they have a more favorable side-effect profile that allows their use in daily practice.

They are usually used as second-line therapy in patients who do not respond adequately to TCS or in whom their use is contraindicated.

Some typical effects of long-term use of corticosteroids, such as atrophy, telangiectasia, and

Table 7.3 Overview of the topical corticosteroids commonly used in AD

Power of corticosteroids	Active principle	Formulation
Very potent	Betamethasone dipropionate	Ointment (0.05 %), cream (0.05 %)
	Clobetasol propionate	Ointment (0.05 %), cream (0.05 %)
Potent	Amcinonide	Ointment (0.1 %), lotion (0.1)
	Betamethasone valerate	Ointment (0.01 %)
	Budesonide	Cream (0.025 %)
	Desoxymethasone	Ointment (0.25 %), cream (0.25 %), gel (0.05 %)
	Fluocinonide	Ointment (0.05 %), cream (0.05 %), gel (0.05 %)
	Fluticasone propionate	Ointment (0.05 %)
	Methylprednisolone aceponate	Ointment (0.1 %), cream (0.1 %), emulsion (0.1 %)
	Mometasone furoate	Ointment (0.1 %)
	Triamcinolone acetonide	Ointment (0.5 %), cream (0.5 %)
Moderately potent	Clobetasone butyrate	Cream (0.05 %)
	Betamethasone valerate	Cream (0.01 %), lotion (0.01 %)
	Fluocinolone acetonide	Ointment (0.025 %), cream (0.025 %)
	Fluticasone propionate	Cream (0.05 %)
	Hydrocortisone butyrate	Cream (0.1 %)
	Mometasone furoate	Cream (0.1 %)
	Triamcinolone acetonide	Ointment (0.1 %), lotion (0.1 %)
Mild potency	Hydrocortisone acetate	Cream (0.5 %)
	Betamethasone valerate	Lotion (0.05 %)
	Triamcinolone acetonide	Cream (0.1 %)

From Luger (2011), modified

striae, are not reported with the use of TCI. TCI are especially indicated in delicate body areas, such as the face (eyelids, perioral skin), intertriginous sites, and the anogenital area.

Burning of the skin or a feeling of warmth is a side effect of these new compounds. It starts about 5 min after each application and may last up to 1 h. These side effects usually disappear after a few days of treatment. Only a transient increase of viral infections such as eczema herpeticum (EH) or eczema molluscatum (EM) has been observed during TCI treatment. These drugs are contraindicated for use in infected skin, and they have to be stopped in case of superinfections. Clinical and preclinical data do not indicate an increased incidence of the induction of lymphoma or photocarcinogenicity for TCI. However, UV avoidance and/or protection has been advised due to the known risk of these side effects from the oral administration of the tacrolimus or cyclosporine.

"New" Proactive Approaches

The chronic and relapsing nature of AD stimulated the insiders to develop long-term management strategies. Research has shown that normal-looking, nonlesional AD skin is not normal at all, but it is characterized by a clinically meaningful barrier function defect and a subclinical eczematous skin reaction.

In the last years, the *reactive* approach (Fig. 7.5a) has been combined with the *proactive* approach (Fig. 7.5b), which is defined as a predefined, long-term, low-dose treatment with anti-inflammatory drugs that have to be applied to the previously affected areas.

These new *proactive* approaches aim to control this subclinical disease with minimal use of anti-inflammatory drugs (Fig. 7.5b). These approaches have been shown to be safe and effective, to reduce relapses and the use of the

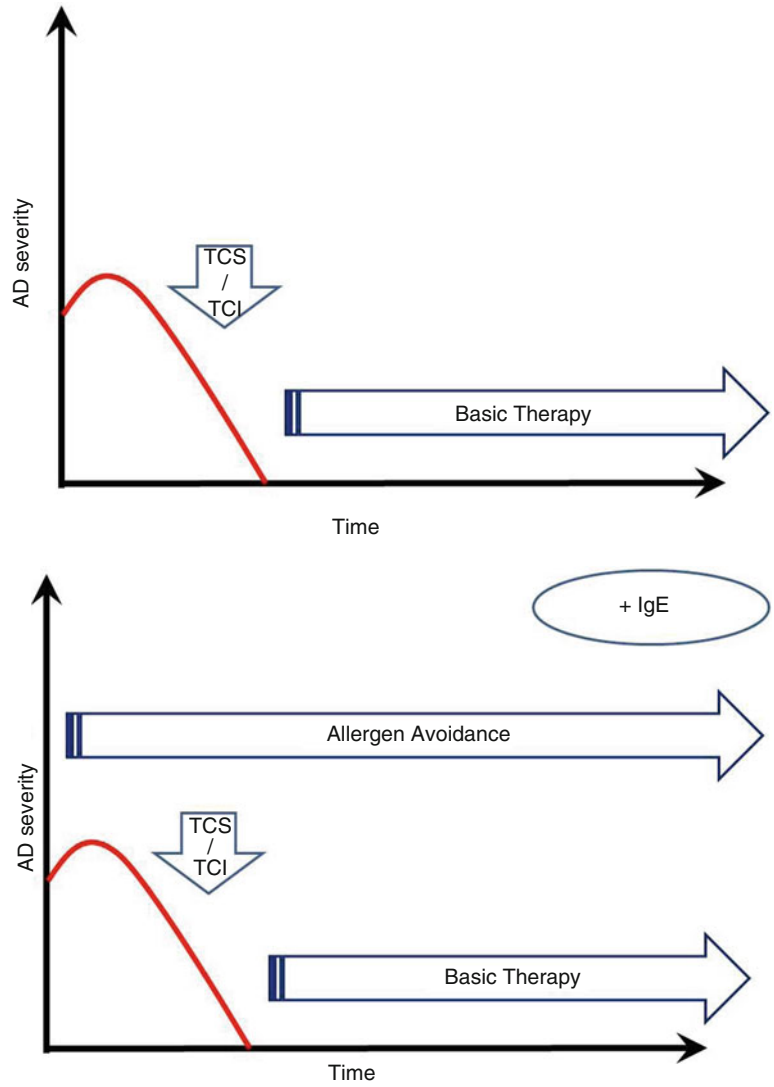


Fig. 7.6 Therapeutic approaches in AD

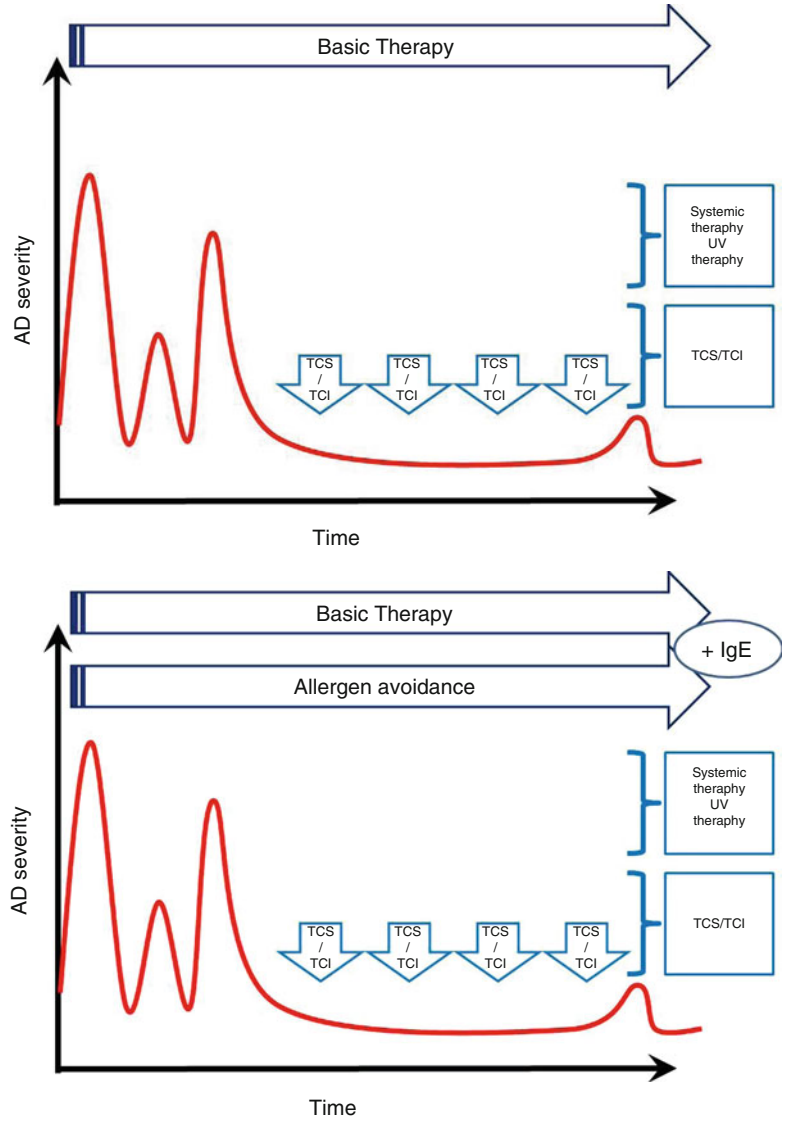
pharmacological treatment, and to improve the quality of life of patients. The choice of proactive strategies is supported by immunological, clinical efficacy, quality of life, and pharmacoeconomic data.

Proactive therapy should be carried out in children and in adults. Long-term studies (up to 4 years) have been performed either with tacrolimus (0.03 % and 0.1 %) or with corticosteroids (i.e., fluticasone propionate cream and ointment and methylprednisolone cream).

In adults, long-term treatment with 0.1 % tacrolimus ointment appears to be as effective as a corticosteroid regimen for the trunk and extremities and more effective in the face and neck area. Moreover, the instauration of these strategies at a very early stage of the disease might even have a beneficial effect also on respiratory symptoms and serum IgE (*atopic march*), but this tempting hypothesis needs to be addressed in future studies.

In daily practice, these new approaches should be explained to each patient (and with parents, family, doctors, and pediatricians) in order to achieve the highest rate of compliance.

Fig. 7.6 (continued)



Topical Therapy at a Glance

Topical corticosteroids (TCS) and, recently, topical calcineurin inhibitors (TCI) represent first-line therapies for AD.

In the correct management, proper strength, dosage, and application have to be taken into consideration.

TCS can be applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flares). It is suggested to use a potent steroid in a short term, followed by a less potent preparation in long-term maintenance treatment.

Tacrolimus ointment (0.% and 0.03 %) and pimecrolimus cream are macrolide-type inflammatory cytokine inhibitors licensed for topical eczema treatment. TCI are especially indicated in delicate body areas, such as the face (eyelids, perioral skin), intertriginous sites, and the anogenital area.

The new *proactive* approaches (low weekly dose/application of TCS/TCI for a long period) aim to control the residuals of the disease and to prevent new flares (Fig. 7.5b). The choice of a proactive strategy is favored by

immunological, clinical efficacy, quality of life, and pharmaco-economic data. These approaches have been shown to be safe and effective, to reduce the use of the pharmacological treatment, and to improve the quality of life of patients.

Phototherapy

Many patients achieve very good results from artificial UV radiation as well as from heliotherapy and balneophototherapy. Thus, development of different ultraviolet (UV) schedules for the management of this disease has been carried out.

Currently, different UV source equipments are available.

- UVA1 (340–400 nm)
- Narrowband UVB (nbUVB = peak: 311–313 nm)
- Broadband ultraviolet B (BB-UVB = approx. 280–320 nm)
- PUVA therapy
- 308 nm excimer laser

UV sources have an immunomodulatory and antimicrobial effect (reducing the colonization of *S. aureus*), and they increase the vitamin D balance.

Phototherapy is usually a part of a wider treatment plan in adults and much less in children. Phototherapy should be avoided in children under the age of 12 years and in those patients who reported a worsening of their dermatitis during sun exposure.

Chronic, pruritic, lichenified forms (which are the most common manifestations of AD in adults) can benefit from phototherapy. In case of acute eczema exacerbation, UVA1 should be the suggested UV source.

Since this treatment cannot be applied at home, one of the major disadvantages is that the patient has to go to the hospital three to five times a week for the treatment.

Narrowband UVB is to be preferred to broadband UVB. Studies have shown that medium-dose UVA1 has similar efficacy as narrowband UVB. The choice of a UV treatment also depends on the availability of the equipment. At the beginning of UV treatment, topical steroids and emollients can be used in combination, whereas TCI should be avoided.

PUVA (photochemotherapy) (UVA in combination with psoralens) has demonstrated the same efficacy as UVA and nbUVB, but due to several side effects (from nausea to headache, irregular skin pigmentation, and proven carcinogenicity), it is not the first choice.

New devices, such as the 308 nm excimer laser, increase therapeutic options, but they are reserved for patients with localized and therapy-resistant AD.

Systemic Therapy

Patients with severe, generalized inflammation who do not respond to treatment including the use of topical treatment and phototherapy may benefit from systemic treatments and sometimes are candidates for hospitalization.

Cyclosporine A (CsA) is an immunosuppressant drug licensed in many European countries for treatment of AD. It is one of the first-line drugs in chronic, severe cases of AD in adults. In children, it may be used "off-label." Despite its well-proved efficacy, its well-known side effects limit its use, especially in long-term treatment.

An initial daily dose between 3 and 5 mg⁄kg⁄day, divided upon two single doses, is recommended. When a satisfactory clinical response is achieved, a dose reduction of 0.25–0.5 mg⁄kg⁄day every 2 weeks is recommended. A detailed patient monitoring, especially of the renal status and blood pressure, is advisable.

The combination with UV therapy should be avoided; the patient should be educated to a proper photo protection in summertime due to the increased risk of cutaneous malignancies (nonmelanoma skin cancers).

Systemic corticosteroids are commonly used in cases of moderate to severe AD. Despite their widespread use, they present a largely unfavorable risk/benefit ratio for the treatment of this disease. For this reason, the European guidelines have recommended to restrict their use to adults with acute and severe flares (resistant cases) for a short period (up to 1 week). Long-term use is not recommended,

especially not in children. The recommended daily dose should be adjusted to body weight.

Azathioprine is used since many years in Great Britain and the United States in adults. It can be used, off-label, as second-line therapy in patients who do not have responded adequately to CsA or in whom the use of CsA is contraindicated. Patients have to be screened for TPMT (thiopurine S-methyltransferase) activity before starting therapy (for the bone marrow toxicity). The suggested dose range is 1–3 mg⁄kg⁄day.

The use of *mycophenolate mofetil* (MMF) and *methotrexate* (MTX) may be an alternative (off-label) in adults with severe AD resistant to other topical and systemic treatments.

The use of the last three drugs in children and adolescents is not supported by published studies.

When AD is severe, unresponsive to topical steroid, and localized at the hands, *alitretinoin* may be used. The use of this drug is allowed only in adults. Small studies have reported an improvement of extrapalmar AD lesions during the treatment.

Dupilumab, a fully human monoclonal antibody that is directed against the shared alpha subunit of the interleukin-4 receptors and that blocks signaling from both interleukin-4 and interleukin-13, have been proved to be efficacy in patients with moderate to severe AD (phase I and phase II study), after a phase II study on asthma (Beck et al., 2014; Wenzel et al., 2013).

The introduction of this new drug, that has the potential to become the first biological systemic therapy for AD approved by US FDA and by EMEA, will significant increase the therapeutic armamentarium of physicians in the management of moderate to severe AD.

Phototherapy and Systemic Therapy at a Glance

A lot of patients achieve very good results from artificial UV radiation as well as *heliotherapy and balneophototherapy*.

Studies have shown that medium-dose UVA1 has similar efficacy as narrowband UVB, and these two UV sources are those to be preferred.

UV has an immunomodulatory and antimicrobial effect (reducing the colonization of *S. aureus*), and they increase the vitamin D balance.

Their disadvantage is that they, with exceptions, cannot be used at home.

Cyclosporine A is an immunosuppressant drug licensed in many European countries for treatment of AD. Despite its well-proved efficacy, its well-known side effects limit its use, especially in long-term treatment.

Systemic corticosteroids are commonly used, but they present a largely unfavorable risk/benefit ratio for the treatment of this disease. Their use should be restricted to adults with acute and severe flares (resistant cases) for a short period (up to 1 week).

Azathioprine, *methotrexate*, *mycophenolate mofetil*, and *alitretinoin* can represent a good alternative choice (off-label) in adults with severe AD resistant to other topical and systemic treatments.

Antipruritic Therapy

Pruritus represents one of the four major features in the diagnosis of atopic dermatitis.

Although it is a very common sign, few studies have investigated the efficacy of treatment on this sign alone. In fact the majority of studies have analyzed it within the global clinical scores,

Table 7.4 Antipruritic therapies in AE

General principles
Cleansing, bathing use of emollients/basic therapy. They reduce dry skin
Elimination of provocative factors: avoidance strategies (i.e., too long and hot bathing, contact with irritant substances or allergens, etc.)
Anti-inflammatory therapy
TCS and TCI
CsA
Phototherapy
Adjuvant specific antipruritic therapies
Creams/lotions containing urea, camphor, menthol, topical polidocanol or N-palmitoylethanolamine, topical capsaicin
Opioid receptor antagonists (e.g., naltrexone)
Sedation by the use of (mainly first generation) anti-H1 antihistamines

From Ring et al. (2012a, b) modified

measured with eczema area and severity index (EASI) and/or SCORAD.

As reported in the European guidelines, pruritus in AD has a multifactorial and complex etiopathogenesis. Thus, it can benefit from several and different treatments with different mechanisms as reported in Table 7.4.

Antihistamines

Although antihistamines have been used for decades, in attempts to relieve pruritus, surprisingly there are no conclusive data concerning their real efficacy in the treatment of pruritus in AD. There are only a few controlled studies evaluating the efficacy of antihistamines in treating the pruritus in AD with controversial results.

Children and adults may benefit from the treatment with the first generation of sedative antihistamines because they may allow a better sleep pattern in acute AD phases. Studies on the second-generation, nonsedating antihistamines, i.e., loratadine, cetirizine, or fexofenadine, demonstrated no or only a weak relief of pruritus. But second-generation antihistamines have the advantage to be very efficacious in the relief of the symptoms of common mucosal comorbidities such as allergic asthma and rhino-conjunctivitis. They are safe to use, also for a long period.

Antipruritic Therapy at a Glance

Although pruritus is a very common and important sign, few studies have investigated the efficacy of treatment on this sign alone.

Pruritus in AD has a multifactorial and complex etiopathogenesis. Thus, it can benefit from several and different treatments with different mechanisms as reported in Table 7.4.

Although antihistamines have been used for decades, in attempt to relieve pruritus, surprisingly there are no conclusive data in the literature concerning the real efficacy of oral antihistamines in the treatment of pruritus in AD.

Conclusion

Barrier dysfunction of the skin and chronic inflammation are peculiar features of AD: the prevention with new individually adapted skin care products, eventually shortly after birth, the inflammation control by the regular use of topical corticosteroids or topical calcineurin inhibitors for long-term periods, the management of pruritus, and the reduction of bacterial colonization have to be considered in the long-term strategies.

Biomarkers will allow to carry out future approaches in the context of stratified or personalized medicine.

Now we can highlight therapeutic approaches in five courses of the dermatitis after its onset:

1. Remission of AD (Fig. 7.6a).
2. Remission of AD and development of high levels of IgE and mucosal sensitization (Fig. 7.6b).
3. AD becomes a chronic disease, without the development of high level of IgE (Fig. 7.6c).
4. AD becomes a chronic disease, with the development of high levels of IgE and mucosal sensitization (atopic march) (Fig. 7.6d).
5. AD becomes a chronic disease, with the development of high levels of IgE, with/without mucosal sensitization, and with the development of high levels of auto-IgE (autoreactivity march). In this case, the therapeutic approach will be the same as case 4.

The therapeutic approaches are shown in Fig. 7.6a–d. Up to now, there are not enough standardized biomarkers that allow us to prognosticate the course of the AD.

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Balanitis

8

Derek Freedman

Key Points

- Balanitis is usually a simple intertrigo with no specific aetiological agent.
- In most cases, the course will be episodic with recurrences, unless specific care is taken to reverse the predisposing factors.
- The vast majority of cases respond to *simple measures*:
  (a) Retraction of the foreskin
  (b) Saline baths
  (c) Simple drying powder
- Topical antifungal creams give temporary relief only: powders are more effective.
- Persisting lesions should be biopsied.

Definition and Epidemiology

Balanitis: Inflammation of the glans penis.

Balanoposthitis: Inflammation of the foreskin and surface of the underlying glans penis. Frequently occurs with a tight or not easily retracted foreskin, or phimosis. Usually a more acute and extensive local inflammation than simple balanitis.

Posthitis: inflammation of the preputial mucosa.

The term 'balanitis' is frequently used to include all of the above.

The condition is common in infancy when the prepuce is adherent, non-retractable and subject to moisture and contamination from urine and faeces.

It is very common in adulthood. It is not related to poor hygiene, but to intertrigo and accumulation of sub-prepuce secretions. It is equally frequent with overzealous, and even obsessive washing, causing irritation. Candida balanitis is a much less common cause of balanitis and is associated with diabetes mellitus. Sexual transmission is not described in the literature, but most physicians have clinical experience of balanitis occurring postcoitus with a woman who has either candida or bacterial vaginosis. It may be an indicator of sexual risk taking and as such warrants a full STD screen, unless risk is specifically denied.

Essentially, diagnosis is anatomical, but there are multiple causes.

Basic Concepts of Pathogenesis

The blind sub-prepuce sac gives a warm moist environment, with an accumulation of desquamated cells – smegma, an ideal culture medium. The epithelium of the glans penis is protected and covered, so that it remains moist,

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_8, © Springer-Verlag Berlin Heidelberg 2015

non-keratinised, thin and sensitive. In many respects, the male preputial sac is the equivalent of the vagina, a closed space, with a polymicrobial ecology and a similar susceptibility to overgrowth of microorganisms normally present to produce symptomatic conditions, and a similar predisposition to recurrence of these conditions.

Most commonly, balanitis is a simple intertrigo with no specific aetiological agent. The majority of cases are mild and may have mechanical or irritant associations. It may present after a recent regretted sexual encounter, where anxiety and increased awareness of genital sensations lead to closer scrutiny of the area. A full STD screening is mandatory in these circumstances.

With infective causes, a more acute inflammatory reaction may be seen, such as with infection/overgrowth of candida or anaerobes. Many dermatological conditions also affect the genital epithelium, where their clinical features may be atypical due to the different morphology of the epithelium.

Sexual transmission has been described with both candidal and anaerobic infections, but it is thought to be infrequent. Partner treatment does not markedly influence the risk of recurrence.

Clinical Presentation

Clinical presentation is variable and is frequently inversely related to guilt and anxiety. The anxious or guilty patient may present with symptoms of non-specific irritation, itching or burning of the glans/prepuce and little or no findings at all. Often there is just a minimal red spotty rash or some macules on the glans. Other patients may present with an obvious red inflamed glans and prepuce, erosive ulcers and an offensive subprepuce discharge: an amine odour indicating anaerobic overgrowth. Inguinal adenopathy is rarely present with simple balanitis and its presence should indicate consideration of a wider differential diagnosis, including the need to exclude sexually transmitted infections and carcinoma.

In most cases, the course will be episodic with recurrences, unless specific care is taken to reverse the predisposing factors.

Diagnosis

In simple balanitis, diagnosis is clinical and tested by response to simple measures.

Microscopy of the sub-prepuce secretions may reveal candida or anaerobes, which may point to the same condition in the sexual partner(s). Potassium hydroxide preparation is useful in the identification of candida; Gram stain will be more specific for anaerobes. Culture will identify bacterial causes, although one must be careful not to attribute the causation to commensals.

The presence of ulceration, adenopathy or a positive sexual risk history should prompt a full screen for sexually transmitted infections. Samples from ulcerated lesions should be examined by dark ground microscopy and/or PCR detection to eliminate syphilis, as well as serology. An HSV DNA detection for herpes virus should be taken – HSV culture being less sensitive. Consideration should be given to chancroid, lymphogranuloma venereum and granuloma inguinale. A high degree of suspicion should be maintained for squamous cell carcinoma of the penis and any persisting or suspicious lesions biopsied.

The skin of the glans penis and prepuce may be affected by a wide variety of dermatological conditions, the more important of which are considered in the differential diagnosis which follows. The presentation and appearance of these conditions is modified in the soft non-keratinised skin. In case of persisting lesions, or if in any doubt, do a biopsy.

Differential Diagnosis

As an area of skin, the prepuce and glans penis is subject to abrasion, trauma, infection and the entire gamut of dermatological conditions, including cancer and precancerous lesions (Table 8.1) (Fig. 8.1).

Table 8.1 Balanitis: differential diagnosis of common or important conditions

Condition	Clinical features	Diagnosis
Sexually transmitted		
Herpes genitalis	Vesicles – sores – crusts	HSV DNA detection
	Painful	Viral culture – less sensitive
Syphilis	Ulcer(s) – painless	TP DNA detection
Primary	Condylomata lata	Dark ground microscopy
Secondary	Multiple circinate lesions	Serology (>3/12)
Chancroid	Painful ulcer(s)	Culture
	Adenopathy	P.C.R.
Lymphogranuloma venereum	Painful shallow ulcer(s)	NAATS
	Adenopathy	
Granuloma inguinale	Beefy lesions	Microscopy
	Painless	Biopsy
Gonorrhoea	Acute ulcers and pustules	Microscopy
	Acute infection of glands and ducts, i.e. tysonitis, Cowper's duct	DNA detection test Culture
Trichomonas	Acute erosive adenopathy	TV DNA detection
		Microscopy (wet – 50 % sensitivity)
Human papilloma virus	Asymptomatic	Aceto – white lesions
	Patchy variable macula	(5 % acetic acid stupes)
	Hypoaesthesia – pruritus Chronic/recurrent	Confirm by biopsy
	Warts	HPV typing
Infections: sexual possibility of transmission		
Candida infection	Short incubation	Microscopy
	Burning, itching – acute pain	KOH preparation
	Variable erythema – dry glazed small papules and pustules coalesce to form erosive patches	'Adhesive tape' sample
	Prepuce edge fissures	
Candida hypersensitivity	Transient post-coital erythema and burning	History
		Check partner
Gardnerella	Mild symptoms	Clinical
	Macular erythema	Culture
	'Fishy' odour	
Anaerobic erosive balanitis (Bacteroides spp.)	Tender ulcers	Microscopy
	Odour	Mixed spirochetes
		Bacteria ++
Group B	Erythema – purulent discharge	Culture
Haemolytic streptococci	Cellulitis	
Infections: sexual transmission unlikely		
Group A	Prepubertal	Culture
Haemolytic streptococci	Erythematous, moist	
Staphylococcus aureus	Prepubertal boys (toxic shock syndrome)	Culture
Pityriasis versicolor	Discrete fine scaling	Fluoresce with 'woods' light
	Hypopigmented areas	
Herpes zoster	Pain ++	Clinical
	Grouped blisters	Dermatome distribution
		Serology
		HVZ – DNA

(continued)

Table 8.1 (continued)

Condition	Clinical features	Diagnosis
Specific balanitides		
Lichen sclerosis et atrophicus	Atrophic white papules or plaques. Phimosis, burning, pruritus, hypoaesthesia, sexual dysfunction	Sclerotic white ring at tip of prepuce
	Lesions progress to sclerotic/atrophic white/ivory/blue flat-topped papules	Biopsy
	Progressive chronic course	
	Fibrosis – obliteration of anatomical features	
Plasma cell balanitis	Solitary glazed-smooth red-orange plaque *cayenne pepper*	Biopsy
Localised balinitides		
Fixed drug eruption	Well-demarcated erythematous areas	History
	Bullous – occasionally ulcerated	Recur at same site on re-exposure to drug
Allergic and contact dermatitis	Intense pruritus/burning	History
	Marked oedema	Patch testing
	Rapid onset	
Trauma	Direct accidental: burn/scald/frostbite suction/vacuum erection devices	History
	Zipper entrapment	
	Sexually induced: pubic hair friction, dental induction, instrumentation, masturbation	
Implantation	Studs, rings, balls, etc.	Clinical
Manifestation of systemic/ generalised disease		
Psoriasis	Well-demarcated erythematous plaques without scale (inverse pattern) in uncircumcised	Other stigmata of psoriasis
		Family history
		Biopsy
Behçet's syndrome	Ulcers	Extragenital lesions
		Biopsy
		Pathergy test
Aphthous ulcers	Painful, solitary halo of erythema	Outrule other causes of genital ulcers – especially Behçet's syndrome
Circinate balanitis	Moist plaque with irregular ragged border – geographic (circumcised – dry scaling)	Other clinical features of Reiter's syndrome HLA B27^{+ve} (80 %)
Seborrhoeic dermatitis	Mild erythema and scaling	Clinical
Lichen planus	Polygonal violaceous flat-topped papules	Clinical
	Lacy erosive ulcers	
Erythema multiforme	Erythematous papules	Clinical
	Vesicles – ulcers	
Pemphigus	Vegetating plaques	Biopsy
Neoplasia		
Erythroplasia of Queyrat	Plaques: glazed – velvety	Biopsy
	Slightly raised	
	Sharp margins	
Penile carcinoma	Pruritus/burning	Biopsy
	Papillary/flat	
	Ulcer with rolled edge	
Verrucous carcinoma	Exophytic lesions	Biopsy (large deep)

Table 8.1 (continued)

Condition	Clinical features	Diagnosis
(Buschke-Lowenstein)	Infiltrative	
Extra mammary	Plaques	Biopsy
Paget's disease	Red-brown	
	Raised, scaly	

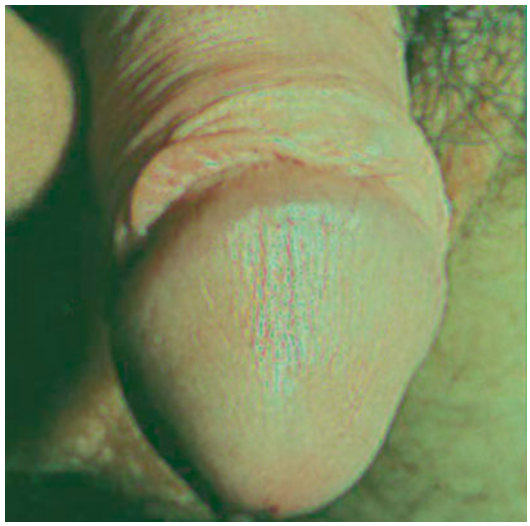

Fig. 8.1 Retracted prepuce. Retraction of the prepuce dries out the epithelium, enhances keratinisation and resolves most cases of balanitis

General Principles of Treatment

The principle is to change the micro-ecosystem of the sub-prepuce sac to one which will not readily become superinfected by candida, anaerobes or other bacteria. Exposure and drying of the skin encourages keratinisation and further enhancement of resistance to infection, abrasion and trauma.

Recommended Therapies

The vast majority of cases respond to *simple measures*:

(a) Retraction of the foreskin
(b) Saline baths
(c) Simple drying powder

Retraction of the Foreskin

Advising patients to change their habits of a lifetime and maintain retraction of the foreskin requires considerable persuasion. Most find it uncomfortable and oversensitive initially, and it takes about 3–4 weeks for the hypersensitivity to settle down as keratinisation occurs. Once this has been achieved, few wish to revert to their previous mode of wearing the foreskin down.

Some men cannot achieve retraction because of a tight prepuce: application of an emollient cream and stretching over a period of time may allow the desired effect to be achieved. Retraction may not be maintained by others because of a natural tendency of the prepuce to slip down. Use of a thin narrow surgical tape (Micropore® 12.5 mm, 3M®) along the shaft of the penis may retain the prepuce back for a sufficient time for keratinisation to occur.

Patients must be warned to guard against paraphimosis on retraction of the foreskin. This may occur at night, with erotic dreams, when patients may awake with an acute paraphimosis.

Some men have a non-retractile prepuce or phimosis. Use of an ultra-potent topical steroid, combined with gentle stretching over a period of several months, may facilitate retraction to take place. The above warning regarding paraphimosis is particularly pertinent.

On occasions, circumcision is warranted for persisting irritation.

Saline Baths

These appear to help dry out the skin and encourage keratinisation and may have a mild fungistatic/bacteriostatic effect. Essentially, a tablespoon (20 ml) of ordinary domestic table salt in a warm bath of water or more convenient for frequent daily use, use a pinch of salt in a

tumbler glass or small jar. The penis and sub-prepuce area should be dried gently, by patting, rather than any rough or abrasive action. Care should be taken not to use too much salt, or the skin will become *pickled* or irritated, which would be quite counterproductive.

If retraction is not possible initially, one can wash out the sub-prepuce space with warm saline by the use of a small syringe to irrigate the area.

Simple Drying Powder

Application of a simple drying powder to the sub-prepuce space can assist in maintaining dryness. A simple talc may be used or one with a mild antiseptic as commonly used for infants (calcium undecylenate 10 % powder, Caldesene®). Care should be taken to ensure that there is no hypersensitivity to the talc or other constituents.

Some soaps, shower gels and shampoos can be an irritant, as well as contain potential allergens. Again, use of simple non-astringent agents is recommended, with advice against overwashing and abrading with drying. This is particularly important where there is broken skin.

Topical treatments at a glance	
Simple measures	Retraction of prepuce
	Saline baths
	Drying powder
Antifungal powders	Miconazole
Antifungal creams	Not recommended
Topical steroids	Not recommended

Alternative Treatments

Antifungals and Steroids

Antifungal creams (clotrimazole, miconazole, nystatin) are very commonly prescribed, and many patients will present having tried antifungal creams, often obtained OTC. The experience is of relapse with these agents, and they can be only useful in providing short-term symptomatic relief. Recurrence occurs shortly after discontinuation of usage. There is danger of hypersensitivity to these agents and their vehicles, especially clotrimazole. Systemic fluconazole has also been recommended, but as only a small proportion of cases are due to Candida infection (Van der Meijden 2014), and these usually respond to simple measures; its utility is questionable.

Antifungal/antibacterial powders produce better results as they dry out the area. They are particularly useful in acute erosive balanitis, with secondary bacterial infection. Miconazole powder, used three to four times a day, is one such agent.

Local corticosteroid applications should only be used sparingly, and where there is a specific need, as they weaken the skin and may mask an infection. Particularly, steroids may reduce the local immune response and facilitate the expression of a latent HPV infection as genital warts.

Simple measures should be tried initially and given sufficient time for patient compliance to be established and for them to show effect. With persisting balanitis, much stronger consideration must be given to the differential diagnosis, taking special care to exclude a sexually transmitted disease, dermatosis or a precancer/cancer. At this stage biopsy becomes mandatory.

Screening for Sexually Transmitted Diseases

This is mandatory in all cases where a history of potential acquisition has been obtained and is a useful reassurance in the majority of other cases. Many patients who present with balanitis have an underlying anxiety regarding STDs, and this must be definitively addressed.

Circumcision

Recognition of the protective benefit of circumcision on male acquisition of HIV has raised a much greater awareness of the procedure. Current estimates show it to confer a 70 %+ protection

after 5 years. It has also been shown to be of some benefit in relation to HPV and HSV acquisition in males (Edwards et al. 2008).

Circumcision is of specific use in lichen sclerosis, after failed topical therapy 3,4, and similarly in lichen planus 5, Zoon's balanitis(Kulkarni et al. 2009). Circumcision is curative in non-specific balanitis.

Whilst circumcision is usually curative in the above conditions, careful consideration should be given to assiduously try the simple measures outlined previously, as they can usually achieve the same effect without the expense and discomfort of surgery. The challenges are lack of awareness by the physician and difficulty in compliance by the patient.

In relation to prevention, the American Academy of Pediatrics (AAP) task force on circumcision of the male infant (2012) Poter et al. (2001) concluded that 'the health benefits of newborn male circumcision outweigh the risks; furthermore, the benefits of newborn male circumcision justify access to this procedure for families who choose it. Specific benefits from male circumcision were identified for the prevention of urinary tract infections, acquisition of HIV, transmission of some sexually transmitted infections, and penile cancer. Male circumcision does not appear to adversely affect penile sexual function/sensitivity or sexual satisfaction'. More widespread adoption of newborn male circumcision will result in reduction of balanitis in the population. However, there are several vociferous anti-circumcision groups and some very strong-held opinions in relation to this topic. The optimal time for circumcision is the newborn period (Kumar et al. 1995).

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Basal Cell Carcinoma

9

Dimitrios Papakostas and Eggert Stockfleth

Key Points

- Basal cell carcinoma (BCC) accounts for 80 % of all nonmelanoma skin cancers (NMSCs) and is the most common human malignancy with higher morbidity than mortality since metastases are extremely rare.
- Sun exposure, genetic predisposition, and immunosuppression are the main risk factors; activation of the sonic hedgehog pathway plays a key role in BCC formation.
- Prognosis, treatment strategies, and follow-up depend on BCC classification as high or low risk after thorough clinicopathological correlation.
- Surgical excision remains the treatment of choice for high-risk BCCs, radiotherapy retaining a complementary role as alternative treatment to surgery or postoperatively in selected cases.
- Nonsurgical destructive methods such as cryotherapy, photodynamic therapy, electrodessication after curettage, and topical treatment with imiquimod should be reserved for the treatment of superficial BCCs and selected low-risk nodular BCCs or in case of inoperability due to patient's medical background or refusal of a more aggressive therapeutic approach.
- Tumor eradication and limited recurrence rates without a disproportionate risk for the patient and an acceptable cosmetic outcome are the key points in the selection of the optimal treatment.
- Novel inhibitors of the hedgehog pathway could revolutionize treatment of inoperable or metastasized BCCs and make an individualized therapeutic approach possible in the years to come.
- Follow-up after treatment is essential, since many BCCs could recur even 5–10 years later. Approximately 45 % of the patients treated will develop a new BCC within the first 3 years after initial diagnosis and treatment.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_9, © Springer-Verlag Berlin Heidelberg 2015

Definition and Epidemiology

Basal cell carcinoma (BCC), also known as basalioma or basal cell epithelioma, is the most common cancer in Europe, Australia, and the USA, accounting for more than a million case per year in the USA. The annual incidence is globally increasing with a peak of 726/100,000 in Australia. In Germany around 100 out of 100,000 inhabitants are diagnosed each year with an average age of presentation of 60 years, though an age shift is the current trend, proposing a further increase of the incidence of BCC in the next decades.

BCCs account for 80 % of all nonmelanoma skin cancers (NMSCs); they present as slowly growing tumors, with local invasive and destructive potential, infiltrating adjacent tissues with fingerlike outgrowths remaining contiguous with the main tumor mass. Metastasis is extremely rare (1:1,000 to 1:35,000) and probably limited to giant BCCs (80 % of metastatic BCCs) and atypical histological variants such as the metatypical BCCs. Thus morbidity rather mortality is the main issue regarding the medical, financial, and social impacts of this common malignancy.

Basic Concepts of Pathogenesis

Eighty percent of all BCCs appear on sun-exposed areas of the face and the neck, preferably of fairly skinned individuals, indicating ultraviolet exposure, genetic predisposition, and skin type as the main predisposing factors, followed by immunosuppression, exposure to arsenic salts, ionizing radiation, and trauma.

Ultraviolet light has a known mutagenic potential and signature mutations such as C→T are found in sun-exposed skin. Patients with xeroderma pigmentosum, a rare genetic disease with impaired DNA correction, report an increased incidence of BCCs among other forms of NMSC. Still, in the majority of BCC patients, this is not the case; the study of the autosomal dominant inherited basal cell nevus syndrome (BCNS) or Gorlin syndrome improved our understanding of the molecular basis of this malignancy. These patients typically develop numerous BCCs at younger ages, they present with skeletal anomalies and other deformations regarding the embryogenesis, and they are prone to the development of other tumors such as the medulloblastoma. Not only in patients with BCNS but also in the majority of sporadic BCCs as well the sonic hedgehog pathway is activated. The hedgehog pathway plays a key role in developmental processes during embryogenesis. In most normal adult tissues, the pathway is silenced though and the reactivation can lead to cancer. Central component of the hedgehog pathway is the transmembrane protein SMO, which is being inactivated by another transmembrane protein called Patched (from the PTCH-1 gene, which is mutated in patients with Gorlin syndrome, resulting in inactivation of the Patched protein and activation of SMO). After binding of the hedgehog ligand to its receptor on Patched, the suppression on SMO is relieved and a downstream phosphorylation cascade is activated, leading to activation of the GLI transcription factors, their accumulation in the nucleus, and the active transcription controlling of hedgehog target genes. Eighty to ninety percent of sporadic BCCs have a PTCH-1 mutation and about 10 % an SMO mutation. In either cases activation of the SMO signaling results in uncontrolled BCC formation.

Clinical Presentation

The typical nodular BCC on sun-exposed areas of the face and the neck presents as a red-yellowish papule, slowly growing in size, with possible ulceration, remaining well circumscribed with a pearly border. Superficial BCCs (Fig. 9.1) on the trunk impose on the other hand as slowly growing flat red plaques, being easily confused with inflammatory diseases of the skin or Bowen disease. Aggressive variants of the BCC are the morpheic BCCs presenting like a scar with unclear borders, making R0 resection rather challenging, and the local destructive variants known as ulcus rodens and ulcus terebrans. Pigmented (Fig. 9.2), cystic, keratotic, and baso-

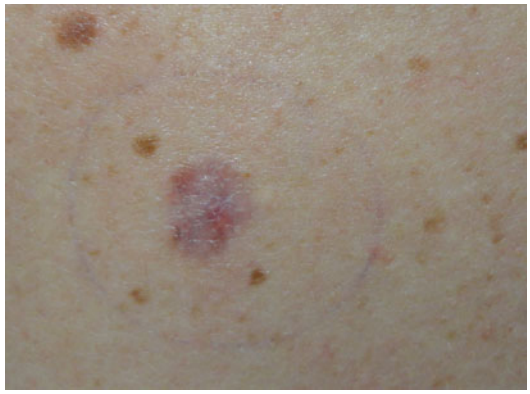

Fig. 9.1 Superficial basal cell carcinoma on the trunk

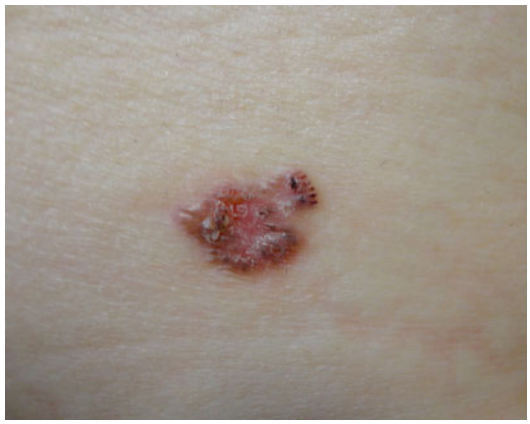

Fig. 9.2 Pigmented basal cell carcinoma

squamous variants emphasize the clinical diversity of BCCs and challenge the physician in making the right diagnosis.

This clinical diversity may be the result of the tumor cells' origin, probably from a stem or progenitor cell of the basal cell layer of the epidermis or the outer root sheath of the hair follicle. This explains the histological diversity as well; histological subtypes include superficial, nodular and micronodular, adenocystic, pigmented, sclerosing, keratotic, basosquamous/metatypical, and infiltrating BCCs and the fibroepithelioma of Pinkus. The primary cellular components of the BCC resemble undifferentiated basal cells of the epidermis and the hair follicle; these cells form palisades at the tumor periphery and are distinctively separated from the adjacent fibroblastic stroma, characteristic for BCC.

The clinical and histological diversity explains the broad spectrum of the clinical course of these skin malignancies, stretching from slowly growing superficial tumors to recurrent and giant ulcerative, infiltrating, and locally destructive tumors with perineural and perivascular involvement. Metastasis, though extremely rare, remains a possibility in the case of giant tumors or basosquamous/metatypical variants.

Diagnosis

Clinical diagnosis should be no problem for the experienced dermatologist in most cases; good lighting, magnification, and dermoscopy could prove really helpful in improving the accuracy of the clinical diagnosis. Still, the variety of histological types with diverse clinical courses and the need for a tumor-adapted optimal treatment emphasize the need for biopsy prior to treatment of high-risk tumors. In an ideal scenario, all BCCs would be biopsied prior to treatment selection; in many cases though, due to various patient-related circumstances such as age, comorbidities, medication, and logistical obstacles, the dermatologist could be justified to skip this diagnostic step. At the time of definite treatment though, e.g., after excision, a pathological specimen should be always submitted for pathological confirmation of the diagnosis. Modern apparative diagnostic methods such as the confocal laser scan microscopy (CLSM) try to bridge the gap between clinical and histological diagnosis and to make possible an individualized diagnostic approach in the cases mentioned above.

In cases of multiple superficial tumors, biopsy (incisional or excisional) of a characteristic tumor should be performed prior to potential selection of non-excisional destructive methods.

Further imaging such as lymph node sonography or CT/MRI should be considered to exclude metastasis in advanced tumors and in the diagnostic approach of locally invasive and destructive tumors.

General Principles of Treatment

A variety of treatment modalities has been successfully involved in the approach of BCC patients in past years, as a result of the diverse clinical appearance and course of the most common cancer, accounting for 5 % of all Medicare cancer costs in the USA. In order to guide physicians through this labyrinth and with the goal of evidence-based treatment selection, a number of national and international guidelines have been developed recently. An algorithm for the therapeutic approach of BCC is depicted on Fig. 9.3.

Though BCCs can be staged following the UICC classification like other skin malignancies (squamous cell carcinoma, malignant melanoma), the lack of lymph node involvement and metastases in most cases make this classification impractical for the choice of treatment.

BCCs are currently assigned as low or high risk of recurrence according to a number of prognostic factors with the goal of a tumor-adapted choice of treatment. Tumor eradication and limited recurrence rates without a disproportionate risk considering the medical background and an acceptable cosmetic outcome for the patient are the key points in the selection of the optimal treatment.

Clinical and pathological correlation prior to treatment selection, meaning a detailed history and clinical examination, including observation and palpation to determine exact location, size, and possible infiltration of adjacent tissues and the consideration of the histological findings actively influence the physician's decision. Diverse criteria such as tumor size, tumor thickness, tumor site, definition of clinical margins, histological subtype, histological features of aggression, recurrence, and immunosuppression make stratification in high and low risk possible (Table 9.1).

The wide range of therapeutic modalities can be divided in surgical, destructive, topical, and systemic treatments and radiotherapy.

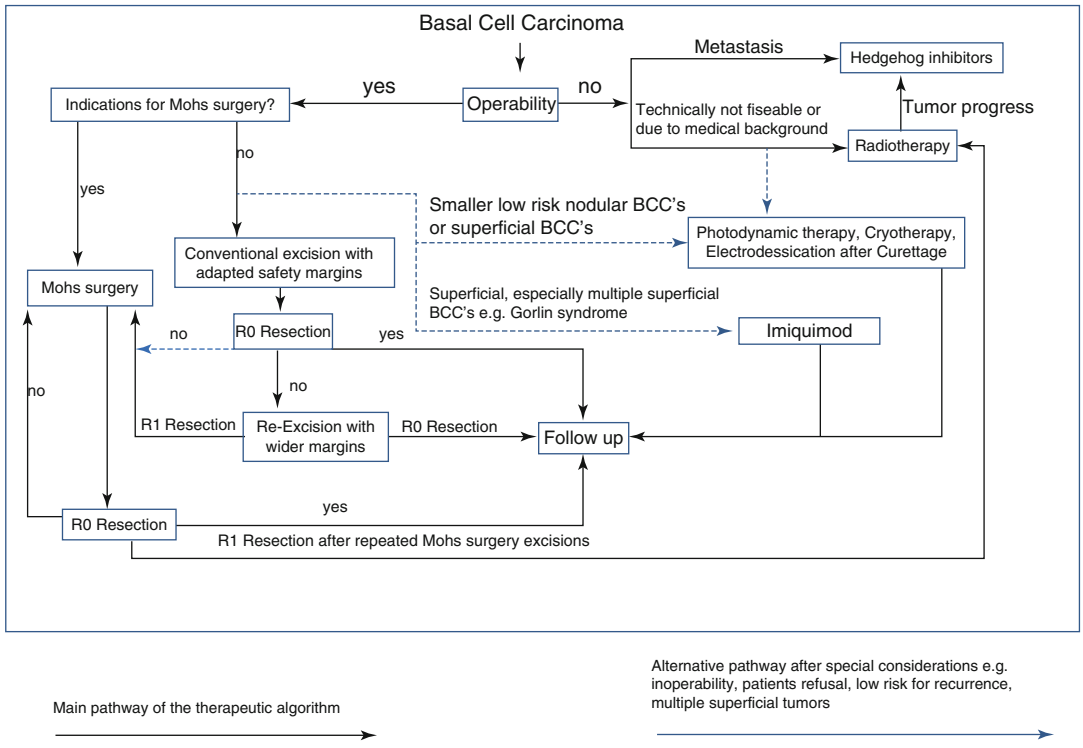

Fig. 9.3 Algorithm for the therapeutic approach of basal cell carcinoma

Table 9.1 High-risk basal cell carcinomas

Tumor size depending on location:
>20 mm in low-risk areas of the trunk and extremities, even smaller tumors in high-risk areas of the head and neck, genitalia, and hands, especially in problematic locations (central face, ears, around the eyes, fingers, and genitalia)
Histological type:
Sclerosing, metatypical, micronodular, infiltrating
Histological findings:
Perineural or vascular involvement, infiltration of adjacent tissues
Poorly defined margins (e.g., *after radiotherapy*)
Recurrence
Immunosuppression

Surgical excision with histological control remains the standard treatment. A conventional excision with respective safety margins should be effective in most primary BCCs. On the other hand, in more demanding clinical cases, Mohs micrographic surgery has superior results in regard to histological verification, recurrence rates, and sparing of healthy tissue. A shave excision with conventional histology plays a role in the therapeutic approach of superficial BCCs, especially on the trunk and extremities. Radiotherapy retains its role in the treatment of selected tumors, as a fair alternative to surgical treatment or in case of inoperability, incomplete excision, or patient's refusal of surgical intervention. Nonsurgical destructive methods without histological control such as cryotherapy, curettage with electrodesiccation, photodynamic treatment (PDT), and topical treatments (immunological therapy with imiquimod 5 %) should be preferably limited to superficial BCCs or in the treatment of BCNS (Gorlin syndrome) patients with multiple tumors. Still, the final choice of treatment should be individualized, taking into consideration comorbidities, age, medication, and disproportionate risk of aggressive surgery or refusal of surgical intervention. The nonsurgical methods mentioned above, alone or in combination, could be reasonable alternatives in selected cases, after individualized risk-benefit evaluation.

Surgical Treatments

Mohs Micrographic Surgery

This demanding technique is generally reserved for high-risk tumors on problematic locations of the face, the hands, and the genitalia, recurrent tumors, or BCCs of aggressive histological subtypes or with aggressive histological findings (Table 9.2). Long-term recurrence rates for primary tumors of less than 1–2 % and for recurrent tumors of less than 6–7 % have been reported. First described by Frederic Mohs (Mohs micrographic surgery, MMS) and further refined in following years, micrographic surgery aims to the total eradication of the tumor mass, leaving no traces of tumor cells behind and thus limiting recurrence rates. Keeping in mind the three-dimensional expansion of subclinical tumor outgrowths, especially in the case of more aggressive subtypes such as the sclerosing BCC, a more subtle histological approach is asked in order to avoid wide excision margins in problematic locations where sparing of healthy tissue can prove of crucial importance for an acceptable cosmetic and functional outcome.

Depending on the facilities of the surgery unit, re-excision and plastic reconstruction of the gap can take place within hours; histology is performed using frozen tissue sections. In centers where the histology takes a number of days for evaluation, the gap is filled with use of alloplastic materials and the excisional material is being embedded in paraffin. Paraffin sections are considered to be of greater accuracy though, compared to frozen tissue section.

Table 9.2 Mohs surgery indications

High-risk tumors in problematic locations of the face, hands, and genitalia where sparing of healthy tissue is essential for a good cosmetic and functional outcome
Aggressive histological variants:
Sclerosing, infiltrating, metatypical, micronodular
Aggressive histological findings:
Perineural or vascular involvement, infiltration of adjacent tissues
Recurrence (e.g., after conventional excision or radiotherapy)
Clinically poorly defined margins

Conventional Excision

A standard surgical excision of primary BCCs is a reliable therapeutic approach with rather limited recurrence rates when performed with tumor-adapted safety margins. Compared to MMS which allows a comprehensive margin examination in a three-dimensional manner, after convention excision only the peripheral and deep surgical margins are examined in paraffin-embedded sections, thus making tumor-adapted safety margins necessary to limit the likelihood of residual tumor and subsequent recurrence. The cosmetic and functional outcome is in most cases good. Small tumors at any site as well as bigger tumors (>20 mm) on trunk and extremities are good candidates for conventional surgical excision. The safety margins vary and depend on tumor size and histological subtypes, tumors bigger than 20 mm or of high-risk histological subtypes (e.g., sclerosing, infiltrating, metatypical) requiring wider safety margins of clinically healthy tissue excised in order to achieve an acceptable 5 % probability of residual tumor compared to 4–5 mm safety margins for tumors smaller than 20 mm or of nonaggressive histological subtypes such as nodular or superficial BCCs. Interestingly enough there is a 15 % chance of R1 resection after conventional excision with 3 mm safety margins of even low-risk tumors. Not all microscopically proven residual tumors would recur though; a safety margin of 3–5 mm is thus currently recommended for low-risk tumors. After conventional excision of aggressive histological variants with 5 mm safety margins, the probability of residual tumor is considerable (18 %) though, requiring wider safety margins (13–15 mm, 5 % likelihood of residual tumor) and highlighting the superiority of MMS in cases where sparing of healthy tissue is essential for a good cosmetic or functional outcome.

In case of R1 resection with histologically proven residual tumor without any clinically seen tumor rests, there is indeed, as mentioned above, enough evidence that a clinical recurrence of the tumor is not obligatory. In such cases wait and see in the context of an individualized follow-up could be a reasonable approach. Still, when dealing with high-risk tumors or with tumors with residual involvement of the deep safety margin, re-treatment should be always performed, either as re-excision with wider safety margins, MMS, or even postoperative radiotherapy.

Shave Excision with Conventional Histology

Tangential (shave) excision with conventional histology may prove of value in cases of multiple superficial BCCs on trunk or extremities, when the burden of multiple conventional surgical interventions can cause more problems than the lesion itself, thus making a more conservative surgical approach coupled with higher recurrence rates reasonable.

The Role of Radiotherapy

Radiotherapy retains its role in the nonsurgical treatment of BCC. Effective in the treatment of primary BCCs, it can be considered a fair alternative to conventional excision, especially in the case of small tumors or patients unwilling or not able to undergo surgery. Postoperatively (R1 or R2 resection) radiotherapy could be used as an adjuvant treatment. Scaring and radiodystrophy, altered pigmentation, and telangiectasia are the most common side effects. Lack of margin control and increased risk for future cancers should also be taken into consideration. In genetic disorders with predisposition to skin cancer, such as Gorlin syndrome or xeroderma pigmentosum, radiotherapy is contraindicated.

In order to improve tolerability and cosmetic outcome, fractioned treatment regiments have been developed, limited though to major medical centers. The total dose of 50–70 Gy depending on site and tumor size is being fractioned in 2–5 Gy single doses. When used as an adjuvant treatment postoperatively, more limited total doses of 40 Gy (R1) and 60 Gy (R2) are used.

Single-fraction strategies could be still considered in the case of elderly patients ready to accept a poorer cosmetic outcome in order to avoid repeated hospital visits and a prolonged course of therapy.

Destructive Treatments

Cryosurgery

Cryotherapy with liquid nitrogen (−196 °C) using either a spray or the contact method aims to deep destruction of tumor and surrounding tissue without histological control. Cryotherapy could be generally recommended for small superficial BCCs, especially of the eyelid, or in selected clinical situations such as elderly patients where better established methods with a higher evidence level are not feasible or are being refused from the patient. Indeed in expert hands cryotherapy could also have a role in the treatment of more advanced lesions, such as nodular BCCs, either alone or in combination with other methods, e.g., after curettage or in combination with modified imiquimod protocols.

Generally double-freeze/thaw cycles are recommended, to the adverse reactions count pain, edema and blister formation, and hyper- or hypopigmentation.

Photodynamic Treatment (PDT)

Photodynamic treatment with methyl aminolevulinate (MAL) is another efficient treatment of superficial BCCs or of patients with BCNS, the indications for its use overlapping with those for cryotherapy. After application the photosensitizing active component is localized in cancer tissue or other diseased cells in case of inflammatory diseases, and the use of energy-rich narrow-length light source results in accumulation of protoporphyrin IX, causing an iatrogenic porphyria, production of free radicals, and selective tumor destruction. When treating BCCs with increased tumor thickness, there is higher rate of residual tumor after PDT treatment, resulting to higher recurrence rates. Considering the general medical background of selected patient groups though, PDT after non-painful superficial curette or even CO_2 laser, aiming to tumor debulking prior to PDT application, could be a reasonable alternative to more aggressive surgery in the treatment of some low-risk nodular BCCs as well.

PDT results generally to good cosmetic outcomes, probably better compared to other non-surgical destructive techniques such as cryotherapy. Some pain and erythema is experienced from the majority of patients though, in some cases even inflammation with crust formation. Supportive measures such as use of a fan or local anesthesia could alleviate pain and improve patients' compliance during treatment.

Curettage and Cautery

Another cost-effective and, in some countries, widely used technique for the treatment of low-risk BCCs is curettage alone or with use of electrodessication. Smaller nodular or superficial BCCs on non-critical locations could be easily treated, the rather high rate of residual tumor cells not directly correlating to recurrence rates, unidentified wound-healing procedures suggested of being possibly responsible for that. On the other hand, when dealing with high-risk tumors, the technique is contraindicated due to very high risk of tumor recurrence. Scarring, hyperpigmentation, and hypopigmentation are the most common side effects.

CO_2 Laser

Some authors report encouraging results with acceptable cosmetic outcomes when treating multiple superficial BCCs with CO_2 laser. New, more elaborate CO_2 laser devices in past years with new functions as the ultrapulse modus have resulted to better cosmetic results than in previous years, postoperative pain and complications

being probably more limited when compared to more established thermal destructive techniques for the treatment of low-risk tumors. Due to lack of sufficient number of respective clinical trials, the recommendation strength and the evidence level remain low so far though.

Topical Treatments

Imiquimod

Imiquimod, an innovative topical immune response modifier, widely used nowadays in the treatment of actinic keratoses (in situ squamous cell carcinoma), has revolutionized the treatment of field cancerization. A 6-week treatment strategy, five times a week, is the current recommendation in Europe for the treatment of superficial BCCs, especially multiple BCCs. Imiquimod binds to Toll-like receptor 7 on inflammatory cells such as the Langerhans cells of the epidermis, dendritic cells, and monocytes and induces cytokine secretion (IFN-α and TNF-α), resulting to a local immune response and eradication of the cancer cells. Sustained clearance rates of 80 % after treatment are reported with the protocol mentioned above. There is evidence that BCCs with a tumor thickness >0.40 mm are more likely to recur, thus limiting its use to the treatment of superficial BCCs. Some authors report acceptable results in the treatment of smaller nodular tumors as well, especially after curettage or when combining with cryotherapy. These treatment strategies could be eventually discussed in selected case, if surgery is refused or contraindicated due to patient-related limitations. Imiquimod, along with cryotherapy, topical FU, and PDT, is also a reliable alternative to surgery in the treatment of patients with BCNS, dealing with multiple eruptive tumors constantly.

Excessive topical inflammation during treatment or systemic flu-like symptoms could affect patient's compliance and result to disruption of treatment. In spite of the frequent inflammation of treated lesions, they usually heal well, leaving no scars but a good cosmetic result instead.

Systemic Treatments

Chemotherapy

For the therapeutic approach of uncontrolled or metastatic disease, many chemotherapeutic protocols have been proposed so far, those based on cisplatin appearing to be the most efficient with relatively high remission rates; unfortunately enough remission in most cases does not last longer than some months.

Hedgehog Inhibitors

Understanding of the molecular biology of BCC and of the role of the sonic hedgehog pathway activation has been a major breakthrough, making possible in recent years the development of elaborate targeted treatments inhibiting the pathway activation. Vismodegib is the first synthetic SMO inhibitor to complete early clinical evaluation successfully (Phase I); a dose of 150 mg/day was recommended as Phase II dose, and based on these data, FDA approved in January 2012 its use for the treatment of advanced basal cell carcinoma, clinically uncontrolled or metastasized, in the context of an early access program. Since about 80–90 % of BCCs harbor PCTH mutations leading to SMO activation and another 10 % demonstrate SMO mutations, the selected use of an SMO inhibitor like vismodegib appears reasonable in either case. Thus treatment can be initiated without any genetic screening required, compared to malignant melanoma where B-Raf mutations are seen only in about 60 % of melanoma patients. Elevated levels of Gli1, a downstream marker of the hedgehog pathway, have confirmed the role of the pathway activation in the pathogenesis of BCCs. The most common adverse reactions include alopecia and dysgeusia, both probably directly related to inhibition of the pathway, since in related tissues the hedgehog pathway seems to retain some role after the embryogenesis. Muscle spasms, weight loss, nausea, and diarrhea are further clinical signs of vismodegib-related toxicity which could lead to treatment discontinuation. A median progression-free survival of 9, 6 months after treatment discontinuation, has been reported.

The drug-related adverse effects make the feasibility of a wider prophylactic use of vismodegib in BCNS patients for the prevention of new BCCs questionable. Another great challenge could constitute the occurrence of drug resistance, already reported in patients with medulloblastoma where the sonic hedgehog pathway also plays a role.

Currently new hedgehog inhibitors are tested. Limiting toxicity and thus optimizing patient compliance may play a key role in the wider use of hedgehog inhibitors. Novel therapeutic agents targeting not only SMO but other points downwards in the pathway cascade as well may be developed, opening new horizons not only in the treatment of advanced BCC but also offering new systemic therapeutic approaches in the treatment of multiple BCCs and of patients with the Gorlin syndrome in the years to come.

Follow-Up

Follow-up for a period of at least 3 years is generally recommended after diagnosis and treatment of any new BCC, not only due to the considerable recurrence rates (recurrent disease can present even after 5–10 years) but considering the possibility of new BCCs as well. Indeed there is a tenfold increase compared to the general population. Patients with high-risk BCCs should be clinically assessed twice yearly; imaging techniques such as ultrasound or CT/MRI could be used if required to exclude metastasis. For patients with low-risk BCCs, a yearly clinical examination should be enough. In any case follow-up strategies should be individualized; in selected patient groups such as the immune compromised or patients with genetic predisposition to BCC formation, a lifetime follow-up should be advised.

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Bowen's Disease

10

Mirna Situm

Abbreviations

5-FU	5-Fluorouracil
ALA	5-Aminolevulinic acid
BD	Bowen's disease
HPV	Human papillomavirus
MAL	Methyl aminolevulinate
PDT	Photodynamic therapy
SCC	Squamous cell carcinoma

Key Points

- Bowen's disease (BD) is an intraepidermal squamous cell carcinoma (SCC) with a tendency for progressive growth and low invasive risk, characterized by slowly growing, erythematous plaque with an irregular border, surface scaling and crusting.
- The aetiology of BD is multifactorial including irradiation, carcinogens (e.g. arsenic), immunosuppression and viral infection.
- The age and sun-exposed body distribution of BD suggest the importance of chronic sun damage as a factor in the carcinogenesis of BD.
- The goal of therapy for Bowen's disease is to reduce morbidity and to prevent complications.
- The choice of treatment should be guided by its efficacy, location and size of BD, number of lesions, availability of the therapy, the clinician's expertise, patient's age, immune status, concomitant medication, comorbidities and patient compliance and, not less important, cosmetic outcome of the treatment.
- There is also an increasing choice of home-applied treatments today, with less treatment-related morbidities.
- Sun avoidance is strongly recommended for all patients with skin tumours.

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Definition and Epidemiology

Bowen's disease (BD) is an intraepidermal squamous cell carcinoma (SCC) with a tendency for progressive growth and low invasive

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_10, © Springer-Verlag Berlin Heidelberg 2015

risk, characterized by slowly growing, erythematous plaque with an irregular border, surface scaling and crusting. The risk of progression to invasive SCC is 3–5 % for extragenital lesions and 10 % for genital lesions. BD is very common in the Caucasian population with an incidence of 14 per 100,000 in some populations. The peak age group for BD is the seventh decade. The ratio of Bowen's disease is approximately equal between males and females. BD is more commonly found on the head and neck of men and on the lower limbs and cheeks of women. BD is usually a solitary lesion, but in 10–20 % of patients, it occurs at multiple sites.

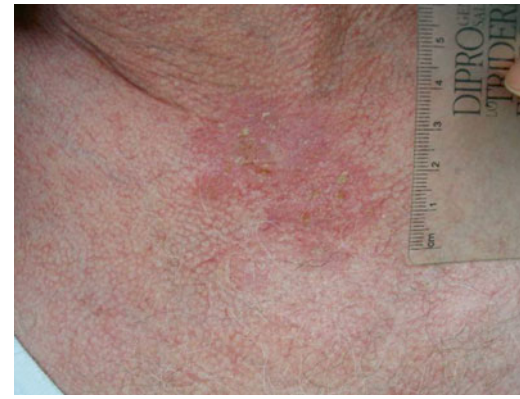

Fig. 10.1 Bowen's disease on the anterior neck

Basic Concepts of Pathogenesis

The aetiology of BD is multifactorial including irradiation, carcinogens (e.g. arsenic), immunosuppression and viral infection. The age and sun-exposed body distribution of BD suggest the importance of chronic sun damage as a factor in the carcinogenesis of BD. Photochemotherapy and radiotherapy are also important irradiation aetiologic factors. Arsenic exposure occurs after a time lag of 10 years. The main sources of arsenic exposure in the past included Fowler solution, a medication formerly used to treat psoriasis, and Gay solution, formerly used to treat asthma, contaminated well water and certain pesticides. Agricultural workers may be exposed to arsenic salts used as fungicide, weedkiller or pesticide. Human papillomavirus (HPV) type 16 is the most common subtype isolated from lesions of Bowen's disease, although other subtypes have also been found (e.g. type 18, 31, 33, 51). Aetiological involvement of HPV has strong therapeutic implications, as HPV-induced BD is responsive to agents that have combined antiviral and antitumour effect. Immunosuppressed patients (e.g. renal transplant patients, AIDS) with BD are more likely to have multiple tumours and more aggressive tumours. Therefore, educating immunosuppressed patients about sun exposure is very important. Other possible causes include genetic factors, trauma, chronic injury or dermatoses.

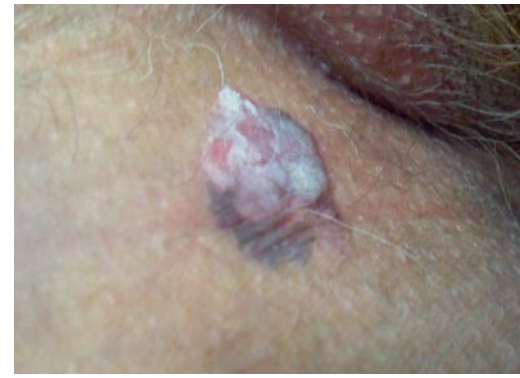

Fig. 10.2 Pigmented Bowen's disease on the right groin

Clinical Presentation

Patients often present with an asymptomatic, slowly growing, erythematous, well-demarcated scaly patch or plaque most frequently occurring on the lower legs but can occur anywhere on the skin or mucosal surfaces (Fig. 10.1). The head, neck and extremities are the most commonly affected anatomic locations in men, while the lower limbs and cheeks are most commonly affected in women. The initial lesion is a small, red, scaly, slightly raised area that gradually enlarges in irregular fashion. The scales can easily be removed from the surface, without bleeding. The surface is usually flat but may become hyperkeratotic or crusted. Ulceration is a sign of invasive carcinoma, usually arising many years after the initial

lesion. Lesions vary in size from a few millimetres to several centimetres in diameter. Lesions are rarely pigmented (Fig. 10.2), especially in the genital region and the nails. Bowen's disease may also occur on mucous membranes. When it arises on the glans penis, it is known as erythroplasia of Queyrat and is characterized by moist, velvety or smooth plaques. BD presents as a single lesion in two-thirds of cases. Multiple lesions are more common in immunosuppressed patients.

Diagnosis

The diagnosis of BD is confirmed by skin biopsy. It is important to sample many areas of larger lesions to exclude evidence of invasion. The normal epidermis is replaced by abnormal keratinocytes, which show disordered differentiation and loss of epithelial polarity. There is a disturbance of epidermal organization, and cells keratinize prematurely losing their intercellular connections. There are a variable acanthosis and thickened interpapillary ridges but intact dermal-epidermal junction. The atypical cells have large, hyperchromatic nuclei. Vacuolization, individually keratinizing cells and multinucleated cells are present in the epidermis. Large pale keratinocytes with abundant ground-glass cytoplasm, so-called pagetoid cells, are often distributed haphazardly throughout the epidermis. Multiple mitotic figures are usually visible. The surface scale is formed by thickened, loose, parakeratotic cells. There is a dense inflammatory infiltrate in the papillary dermis. Although the basal cell layer is intact, extension of keratinocyte atypia down the follicular epithelium is seen (Fig. 10.3a, b).

Bowen's disease must be distinguished from papulosquamous dermatoses like lichen simplex and psoriasis. The lack of improvement to topical steroids is suggestive of Bowen's disease. Malignant tumours like superficial basal cell carcinoma or premalignant lesions like actinic keratosis may also mimic BD. The diagnosis of BD is confirmed by pathological examination of lesional skin biopsy. Complete skin examination must be performed in patients with BD, especially of sun-exposed skin, because of higher incidence of nonmelanoma skin cancer in these patients. Dermoscopy has become an integrative part of the clinical examination of skin tumours and premalignant lesions like actinic keratosis and Bowen's disease.

Differential Diagnosis

Differential diagnosis of well-demarcated pink-red plaque(s) of BD includes nummular eczema, contact eczema, psoriasis, lichen planus, seborrheic keratosis, tinea corporis, actinic keratosis, verruca vulgaris, condyloma acuminatum, superficial basal cell carcinoma, squamous cell carcinoma, melanoma, Merkel cell carcinoma and Paget's disease.

General Principles of Treatment

The history of Bowen's disease and other intraepithelial neoplasia is not yet completely understood; therefore it is difficult to determine how aggressive treatment should be. The age group, number and size of lesions and affected site(s) may all influence therapeutic choice. In the elderly patients with slow progressive thin lesions on the lower leg where healing is poor, there is an argument for observation rather than intervention. Therapeutic aim should be to avoid mutilating surgery. Most treatments have a recurrence risk; therefore follow-up at 6–12 months is recommended. The shorter follow-up is recommended with history of past recurrence, presence of multiple lesions and immunosuppression.

5-Fluorouracil

Topical chemotherapy with 5-fluorouracil (5-FU) is used for the treatment of single or few small lesions at good healing sites like the face. It should be avoided for lesions at poor healing sites and for perianal lesions, due to a higher recurrence

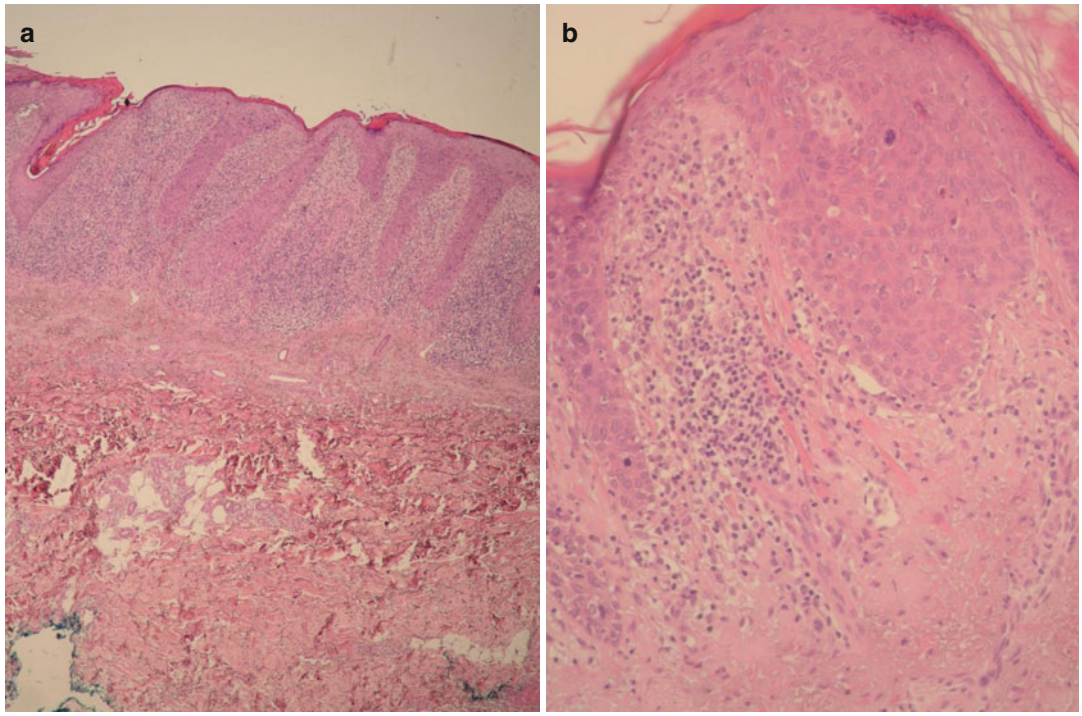

Fig. 10.3 (**a**) Bowen's disease on the left wrist (40×). (**b**) Bowen's disease on the left wrist (200×)

rate of perianal BD treated with 5-FU cream. Five percent 5-FU cream is applied once or twice daily for a period between 1 week and 2 months, and the treatment is repeated if required. Efficacy is increased by occlusion or iontophoresis. In erythroplasia of Queyrat, application of 5 % 5-FU cream twice daily for 4–5 weeks is recommended, but irritation and inflammation usually limit the treatment.

Imiquimod

Topical 5 % imiquimod cream should be used for the treatment of small and large, single lesions on poor healing sites, as well as on good healing sites and for penile lesions. It is not licensed for BD treatment in many countries. It has both anti-HPV and antitumour effects and is therefore useful for HPV- and non-HPV-associated BD. The recommended duration of treatment is 16 weeks and the dose varies from once weekly to five times per week. Five percent imiquimod cream is also beneficial in the treatment of BD in immunosuppressed patients. It can be used in combination with topical 5 % 5-FU. There is evidence that cytokines induced by imiquimod improve the therapeutic efficacy of 5 % 5-FU in Bowen's disease (Smith et al. 2001a, 2001b).

Diclofenac

Diclofenac 3 % gel has been successfully used in the treatment of actinic keratosis. There are promising data of BD successfully treated with 3 % diclofenac gel once or twice daily for 8 weeks (Dawe et al. 2005). The treatment was well tolerated with mild inflammation after 6 weeks and mild side effects like itching and dryness. Complete clinical and histological clearance was proven by biopsies taken 4 weeks after end of treatment (Patel and Stockfleth 2007). Given its mechanism of action, diclofenac 3 % gel may have potential to halt the progression

of actinic keratoses (AKs) in the setting of field cancerization and BD. These promising data have to be proven in randomized controlled trials, and recurrence rates in long-term follow-up have to be investigated.

Cryotherapy

The results of BD treatment with cryotherapy depend on the used techniques and regimens. Liquid nitrogen cryotherapy is used in single freeze-thaw cycle (FTC) of 30 s or two FTCs of 20 s with a thaw period. These regimens cause discomfort and may cause ulceration on the lower leg. Cryotherapy is recommended for the treatment of multiple BD on good healing sites, facial BD as well as digital, penile and small, single lesions on poor healing sites. Cryotherapy has good success rate with adequate technique. It is less effective than curettage and PDT but also less expensive and less time consuming.

Curettage with Cautery/ Electrocautery

Curettage is the treatment of choice for small, single or few lesions on good or poor healing sites and facial lesions. It should be avoided for the treatment of perianal BD and large lesions on good or poor healing sites. Cure rates ranged from 81 % for curettage up to 98 % for curettage and cautery with a follow-up of 2.5–4 years. Curettage and cautery are a safe and effective therapy of BD with a very good cost-benefit analysis.

Excision

Surgical excision of BD is the treatment of choice for small and single lesions, as well as digital and perianal BD. The main advantage is the securing of histological free excision margins. Mohs micrographic surgery is the recommended treatment for digital and genital BD, the sites of the body where tissue-sparing surgery is necessary (e.g. fingers and nail unit, penis). Mohs micrographic surgery uses the removal of skin cancers with very small margins of normal tissue followed by frozen section examination of nearly 100 % of the tissue margin. It is also an excellent method for larger lesions, poorly demarcated lesions and recurrent lesions on the head and neck.

Photodynamic Therapy (PDT)

Photodynamic therapy involves the introduction of a photosensitizing agent into the body, which is retained preferentially by the tumour cells. PDT is based on the combination of light and light-sensitive agents (e.g. porphyrins) in the presence of oxygen. The energy of photons is absorbed by porphyrins and then transferred to surrounding oxygen molecules resulting in formation of singlet oxygen and free radicals responsible for cell death. Most commonly used topical photosensitizers are 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). For the production and accumulation of these photoactive porphyrins, a sufficient period of time is necessary before the light activation, for MAL 3 h, for ALA 4–18 h. PDT is well suited for single or multiple large lesions and poor healing sites. The adverse effects include local side effects, such as burning and stinging, and, rarely, erosions, ulceration and hyperpigmentation or hypopigmentation. PDT has been particularly useful in immunosuppressed subjects (e.g. transplant recipients) because of the possibility for repeated treatment of large lesional areas.

Radiotherapy

Different radiotherapy techniques like external beam radiotherapy, grenz rays and radioactive skin patches have been used in the treatment of BD with reported cure rates between 94 and 100 %. Radiation therapy should be considered for poor surgical candidates or patients with multiple lesions. It should be avoided for lower extremity lesions due to impaired healing.

Laser

Lasers have been used to treat lesions at difficult sites, such as the fingers and genitalia. Case reports and series have shown a benefit of using argon, carbon dioxide and Nd:YAG lasers in the treatment of some BD lesions. There are also reported laser treatment failures or progression to invasive SCC of lower leg lesions after 100 % healing at 2 months and complete response at 6 months. Therefore, CO_2 laser can be used for penile or digital BD, but there is limited data of recurrence rates (Table 10.1).

Other Treatments

Acitretin

Retinoids have been used alone or in combination with 5-FU in anecdotal cases, but the relative merits of each are unclear in the combination approach. The other patient did not tolerate the acitretin and no improvement was seen in BD lesions.

General Therapy Guidelines

The goal of therapy for Bowen's disease is to reduce morbidity and to prevent complications. The choice of treatment should be guided by its efficacy, location and size of BD, number of lesions, availability of the therapy, the clinician's expertise, patient's age, immune status, concomitant medication, comorbidities and patient compliance and not less important, cosmetic outcome of the treatment. There is also an increasing choice of home-applied treatments today, with less treatment-related morbidities. Sun avoidance is strongly recommended for all patients with skin tumours, and due to a 10 % recurrence rate with most treatment options, patients with a history of Bowen's disease or other skin cancers should be evaluated with a total body skin examination every 6–12 months.

Table 10.1 Summary of treatment options for Bowen's disease

	Application	Treatment duration	Advantages	Disadvantages	Lesion characteristics
5-Fluorouracil 5 % cream	Once or twice daily	1–8 weeks	High cure rates	Irritant	Small, single/few on poor healing site
Topical imiquimod 5 % cream	Once daily	Up to 16 weeks	High cure rates	Expensive	Large, single/poor healing site
Cryotherapy	Single freeze-thaw cycle	30 s	Low recurrences	Slow healing, painful	Facial, multiple, good healing site
Curettage		Single treatment	Cheap, high cure rates	Morbidity	Small, single, few on good and poor healing site
Excision		Single treatment	Cheap, high cure rates	Morbidity on lower leg wounds	Perianal, digital, small, single/few on poor healing site
PDT	Topical PDT using topical 5-ALA	One or two treatments	High cure rates	Expensive, painful	Large or small, single, poor healing site
Radiotherapy	External beam X-radiation	Single/repeated	High cure rates	Acute radiation reactions	Perianal, penile
Laser	CO_2 laser	Single/repeated	Penile lesions	Depth of treatment, progression to SCC	Penile, digital

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Bullous Pemphigoid

11

Panagiotis G. Stavropoulos and Eleni Remoudaki

Key Points

- Bullous pemphigoid is considered the most common autoimmune blistering disease.
- The target antigens are the BP antigens with molecular weights of 230 and 180 kDa, BPAG1 and BPAG2, respectively.
- Treatment can be divided into three phases: initial control, consolidation, and withdrawal.
- Severity, age of patient, and presence of underlying disease must be considered in determining therapeutic agents and doses.

Definition and Epidemiology

Bullous pemphigoid (BP) is an acquired, non-scarring, subepidermal blistering disease, usually occurring in the elderly, but may rarely affect children and younger adults. BP is considered the most common autoimmune blistering disease. Women and men are equally affected and no racial or geographical predilection is recognized. There is no known specific HLA correlation. BP has been reported in association with a variety of autoimmune diseases, including systemic lupus erythematosus, diabetes mellitus, lichen planus, rheumatoid arthritis, Hashimoto thyroiditis, pemphigus vulgaris, psoriasis, and neurological disorders, particularly dementia and Parkinson's disease. There have been many reports of BP associated with malignancy, although there is much controversy over this association.

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Basic Concepts of Pathogenesis

BP is an autoimmune skin disease and the cause of the autoantibody production remains obscure. The target antigens are the BP antigens with molecular weights of 230 and 180 kDa, BPAG1 and BPAG2, respectively. BP180 is a type II transmembrane protein that spans the lamina lucida and projects into the lamina densa of the epidermal basement membrane. Furthermore the 230-kDa protein called BP230, which was originally identified as the major antigen of BP, is a cytoplasmic component of hemidesmosomes that belongs to the plakin family; it promotes the linkage of keratin intermediate filaments to hemidesmosomes. Antibody binding to BP antigen is postulated to be the initial step in blister formation. Fixation of immunoglobulin G to the basement membrane zone activates the complement cascade (mainly C3, C5a), which causes

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_11, © Springer-Verlag Berlin Heidelberg 2015

chemotaxis of leucocytes and degranulation of mast cells. Eosinophils and neutrophils are recruited by mast cell-produced factors to the basement membrane zone, where they release tissue-destructive enzymes (proteases) resulting in dermal-epidermal separation. Several drugs have been associated with the onset of BP including furosemide, spironolactone, neuroleptics, sulfasalazine, penicillamine, and captopril. Local irritation and damage to the skin have been all implicated in the induction of disease. Ultraviolet (UV) light or psoralen and UVA (photochemotherapy) and other physical agents including thermal burns, wounds skin grafts, and radiotherapy have been reported to induce BP in normal skin.

Clinical Presentation

Urticarial and figured erythemas are common prodromal eruptions in BP, by weeks or months. In some cases, bullae may not become clinically apparent. Subsequently, large tense blisters arise with a base of normal or erythematous skin (Fig. 11.1). Grouping may be present and lower abdomen, inner thighs, groin, axillae, and flexural aspects of the forearms and the legs are sites of predilection for the lesions. However, localized forms of BP are not uncommon. Pemphigoid nodularis, vegetans, and dyshidrosiform represent some clinical variants of "classical" BP. Nikolsky's sign is negative and mucosal lesions are usually clinically insignificant, consisting of small tense bullae in the oropharynx. The natural history of BP is that of persistent disease with eventual remission occurring within 5 years in the majority of patients. Prognosis is considered fair, but BP is a potentially fatal disease particularly in the elderly, where health may already be fragile.

Diagnosis and Differential Diagnosis

A subepidermal split and a mixed dermal infiltrate of numerous eosinophils, some neutrophils, and lymphocytes are found in biopsy specimens. IgG and/or C3 is deposited along the basement membrane zone in virtually all active cases of BP (direct immunofluorescence), and about 70–80 % of patients are found to have circulation IgG to the

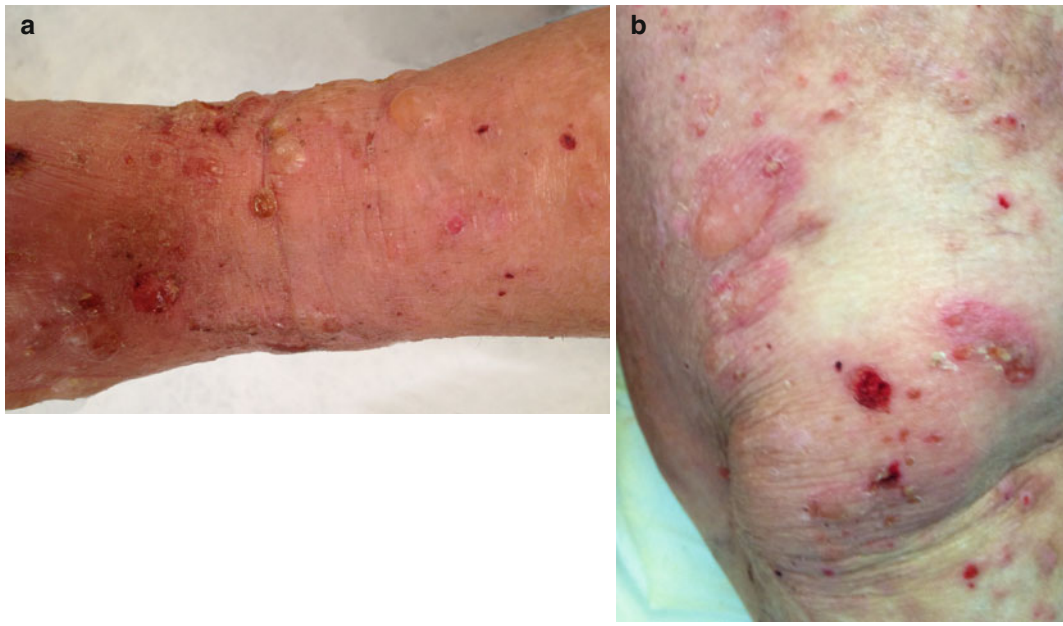


Fig. 11.1 Typical clinical pictures of BP, with tense blisters, erosions, and crusts

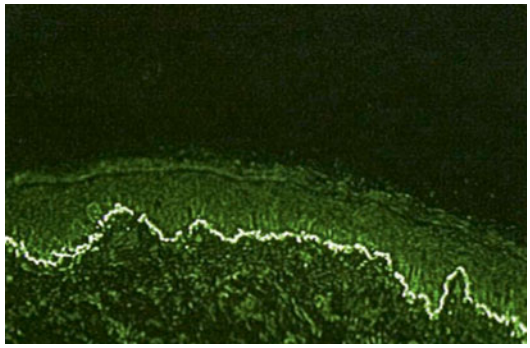


Fig. 11.2 Direct immunofluorescence findings in bullous pemphigoid. Linear deposition of mainly IgG and C3 along the epidermal junction

basement membrane zone of normal stratified squamous epithelia (indirect immunofluorescence) (Fig. 11.2). When 1 mol/L sodium chloride split skin is used as the substrate, circulating autoantibodies from the patient's serum deposit on the roof side of the artificial blister at the dermoepidermal junction (DEJ). In occasional cases, these diagnostic techniques will require supplementation with immunoelectron microscopy, immunoblotting, and immunoprecipitation (Table 11.1).

Table 11.1 Differential diagnosis of bullous pemphigoid

Pemphigoid gestationis	Rare disease of pregnancy and postpartum period
Cicatricial pemphigoid	Scarring autoimmune bullous disease primarily affecting mucosal surfaces
Epidermolysis bullosa acquisita	Trauma-induced blisters healing with scars, different target antigen
Dermatitis herpetiformis	Young adults, pruritic papules and vesicles symmetrically distributed over extensor surfaces. Enteropathy (80 % of cases). HLA-B8-DR3
Linear IgA dermatosis	Younger age group, linear IgA deposition at basement membrane zone (direct immunofluorescence)
Erythema multiforme (bullous)	Typical distribution of lesions, different immunofluorescence findings
Bullous systemic lupus erythematosus	Lesions distributed on sun-exposed areas, subepidermal blisters with neutrophils, different immunofluorescence findings
Other disorders	Porphyria cutanea tarda, drug reactions, insect bite reaction, bullous lichen planus, etc.

General Principles of Treatment

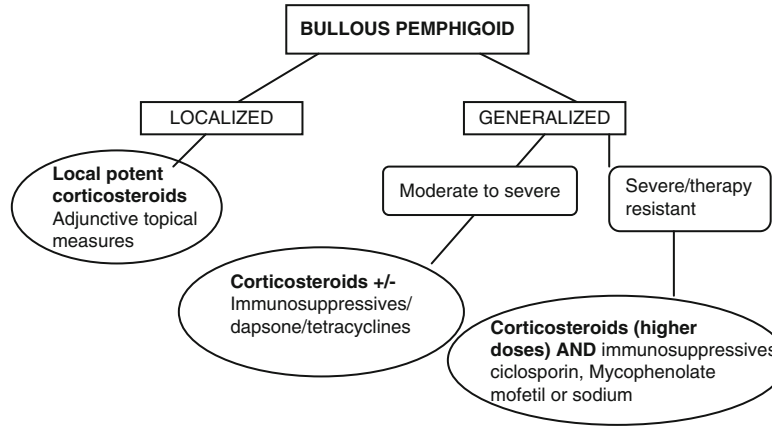
- Treatment can be divided into three phases: initial control, consolidation, and withdrawal. The first objective is stopping or significantly reducing new blister formation. Therapy is introduced and adjusted upward as required and slowly reduced to the lowest possible level while maintaining a low level of disease activity. Complete withdrawal of therapy is carried out if possible.
- The severity of disease, age of patient, and presence of underlying disease (diabetes mellitus, hypertension, peptic ulceration, osteoporosis, malignancy) must be considered in determining therapeutic agents and doses.
- Localized disease may initially be managed with local very potent steroids and adjunctive measures.
- Moderate (20–60 lesions) to severe (more than 60 lesions) disease will usually require systemic steroids in moderate doses alone or in combination with immunosuppressives, dapsone, or tetracyclines.
- Severe therapy-resistant disease requires systemic steroids in higher doses and immunosuppressives, cyclosporin, plasmapheresis, or γ-globulin therapy as adjunctive agents.
- Immunosuppressive agents, due to their delayed onset of action (4–8 weeks), can be started at the same time as systemic steroids. Thus, steroids are used to achieve initial control then tapered at the time when the immunosuppressives are taking effect.

Recommended Therapies (Table 11.2)

Supportive care and adjuvant therapy

Supportive care is essential in cases in which widespread skin denudation and immobility render the patient susceptible to fluid loss, electrolyte imbalance, infection, and thromboembolic events. A bed that spreads pressure is useful in severe disease. The blisters caused by widespread cutaneous and mucosal erosive disease may

Table 11.2 Algorithm of recommended therapies



require frequent oral analgesics, and sedating antihistamines are frequently given in the initial stages of BP to reduce pruritus. Diluted saline or potassium permanganate compresses and baths assist in keeping the lesions clean. Gastric protection, usually with a proton pump inhibitor, should be considered in patients receiving systemic steroids. Calcium supplementations, vitamin D, and bisphosphonate are recommended and have been shown to be effective in preserving bone density in patients receiving systemic corticosteroids, especially in postmenopausal women and men over 50 years.

Topical Therapy

Topical steroids should be considered first-line treatment in localized or moderate BP, and they are also extremely useful adjuvants to systemic therapy when disease is more severe. Very potent topical steroids (clobetasol propionate 0.05 % twice daily) are usually required initially, with tapering to lower potency agents. However, their use in extensive disease may be associated with systemic absorption and adverse events. Triamcinolone acetonide 3.10 mg/mL may be injected weekly to resistant lesions. In the event of secondary infection, topical antibacterial agents may be safely applied. Oral hygiene should be maintained with antiseptic mouthwashes between meals. A soft diet including pureed food and liquid protein supplements is best during active disease. Severe pain may be treated with topical anesthesia (lidocaine (lignocaine) 2 % viscous solution) particularly before meals. Tetracycline mouthwashes (250 mg dissolved in 50 mL of water) may be used to treat oral mucosa infections.

Systemic Corticosteroids

These are most useful drugs in the treatment of BP, rapidly inducing remission in the majority of patients. Our experience and most large series show that the majority of patients respond to 40-80 mg daily of prednisone or prednisolone and it is only rarely necessary to exceed 100 mg daily. In general, doses of prednisolone 0.75–1.0 mg/kg daily in widespread BP are effective within 1–4 weeks in about 60–90 % of the patients. However, depending on the severity of the disease, the doses can be adjusted. For patients with severe involvement, doses of 0.75–1 mg/kg are recommended and lower doses of 0.5 mg/kg for moderate disease and 0.3 mg/kg for mild or localized disease, respectively. Healing of existing lesions and cessation of new blister formation reflect a positive response to therapy. Once the disease is under control, the steroid dose should be tapered slowly and eventually changed to an alternate-day regimen to minimize the steroid side effects. The duration of systemic steroid treatment is likely to be many months and sometimes indefinite. Corticosteroid pulse therapy, in which patients are given 1 g of methylprednisolone intravenously for three consecutive days, may be given for resistant disease. Oral steroids must then be given as maintenance therapy.

However, caution must be recommended in utilizing this type of therapy, particularly concerning the effects of prolonged systemic steroid therapy which are numerous: diabetes mellitus, hypertension, gastrointestinal bleeding, osteoporosis, cataracts, and increased susceptibility to bacterial, fungal, and viral infections. Immunosuppressive and metabolic adverse events are considered dose dependent. Appropriate monitoring includes urinalysis for glucose, fluid imbalance, blood pressure, and body weight. Routine biochemistry may be done at weekly or twice weekly intervals in the first instance, dropping to monthly thereafter. Osteoporosis profile tests and ophthalmological examination for cataracts should be performed as a baseline and thereafter every 6 months, particularly in postmenopausal women.

Immunosuppressive Agents

Azathioprine

This drug is most commonly employed in combination with steroids and sometimes for maintenance following steroid withdrawal. The usual dose is 50–100 mg daily. Azathioprine dose can be optimized with regard to myelosuppression risk by prior assay of thiopurine methyltransferase (TPMT). However a normal TMPT lever does not totally preclude myelotoxicity. The usual dose of azathioprine use, the steroid maintenance dose, may be significantly reduced and in some instances discontinued. Side effects of azathioprine include dose-dependent bone marrow depression, idiopathic hepatitis, increased susceptibility to infection, teratogenicity, and increased risk of internal and cutaneous liver function tests and urinalysis. The full blood count and renal and liver function tests are repeated weekly for 8 weeks and then monthly.

Cyclophosphamide

Cyclophosphamide is more toxic than other immunosuppressive drugs used for BP. It may be considered only for exceptionally refractory disease. The drug may be given initially in doses of 100–200 mg daily and 3 weeks later in maintenance doses of 100 mg daily. A pulsed steroid cyclophosphamide regimen is effective in severe cases of BP, permitting low cumulative steroid doses. Dexamethasone 100 mg i.v. given on three consecutive days, with the addition on day 1 of cyclophosphamide 500 mg, is given per day between pulses. The pulses are initially repeated every 2 weeks, reducing to every 10 weeks in combination with ongoing oral cyclophosphamide over a period of 6 months. Side effects include nausea and vomiting, bone marrow depression, hemorrhagic cystitis, and increased risk of malignancy. Monitoring is as for azathioprine, with the addition of urinalysis weekly for the first 8–12 weeks and every 2 weeks thereafter. Cardiac monitoring is required during pulse therapy.

Chlorambucil

Chlorambucil has been used as a steroid-sparing agent in the treatment of BP with excellent results. However, its use is not recommended except in special cases because of concern about the induction of hematological malignancy (acute myeloid leukemia). The drug is initially given at 0.1 mg/kg per day in combination with prednisolone 40–60 mg/day. The chlorambucil dose is reduced over 6 weeks to a maintenance dose of 2 mg daily. Prednisolone is gradually withdrawn over a 4-month period, chlorambucil being discontinued some weeks later. There is a 50 % reduction in the cumulative dose of prednisolone. Side effects include bone marrow suppression, which can be severe, often resulting in transient dose-related thrombocytopenia. Appropriate monitoring is with baseline and weekly blood counts. Hematological malignancies may be related to a cumulative dose of 1 g or more of the drug.

Cyclosporin

Cyclosporin cannot be recommended in the routine treatment of BP. However it has been used in the treatment of BP at doses of 5–8 mg/kg per day as a single agent or of 5 mg/kg per day in combination with steroids. According to our experience, combined therapy has a significant steroid-sparing effect and induces remission of BP in all patients, with monotherapy being less successful. The side effects include hypertension, renal dysfunction, raised lipids, hypertrichosis, gum hyperplasia, susceptibility to infection, and

increased risk of malignancy. Baseline blood pressure should be recorded, and the laboratory investigations required include complete blood picture, urea, serum creatinine, creatinine clearance, liver function tests, fasting lipids, and urinalysis. Serum creatinine should be repeated every 2 weeks for the first month with all the other previously mentioned laboratory parameters.

Dapsone and Sulfonamides

BP may respond well to dapsone or the sulfonamides (sulfapyridine and sulfamethoxypyridazine) either alone or in combination with other agents. Dapsone is started at 50 mg daily and increased to 100 mg daily after 5–7 days if no response is apparent. Response is rapid, within 2 weeks. Dapsone may be used in combination with topical steroids or may be added (150–300 mg daily) to prednisolone or azathioprine therapy, achieving adequate control of disease activity and permitting a reduction in the steroid dose. Although these are not drugs of first choice for BP, they may be useful in the management of patients in whom corticosteroids are contraindicated or not tolerated. Side effects include dose-related hemolysis and methemoglobinemia, cutaneous hypersensitivity reactions, peripheral neuropathy, hepatic damage, and renal failure. Monitoring should be with baseline tests and electrolytes. Glucose-6-phosphate dehydrogenase deficiency must be excluded prior to commencing therapy. Estimation of methemoglobinemia is obtained as clinically indicated.

Alternative and Treatment Suggestions

Topical Tacrolimus

The use of topical tacrolimus is limited due to local irritation and high price compared to topical steroids. It may be used as an alternative in localized disease as it is not implicated in skin atrophy.

Mycophenolate Mofetil (MMF) or Sodium (MMS)

MMF is an inhibitor of purine synthesis in activated T and B cells and is considered a generally well-tolerated immunosuppressive agent. They are both used for prevention of allograft rejection in transplantation medicine. MMF is a well-tolerated and effective corticosteroid-sparing agent in autoimmune bullous disease, and several suggest that complete remission is achieved more frequently with the use of MMF over azathioprine, with less hepatotoxicity. They have been reported as effective in controlling BP in doses of 0.5–1 gr twice daily, both as adjunct to systemic prednisolone and as monotherapy following disease relapse.

Anti-inflammatory Antibiotics/ Niacinamide

Tetracyclines and niacinamide (nicotinamide) may be considered as treatment in adults, perhaps in combination with topical corticosteroids. Niacinamide is used between 500 and 2,500 mg daily, usually started at 500 mg and then gradually increased. Tetracycline has been used at doses of 500–2000 mg daily, doxycycline at 200–300 mg daily, and minocycline at 100–200 mg daily. Minocycline has a worse side-effect profile and therefore is not the first choice. Erythromycin should be considered for treatment, particularly in children and perhaps in combination with topical corticosteroids. Side effects include gastrointestinal symptoms, photosensitivity, headache, benign intracranial hypertension, hyperpigmentation (minocycline), and candidosis. The combination of tetracycline 500 mg four times daily or minocycline 100 mg twice daily and niacinamide 500 mg twice daily is efficacious in some BP patients.

Plasmapheresis

Plasmapheresis is used as an adjuvant to corticosteroids in the treatment of BP, showing a steroid-sparing effect. Prednisolone is administered in combination with eight large-volume plasma exchanges over 4 weeks. In our experience a higher mean daily steroid dose is required to control disease activity when steroid is given alone (1 mg/kg) than with the dual therapy (0.6 mg/kg). The mild side effects of fever, chills, and hypertension are relatively common. However, the potential difficulties include maintaining venous access, a bleeding tendency, electrolyte imbalances, allergic reactions, pulmonary edema, and septicemia.

Deaths may also occur. Frequent observation of vital signs and cardiac monitoring are required during the procedure. It is suggested that weekly full blood examination, electrolytes, coagulation studies, and liver function tests are carried out.

Gammaglobulins

Gammaglobulins given alone in a dose of 100–400 mg/kg for five consecutive days do not appear to be more than temporarily effective in the treatment of BP. The possible steroid-sparing effect awaits further investigation.

Methotrexate

Methotrexate (5–15 mg weekly) can be effective at controlling BP in elderly patients, either as monotherapy or in combination with topical or systemic steroids**.**

Biologic Agents

Only a few reported cases have been treated with tumor necrosis factor-α (anti-TNF-α) and the anti-CD20 agent, rituximab. Regarding anti-TNF-α agents, there is conflicting evidence as to whether these agents treat or induce BP. Until further supportive evidence is available, their role in BP remains limited.

Childhood Bullous Pemphigoid

Due to its rarity and benign nature, preference should be given to low-toxicity treatments (e.g., erythromycin) and topical steroids.

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Candidiasis

12

Dimitris Rigopoulos

Key Points

- Candidiasis refers to infections caused by *Candida* species.
- The most common encountered infections include oral candidiasis, superficial cutaneous candidiasis, candida balanitis, vaginal candidiasis, candida paronychia, candida onychomycosis and chronic mucocutaneous candidiasis.
- Therapy should always include removal of underlying predisposing factors with encouragement for dental and mouth hygiene, keeping dry skin folds, avoidance of detergents that flare up chronic paronychia and reduction of the *Candida* reservoir in the mouth and gut.
- Topical agents used in the treatment of candidiasis include amphotericin B, nystatin, natamycin, miconazole, ketoconazole, econazole, omoconazole, tioconazole and clotrimazole.
- Systemic agents used include itraconazole and fluconazole.

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Definition and Epidemiology

The term candidiasis refers to infections caused mainly by the classic opportunistic pathogen *Candida albicans* or occasionally by other species of *Candida*, such as *C. tropicalis*, *C. guilliermondii*, *C. parapsilosis*, *C. krusei*, *C. stellatoidea*, *C. pseudotropicalis* and *C. glabrata*. These various yeast species differ in their potential to invade and colonize epithelial and epidermal sites, *C. albicans* being the species with the greatest such potential. Infections of the skin, nails and mucous membranes are the most often encountered candida infections.

Basic Concepts of Pathogenesis

C. albicans, which is part of the normal human flora, is a dimorphic organism, developing in different morphological forms, such as yeasts, hyphae and pseudohyphae. This development is dependent on local conditions. *Different predisposing factors exist, which lead to different types of candidiasis*. Immunosuppression or leukopenia usually leads to systemic candidiasis, which is rare; endocrinopathies (hypoparathyroidism, hypothyroidism, diabetes mellitus), iron or zinc deficiencies and inherited defects of immunity lead to chronic mucocutaneous candidiasis, which is also rare; and diabetes, pregnancy,

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_12, © Springer-Verlag Berlin Heidelberg 2015

antibiotic therapy, high humidity, immersion in water and oral contraceptive drugs lead to *localized cutaneous candidiasis*, which *is the commonest type of disease*. These predisposing factors are extremely important in the management of candidiasis patients, since the reversal of these factors is of great significance and part of the treatment protocol.

Clinical Presentation

Oral Candidiasis

This disease is most commonly seen in infants and the elderly (associated with denture plates). The lesions may be situated on the mucosal surfaces of the tongue or at the corner of the mouth. *One or more whitish*, *sharply defined*, *adherent plaques are the characteristic signs of the condition*. If these plaques are wiped off, an underlying erythematous base is seen. Erosions or ulcerations are occasional complications.

In some cases, patients present with erythema, soreness, marked pain, atrophic mucous membranes and lack of whitish plaques (acute atrophic oral candidiasis).

Hyperplastic plaques on the cheek or the tongue that are not easily removed and develop especially in men who are smokers and over the age of 30 constitute a condition known as candida leukoplakia (chronic hyperplastic candidiasis).

Median rhomboid glossitis is another condition associated with candidiasis and presents with erythema of the tongue surface in the absence of papillae, pain and tenderness.

Chronic atrophic candidiasis (denture stomatitis) affects nearly 25 % of all denture wearers and sometimes children with orthodontic appliances. The condition is characterized by bright red of dusky erythema of the palate and gums, with atrophy of the epithelium and sometimes oedema.

Angular cheilitis (perleche) occurs at the corner of the mouth and it is not always associated with *Candida*. The area is moist, red and fissured, and the symptoms include pain.

Superficial Cutaneous Candidiasis (Candidal Intertrigo)

Any occluded skinfold, especially in hot and humid weather, may become moist and macerated, favouring the development of candidiasis. *Erythema and moist exudation deep in the fold are the characteristic symptoms at the beginning*. Erythema with well-defined borders though not razor sharp as in tinea cruris, subcorneal pustule, satellite pustular or papular lesions, itching and soreness make up the typical clinical pictures as the condition progresses.

Candida Balanitis

Although *candida balanitis* (which *is seen mostly in uncircumcised men*) is usually acquired form a sexual partner with vulvovaginitis, the possible oral and anal origins of the disease should not be forgotten. In mild cases, erythema and tiny papules predominate and are seen after intercourse; in more severe cases, the entire glans can be involved, and soreness may prevent sexual intercourse as it becomes painful.

Vaginal Candidiasis

It has been estimated that 75 % of all adult women will suffer from vaginal candidiasis at some time during their lives. There are two types of the disease, the occasional and the recurrent. In the case of occasional vaginal candidiasis, *C. albicans* is the commonest causative yeast, accounting for over 80 % of isolates. The predisposing factors are antibiotics (which alter the normal vaginal flora), peak production of oestrogen before menstruation or use of high-oestrogen contraceptives (increase of glycogen, a nutrient source of *C. albicans*), pregnancy (increased levels of circulating oestrogen and progesterone raise the glycogen content of vaginal epithelial cells), immunosuppressive drugs of disease, increased sugar levels of the urine

and vaginal secretions and synthetic or tight-fitting clothes (they create a warm and moist environment). The condition presents with itching, soreness, erythema and a thick, creamy-white discharge. *Vaginal candidiasis is recurrent in 10–20 % of patients*, and the male partner may play a part in reinfection (50 % of male partners carry the same strain of *Candida* on the penis or in the mouth). Symptoms are the same as in occasional vulvovaginitis, and only in chronic cases does the vaginal mucosa become glazed and atrophic.

Candida Paronychia

This is a chronic condition found *mainly in those who frequently immerse their hands in water* (housewives, chefs, etc.) The nail fold is red and swollen, thick white pus may be discharged and the patient complains of pain. Nail dystrophy, with onycholysis and nail plate discoloration, is also found.

Candida Onychomycosis

C. albicans infection of the nail may be seen *secondary to chronic paronychia or onycholysis*. The nail plate is opaque, brownish-green in colour and altered in shape. There may be nail plate changes secondary to the inflammation of the nail fold.

Chronic Mucocutaneous Candidiasis

This is an immunodeficiency disease, which is characterized by persistent candidiasis of mucous membranes, skin and nails. The infection may vary from mild, localized, persistent lesions to a severe, generalized condition. The disease usually starts in infancy and is often associated with endocrinopathy (mainly Addison's disease and hypoparathyroidism). A few late-onset cases are associated with thymic tumours; candida granulomas may appear on the scalp and face.

Diagnosis

Diagnosis is based on the clinical examination and the history and is usually confirmed by laboratory examination (direct microscopy and culture).

Direct Microscopy

Skin scrapings are examined microscopically for yeasts, pseudohyphae or hyphae, after the addition of 10 % KOH solution to the slide preparation.

Culture

Swabs from suspected areas are cultured on Sabouraud's agar. *C. albicans* is a fast grower; colonies mature in 1–3 days (with the exception of nail-clipping cultures, which must be kept for at least 7 days). Other candida species may require longer time to mature.

Differential Diagnosis

Leukoplakia	Does not clear with prolonged anti-*Candida* therapy
Flexural psoriasis	Histology, microbiology
Bacterial intertrigo	Microbiology
Tinea	Microbiology, sharp edges
Seborrhoeic dermatitis	Microbiology
Hailey-Hailey disease	Histology
Flexural Darier's disease	Histology
Trichomonas vaginitis	Watery brown discharge, microbiology
Contact dermatitis of vagina	Microbiology, history
Herpes simplex of the penis	Anti-HSV antibodies positive (1gM), history
Psoriasis of the penis	Chronic psoriasis plaques in other body areas
Erythroplasia	Chronic, persistent more dusky colour
Napkin dermatitis	The skin deep in the fold is free of symptoms
Bacterial paronychia	Microbiology, acute onset

General Principles of Treatment

- Removal of underlying predisposing factors.
- Denture hygiene and frequent mouth toilet plus abstention form smoking will help those suffering from oral candidiasis.
- Infected skinfolds should be kept dry and if possible separated.
- Patients with chronic paronychia should keep their hands warm and dry.
- In most cases of candida infection, topical treatment alone is sufficient.
- Consideration should always be given to reduction of the *Candida* reservoir in the mouth and gut.

Recommended Therapies

(a) Topical therapeutic agents
(b) Systemic therapeutic agents
(c) Treatment of clinical forms

Antifungal drugs belonging to the polyene and azole families are the ones used in the treatment of *Candida* infections. A morpholine antifungal agent, amorolfine, is also active.

Topical Therapeutic Agents

These drugs are used in the forms of creams, solutions, suspensions, vaginal suppositories, lacquers, shampoos and powders.

The members of the polyene family used are topical amphotericin B, nystatin and natamycin, while the azole family provides the imidazole derivatives miconazole, ketoconazole, econazole, omoconazole, tioconazole and clotrimazole for use in these conditions.

Amorolfine is also used in the form of cream of nail lacquer.

The use of topical preparations is effective in the majority of *Candida* infections, but their use is restricted by the extent of the area involved. Factors that should be considered when choosing topical agents include the lack of side effects of these drugs, when administered topically; the minimal development of resistance, except in the case of nystatin; and their lack of interaction with other classes of drugs.

The topical formulations (except amorolfine nail lacquer) should be used one to three times daily, and their application should continue at least for 1 week after clinical resolution of the disease, to allow reconstitution of the stratum corneum.

The type of formulation selected for treatment depends on the site and the symptoms of the disease (for dry lesions, lotions of creams are preferable, for wet lesions powders, for oral lesions suspensions, for vaginal lesions pessaries and for nail lesions lacquers).

Topical Treatment at a Glance

- The use of topical preparations is effective in the majority of Candida infections, but their use is restricted by the extent of the area involved.
- Use lotions or creams for dry lesions, powders for wet lesions, suspensions for oral lesions, pessaries for vaginal lesions and lacquers for nail lesions.
- The main treatment agents for oral candidiasis are topical nystatin suspension and miconazole oral gel.
- Amorolfine and ciclopirox nail lacquers for 12 months are the main treatment for mild nail candidiasis.

Systemic Antifungal Agents

For systemic candidiasis or extensive skin disease, in immunosuppressed patients and when there are frequent relapses after topical treatment of high patient compliance is needed, the triazoles i*traconazole* and *fluconazole and* the imidazole *ketoconazole are used for systemic treatment*. The major disadvantages of these drugs are the potential toxicity (ketoconazole) and the development of both clinical and microbiologically proved resistance (fluconazole). Another serious disadvantage of these antifungals is their interaction with other drugs.

The chief side effects of ketoconazole are nausea, pruritus, transient elevations in liver enzymes and significant liver toxicity, which can lead to death.

The incidence of adverse events is higher during long-term itraconazole therapy (16.2 %) than during short-term administration (7.0 %). The side effects observed with itraconazole are not severe and mainly take the form of gastrointestinal disturbances (nausea, epigastralgia and diarrhoea).

The most frequent side effects of fluconazole are gastrointestinal symptoms and rash.

Use of the azoles is not recommended in pregnancy. Azole resistance is substantial problem. It is found in AIDS patients, in intensive care units and in leukaemia patients. It is manifested in two ways. The first is replacement of susceptible *Candida* isolates with resistant *Candida* spp., such as *C. glabrata* and *C. krusei*. The second is in situ development of resistance in a certain isolate. The problem of the resistance is focused chiefly on fluconazole, although cross-resistance to the other azoles in common.

Some of the drugs with which ketoconazole interacts are agents decreasing gastric acidity: rifampicin, acyclovir, coumarins, cyclosporin, phenytoin, terfenadine and astemizole. Fluconazole is reported to interact with amphotericin B, coumarins, cyclosporin, phenytoin, oestradiol, cimetidine, astemizole, terfenadine, sulfonyl ureas, thiazides, etc.

Itraconazole interacts mainly with cyclosporin, food, digoxin, phenytoin, rifampicin, H2 antagonists, terfenadine and astemizole.

Systemic Treatment at a Glance

- Itraconazole or fluconazole should be used for systemic candidiasis or extensive skin disease.
- Fluconazole 50–100 mg daily for 1 week, or itraconazole 100 mg daily for 1–3 weeks are effective in persistent oral candidiasis.
- Recurrent vulvovaginitis is treated with a single dose of 150 mg fluconazole, given on day 21 of each menstrual cycle or clotrimazole as a 500 mg vaginal pessary once a week for 6–12 months.

Treatment of Clinical Forms

Oral Candidiasis and Perleche

The main treatment agents are topical nystatin suspension and miconazole oral gel. For more persistent disease, oral antifungals are used: ketoconazole 200 mg daily for 1–2 weeks, fluconazole 50–100 mg daily for 1 week or itraconazole 100 mg daily for 1–3 weeks. Fluconazole is reported to be effective with a single 150 mg dose. Perleche is treated with topical antifungal creams.

Cutaneous Candidiasis

Topical antifungal preparations are used, with excellent results. For widespread disease, oral antifungal drugs are used: itraconazole 200 mg daily for 1 week or fluconazole 50–100 mg for 1–3 weeks. A dose of 150 mg fluconazole once a week for 2 weeks has also proven to be very effective in the treatment of cutaneous candidiasis.

Candida Balanitis

Topical treatment has proven sufficient in treating this condition. Fluconazole in a single 150 mg dose is effective in more resistant cases

Vaginal Candidiasis

Topical treatment generally results in a good mycotic and clinical cure rate. Owing to common relapses and complaints from patients that intravaginal products are messy and often leak, oral treatment is prescribed. Cases of occasional vulvovaginitis are treated with fluconazole orally in a single dose of 150 mg, ketoconazole 200 mg daily for 5 days or itraconazole 400 mg in a single dose. Recurrent vulvovaginitis is treated with a single dose of 150 mg fluconazole, given on day 21 of each menstrual cycle for 6–12 months. Clotrimazole as a 500 mg vaginal pessary once a week has proven efficient in suppressing relapses of recurrent vaginitis.

Candida Paronychia

This condition requires prolonged topical treatment. The hands should be kept warm and dry.

Candida Onychomycosis

Topical treatment with the ordinary polyene or azole antifungal drugs *is not effective*, as these drugs are not absorbed from the nail plate. For mild candida onychomycosis of the hands involving not more than 60 % of the entire nail plate, amorolfine nail lacquer is used once a week

for 6 months. For more severe onychomycosis of the hands, itraconazole is used in a pulsed regimen of 400 mg daily for 1 week. This scheme is repeated for 3 months.

For mild onychomycosis of the feet, amorolfine nail lacquer is used once weekly for 12 months and for more severe cases itraconazole pulse therapy with 400 mg daily for 1 week. This scheme is repeated for 4 months.

Fluconazole is used in a dose of 150 mg weekly for 6 months for hand onychomycosis and for up to 9 months for foot onychomycosis.

Chronic Mucocutaneous Candidiasis

A combination of antifungal drugs and immunological reconstruction is needed in the treatment strategy for this condition. A restoration of T-cell function is attempted by using transfer factor of thymosin or by grafting compatible lymphocytes from blood or marrow or foetal thymic tissue.

The antifungal drugs most commonly used are ketoconazole, fluconazole and itraconazole, which are used for some years. The main problems encountered with the use of these drugs are the growing problems of infection with *Candida* that has become resistant and hepatotoxicity with long-term use of ketoconazole.

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Cheilitis and Oral Disease

13

Eleni Gagari

Key Points

- Cheilitis presents with a variety of pathogenetic mechanisms and etiologies. Proper diagnosis is essential for effective treatment.
- Combination of different types of cheilitis may be present in the same patient making this disease entity a therapeutic problem.
- Biopsy is necessary in actinic cheilitis, cheilitis glandularis, and cheilitis granulomatosa.
- Association of cheilitis with oral and systemic disease entails a different therapeutic approach than local disease and needs to be evaluated carefully.
- Moisturizing agents are necessary for optimal effect of topical treatment modalities.
- Choice of topical vs. systemic treatment depends on the type of cheilitis and the severity of the lesions.

Definition and Epidemiology

Cheilitis is etymologically a term of Greek origin and indicates a nonspecific inflammation of the lips. It is therefore essential to qualify this term with specific descriptors in order to provide diagnostic definitions, namely:

- *Angular cheilitis:* Bilateral inflammation of the commissures of the lips of multifactorial etiology, presenting with redness, scaling, and erosions limited to the corner of the lips.
- *Allergic contact cheilitis:* Redness, crusting, and superficial ulceration of the vermillion of the lips often associated with perioral dermatitis, caused by contact hypersensitivity to a variety of topical agents.
- *Exfoliative cheilitis:* Increased production of keratin of the vermillion of the lips and persistent subsequent desquamation resulting in scaling and flaking appearance. Most frequently caused by habitual lip licking and self-caused injury (factitial cheilitis).
- *Actinic cheilitis:* Mottled discoloration, scaling, and focal ulceration of the lower lip vermillion border, representing premalignant or malignant change (in later stages) caused by sun damage.
- *Cheilitis glandularis:* Inflammation of the minor salivary glands of the lower lip causing suppuration and ulceration of the lower lip. A significant percentage (18–35 %) is associated with development of squamous cell carcinoma of the lower lip.
- *Cheilitis granulomatosa:* Pronounced swelling of the lips caused by submucosal or subcutaneous

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_13, © Springer-Verlag Berlin Heidelberg 2015

granulomata. The condition may arise in the context of orofacial granulomatosis or as a clinical manifestation of granulomatous diseases (more frequently Crohn's disease or sarcoidosis).

Basic Concepts of Pathogenesis

The vermillion border of the lips represents a very finely constructed meeting point of skin and oral mucosa. The major pathogenetic mechanisms involved can be separated into the following broad categories:

- Reaction to mechanical or environmental stimuli or compromised anatomy (reduced vertical dimension due to lack of teeth and aging of the skin).
- Allergy to local antigenic challenge (contact hypersensitivity) or part of a generalized allergic reaction that affects the orofacial structures.
- Candidal and/or bacterial infection.
- Systemic disease such as Crohn's disease, sarcoidosis, tuberculosis, chronic granulomatous disease and leprosy. Indirectly, anemia, iron deficiency, and diabetes may predispose to a candidal infection of the lips.
- Idiopathic when there are granulomata present in the lips, but there is absence of any systemic disease that can account for them. Orofacial granulomatosis is a "blanket" term currently used to encompass entities such as cheilitis granulomatosa of Miescher and Melkersson-Rosenthal syndrome.

Often, cheilitis may present with a composite of pathogenetic mechanisms. For example, angular cheilitis or exfoliative cheilitis may develop in the presence of cheilitis granulomatosa due to the altered anatomy of the swollen lips.

Clinical presentation

Angular Cheilitis

The location of the lesions at the corners of the lips is characteristic. The lesions are red, occasionally speckled with white detachable plaques of candidal infection and may also have mildly erosive areas (Fig. 13.1). Several factors contribute to this clinical appearance and should be methodically evaluated. The loss of vertical dimension due to edentulous alveolar ridges or ill-fitting dentures, as well as slacking/wrinkling of the skin due to aging, creates a compromised anatomy of the area that allows pooling of saliva. This favors the development of a yeast infection that is combined with a bacterial infection. Microbiologic studies have indicated that 20 % of these lesions represent *C. albicans*, 20 % bacterial infection with *S. aureus*, and 60 % of these lesions represent a mixed infection of the two. It is important to examine the oral cavity for presence of oral candidiasis and to rule out anemia, diabetes, immunosuppression, and B12 or iron deficiency as predisposing factors. Presence or absence of mucosal erythema, atrophic glossitis, or pseudomembranous/atrophic oral candidiasis should be carefully evaluated. Due to a feeling of irritation the patient may engage in lip licking causing a secondary presentation of exfoliative cheilitis.

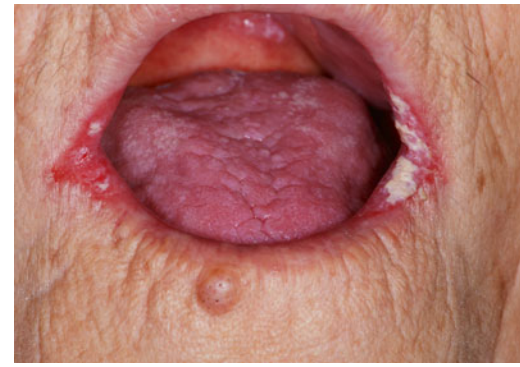


Fig. 13.1 Angular cheilitis

Allergic Contact Cheilitis

Both lips appear red, crusted, fissured, and bleeding on occasion (Fig. 13.2). There is often perioral erythema and dermatitis. The sudden appearance and association with a cosmetic or topical agent being applied is important for the diagnosis. Occasionally the local allergen is mild and may be more difficult to discover. A careful and thorough history of habits involving the area

needs to be obtained. Usually there is no presence of oral disease, with the exception of oral food allergen syndrome where the lip manifestations are part of anaphylactic stomatitis (redness and discomfort) in those parts of oral mucosa that come into contact with food the most during mastication (buccal mucosa, lips, tip of the tongue).

Exfoliative Cheilitis

Scaling, cracking, and peeling of the vermillion borders of the lips is noted. Thick, yellowish hyperkeratotic crusts that may leave extensive fissuring or a hemorrhagic surface behind may also develop as the condition worsens (Fig. 13.3a, b). Perioral skin may become involved and exhibit the same features. It is prevalent in people younger than 30 years of age with a predilection for females. The exact cause is unknown, but it is thought chronic irritation of the area, such as lip licking and mouth breathing, is involved. There appears to exist a relationship with psychiatric disorders, atopy, and photosensitivity, although it has not been well substantiated. A chronic form of candidiasis such as is encountered in immunosuppressed patients may also contribute to the clinical appearance. Exfoliative cheilitis is a common side effect of chronic isotretinoin use and appears to be linked to excessive dryness of the lips caused by the medication.

Actinic Cheilitis

Most common on the lower vermillion of the lip, actinic cheilitis represents a premalignant condition caused by chronic sun damage. The lack of homogeneity of color and the appearance of uneven scaly patches or focal ulceration are characteristic (Fig. 13.4). A biopsy is often indicated to rule out development of squamous cell carcinoma.

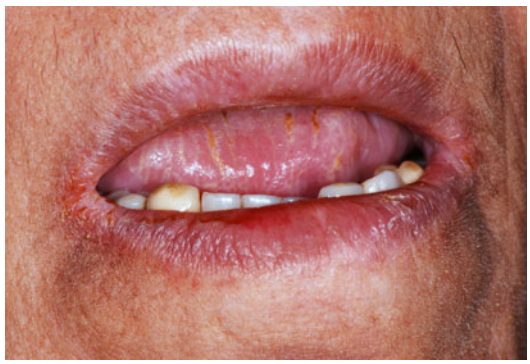


Fig. 13.2 Allergic contact cheilitis to propolis

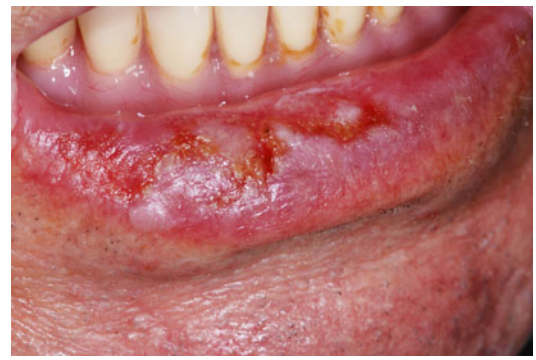
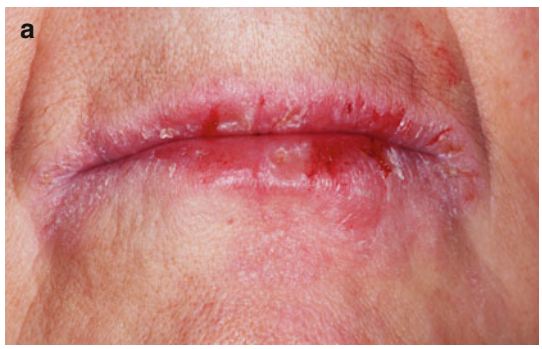


Fig. 13.4 Actinic cheilitis



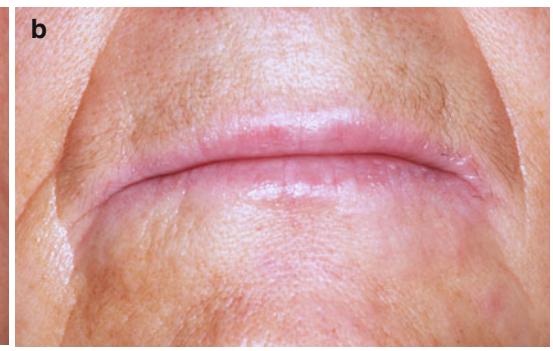


Fig. 13.3 (**a**) Exfoliative cheilitis. (**b**) Exfoliative cheilitis after topical tacrolimus 0.1 % treatment

Cheilitis Glandularis

The orifices of minor salivary gland ducts of the lower lip give rise to suppurating fistulae that can be probed using a dental probe (Fig. 13.5). The etiology of this inflammatory condition is unknown, but it is most common in middle aged or older men. A biopsy may be indicated due to the association with squamous cell carcinoma.

Cheilitis Granulomatosa

Swelling, fissuring, and deformation of the upper lip is most common (Fig. 13.6), although swelling may also be present in the lower lip. Biopsy is needed to establish the presence of granulomata. This form of cheilitis may be part of a disease entity called "orofacial granulomatosis" in which granulomatous inflammation of the lips and other parts of the oral mucosa, such as buccal mucosa, palate, gingival, and mucobuccal fold, *exist in the absence of systemic disease*. There is a "cobblestone" appearance of the oral mucosa accompanied by erosions or focal ulcerations. The lips may be the only part affected, and this represents Miescher's cheilitis. Concomitant presence of facial nerve paralysis and fissured tongue constitutes Melkersson-Rosenthal syndrome.

Cheilitis granulomatosa may represent a clinical manifestation of Crohn's disease especially in young male adults and should be ruled out by colonoscopy. Other granulomatous diseases such as sarcoidosis and tuberculosis should also be ruled out with appropriate testing.

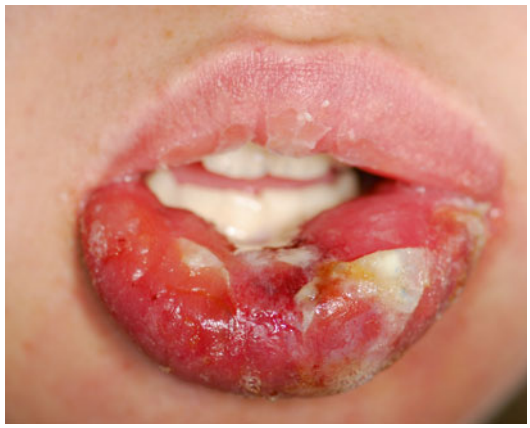


Fig. 13.5 Cheilitis glandularis

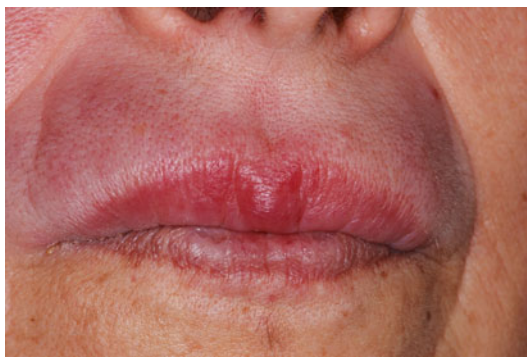


Fig. 13.6 Cheilitis granulomatosa

Differential Diagnosis

Appropriate diagnostic workup and accurate diagnosis of the type of cheilitis present are essential in implementing the correct treatment.

Step 1: Careful evaluation of clinical appearance of the lip lesions. Some clinical features are "hallmarks" of specific types of cheilitis:

- Lesions confined to the commissures of the lips: *angular cheilitis*
- Presence of extensive swelling on one or both of the lips: *cheilitis granulomatosa or allergic contact cheilitis*
- Peeling, fissuring, and thick crusting of the lips: *exfoliative cheilitis*
- Suppuration of lower lip: *cheilitis glandularis*
- Discoloration and loss of distinct color margins of the vermillion of the lower lip: *actinic cheilitis*

Step 2: Evaluation of oral mucosa and perioral skin:

- Erythematous oral mucosa, presence of red and white detachable lesions, atrophic glossitis, and point to oral candidiasis more often associated with angular cheilitis.
- Erythematous patches of oral mucosa, "cobblestone mucosa," and presence of erosions suggest orofacial granulomatosis

and mandate diagnostic exclusion of Crohn's disease.
- Perioral redness and scaling: associated most often with exfoliative cheilitis and point to excessive lip licking.

Step 3: Evaluation of medical history for medication and allergies:
- Report of contact challenge with local factors such as lipstick, balms, or ointments and history of oral food allergy syndrome: allergic contact cheilitis
- Medical history of food allergies, atopy: cheilitis granulomatosa
- Use of isotretinoin for acne: exfoliative cheilitis

Step 4: Exclusion of underlying systemic disease:
- If the clinical diagnosis is angular cheilitis, blood test evaluation for anemia, diabetes, and immunocompromised status may be required, especially if the condition recurs often.
- If the clinical diagnosis is cheilitis granulomatosa, biopsy, colonoscopy, chest X-ray, SACE levels, and Mantoux are indicated along with detailed blood tests, in order to rule out Crohn's disease, sarcoidosis, and tuberculosis
- If the clinical impression is swelling of the lips, angioedema must be ruled out with biopsy of the lip lesions.

General Principles of Treatment

Cheilitis is a challenging treatment problem. Accurate diagnosis is the most important determining factor in obtaining optimal treatment outcome. The guidelines for successful treatment revolve around maintaining optimal anatomy and hydration of the vermillion border of the lips, reducing inflammation, treating local opportunistic infections, and managing underlying systemic disease.

Depending on the etiology and pathogenesis of cheilitis, a wide variety of therapeutic agents have been used:
- Moisturizing agents that create a "barrier" on the vermillion of the lips in order to avoid the detrimental effect of saliva
- Topical corticosteroids
- Intralesional corticosteroids
- Systemic corticosteroids
- Antibiotics
- Calcineurin inhibitors
- Immunomodulatory agents
- Monoclonal antibodies

It is essential to note that in those cases where cheilitis is a clinical manifestation of systemic disease, successful treatment of the underlying disease is required in order to achieve complete resolution of the lip lesions.

Topical Treatments

Topical Corticosteroids

Topical corticosteroids have been used widely for the treatment of cheilitis. The most popular formulations are cream and ointment formulations of hydrocortisone, fluticasone propionate, betamethasone, and clobetasol propionate in varying concentrations (0.05–0.1 %) twice daily. They should be used along with moisturizing agents especially where cream formulations are concerned as there is a drying effect on the lips that may worsen scaling and peeling. The use of topical steroids entails the risk of exacerbating a candidal or bacterial infection if used alone, especially in angular cheilitis. These formulations are not effective alone, but when used along with another immunomodulatory agent, they may improve allergic contact cheilitis, exfoliative cheilitis, and very mild cases of cheilitis granulomatosa. Complete resolution of cheilitis on the basis of single-agent topical steroid use can only be observed in very mild cases of cheilitis.

Topical Antibiotics

Topical antimicrobial agents and antibiotics, when used as a single-agent treatment, are not successful in cheilitis treatment. Neomycin and mupirocin ointments have been used, but they often worsen the condition because they cause dryness and they create an imbalance in microbial flora

that predisposes to candidiasis. The bacterial component plays only a limited role in the etiology of cheilitis, and therefore topical antibiotic treatment is only relevant in cases of angular cheilitis.

Combination Topical Treatment

The combination of topical antifungal, corticosteroid, and antimicrobial treatment is effective in cases of angular cheilitis. Triamcinolone acetonide 1 mg/g nystatin 100,000 units/g, neomycin 2.5 mg/g, and gramicidin 0.25 mg/g may be used twice daily for 7–10 days with good results. Triamcinolone counteracts the drying effects of neomycin and gramicidin, while nystatin controls the yeast infection that could worsen from the combined use of corticosteroid and antibacterial agents. Bacterial resistance is a potential caveat. Combination topical treatment is not useful in other forms of cheilitis.

Calcineurin Inhibitors

Tacrolimus ointment (0.03 % and 0.1 %) and pimecrolimus ointment 1 % have been used with considerable success in the treatment of exfoliative cheilitis at a regimen of twice daily for 7–10 days and with partial success as an adjunct to the treatment of cheilitis granulomatosa. Calcineurin inhibitor action is unknown but thought to inhibit T-lymphocyte activation. Due to the "black box" warning of skin cancer or lymphoma, long-term use is not recommended. However, exfoliative cheilitis responds well with a short course, and the medication is well tolerated (Fig. 13.3b). The more serious side effects of HSV or HVZ infection are not encountered. Occasional burning sensation is the most common side effect observed in the above treatment regimen.

Intralesional Injections of Corticosteroids

Triamcinolone acetonide 40 mg/ml has been used for intralesional injections in cases of cheilitis granulomatosa. The regimen is usually two to three injections every 14–21 days depending on the severity of the lesions and the response after the first cycle. In a number of cases, intralesional injections require additional systemic immunomodulatory medication use to maintain a long remission. The regimen provides a systemic steroid-sparing effect to young patients. The most common side effect is local scarring or atrophy which is not often encountered. They are not used in any other form of cheilitis.

Systemic Treatments

Antibiotics

Systemic antibiotic treatment has been used in the treatment of cheilitis granulomatosa. Minocycline 100 mg/day, roxithromycin (an erythromycin derivative) (150–300 mg/day), and metronidazole 750–1,000 mg/day have all been used in conjunction with systemic or intralesional corticosteroid treatment of cheilitis granulomatosa. The benefit from the use of these antibiotics lies in their antiinflammatory not in their antibacterial properties. A significant drawback is that the protracted use of these agents (needed to achieve remission) may cause antibiotic resistance. Broad-spectrum antibiotics may also be prescribed if suppuration is present in cheilitis glandularis or if there is resistance to topical antibacterial agents in angular cheilitis.

Corticosteroids

Systemic administration of prednisolone is often used in cheilitis treatment to reduce inflammation or the immune response (granulomata). In the literature, the dosage reported varies from 20 to 50 mg/day, although in the vast majority of cases, dosages no higher than 30 mg/day are enough to achieve satisfactory treatment outcome. Prednisolone is often administered together with an antibiotic for the treatment of cheilitis granulomatosa, or with an antifungal, systemic, or topical for angular cheilitis. Usually

the duration of administration is not long enough to cause significant side effects, although caution should be exercised in young and in immunocompromised patients. Careful monitoring of development and endocrinological evaluation should be performed in patients <18 years of age.

Antifungals

Systemic administration of antifungal agents is indicated when there is evidence of candidal infection of the oral mucosa or the perioral skin in association with angular cheilitis. Fluconazole is a cytochrome p450 inhibitor and is the drug of choice for oral candidiasis. An indicative regimen for oral candidiasis is initiated at 200 mg/day the first day and 100 mg/day for the next 9 days for a total of 10 days. Fluconazole presents with a variety of drug interactions so careful monitoring of patient medication is required to avoid serious side effects. It is otherwise well tolerated.

Immunomodulators and Monoclonal Antibodies

Systemic administration of immunomodulating agents has only been used in cases of cheilitis granulomatosa that are refractory to treatment. It is not always clear in the literature that these instances do not represent cheilitis as a manifestation of Crohn's disease. Clofazimine, a medication derived from the phenazine dye that has bacteriostatic and immunomodulatory activity, has been used with promise. Infliximab, a chimeric anti-TNF-a monoclonal antibody, has also been proposed at infusion dosages ranging from 3 to 5 mg/kg. Thalidomide at 100 mg/day every other day has been used and methotrexate at 5–10 mg administered orally on a weekly basis has also been reported. Given the safety profile of these medications and the benign nature and course of most types of cheilitis, the risk to benefit ratio is currently not favorable enough to recommend these agents in the treatment of cheilitis.

Cheilitis: Treatment at a Glance

Angular Cheilitis

- Establish the presence/absence of intraoral candidiasis, anemia, or diabetes.
- Correct vertical dimension.
- If there is intraoral candidiasis present, treatment with systemic antifungal agents precedes any topical treatment.
- Topical treatment with a combination steroid/antifungal/antibacterial ointment twice a day for 7–10 days.
- If lesions persist, obtain microbial culture from commissures and administer targeted systemic antibiotic treatment in combination with topical treatment.

Allergic Contact Cheilitis

- Discovering the allergen responsible is of paramount importance.
- Patch testing may be necessary.
- Moisturizing agents.
- Topical corticosteroid treatment in mild cases.
- Systemic corticosteroid treatment with per os prednisolone at dosages of 20–30 mg/day for short duration in order to achieve speedy remission.

Exfoliative Cheilitis

- Careful evaluation of patient habits, psychological profile, and history of isotretinoin use
- Moisturizing agents for lips and perioral area
- Tacrolimus ointment 0.1 % twice daily for 7–10 days

Actinic Cheilitis

- Sun protection.
- Biopsy to rule out squamous cell carcinoma.
- Cryotherapy or surgical treatment is treatment of choice.
- Imiquimod has been used.

Glandular Cheilitis

- Systemic broad-spectrum antibiotic treatment for cases of suppuration, preferably after microbial culture is performed for sensitivity.

- Biopsy to rule out SCC when ulceration is present.
- Surgical treatment may be indicated if there are frequent recurrences.

Cheilitis Granulomatosa

- Biopsy to establish diagnosis.
- Evaluation of oral mucosa for other sites of involvement.
- Colonoscopy, chest X-ray, Mantoux, and blood tests (serum angiotensin-converting enzyme and calcium levels) need to be performed to rule out Crohn's disease, sarcoidosis, and tuberculosis.
- If systemic disease has been ruled out, systemic corticosteroids (30 mg prednisolone/day) and minocycline (100 mg/day) is initiated with a 3-week taper.
- Intralesional triamcinolone injections (40 mg/ml) with or without minocycline may alternatively be used in cycles of 14–21 days.
- If systemic disease is present, effective treatment of the systemic disease will either resolve the cheilitis completely or put it in long-term remission.
- If the patient is <18 years of age, careful monitoring of endocrinological status and development is needed during systemic corticosteroid administration.

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Chronic Actinic Dermatitis

14

Sally Jane O'Shea, Christian Gulmann, and Gillian M. Murphy

Key Points

- Drug-induced photosensitivity must be carefully excluded.
- Strict photoprotection and allergen avoidance are essential.
- Treatment options include topical steroids, topical tacrolimus and systemic immunosuppressant medications such as azathioprine, cyclosporine and mycophenolate mofetil.

Definition and Epidemiology

Chronic actinic dermatitis is a persistent photodermatitis that has a predilection for older men but has also been known to occur in individuals with atopic dermatitis and in the presence of human immunodeficiency virus (HIV) infection (Ive et al. 1969 and Hawk et al. 2010). It tends to affect sun-exposed skin; however, covered skin may also be affected to a lesser degree. It is postulated that a delayed-type hypersensitivity reaction to photoinduced allergens underpins the diagnosis. UVA, UVB and even visible light are capable of evoking changes Hawk (2010). Therefore, the clinical findings are usually more pronounced during summer months.

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Basic Concepts of Pathogenesis

A chromophore is the part of a molecule which is responsible for its colour, arising as a result of the absorption of certain wavelengths of visible light and the reflectance of others. DNA damage can be induced when UV light comes into contact with chromophores in human skin that do not possess the ability to rapidly convert the energy into harmless heat energy. Exposure to UV irradiation at doses considerably lower than the minimal erythema dose (MED) can induce clinical signs in patients with chronic actinic dermatitis. Patients with this disorder are usually very photosensitive. The action spectrum in chronic actinic dermatitis is similar to that of sunburn and the action spectrum for the formation of thymine dimers, implicating DNA as the chromophore (Menagé et al. 1995).

Clinical Presentation

The condition manifests as a photo-distributed, pruritic, eczematous rash. A sharp cut-off is often seen between the affected, sun-exposed

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_14, © Springer-Verlag Berlin Heidelberg 2015

skin and covered, normal skin. Skin sparing may be noted in the post-auricular areas and in shaded areas, such as between the fingers, under a watch strap, in the submental area and under the hair. Lichenification is a feature, and a pseudolymphomatous appearance (Fig. 14.1) or even erythroderma (Fig. 14.2) can develop in severe cases, making the diagnosis more elusive. It is estimated that resolution of the condition occurs in approximately 10 % of those affected after 5 years (Dawe et al. 2000).

Diagnosis

A detailed history is essential to rule out a drug-induced photosensitivity. Laboratory investigations to exclude other causes should also be done, including anti-nuclear antibodies, extractable nuclear antigens and a porphyrin screen. As patients with chronic actinic dermatitis may also have contact allergy to airborne allergens, including plant antigens and fragrances, patch and photopatch testing is done to identify precipitating allergens and to differentiate chronic actinic dermatitis from other conditions. Testing is done at lower doses than the MED, but identification of photoallergens may still be possible with a UVA dose of 1 J/cm^2.

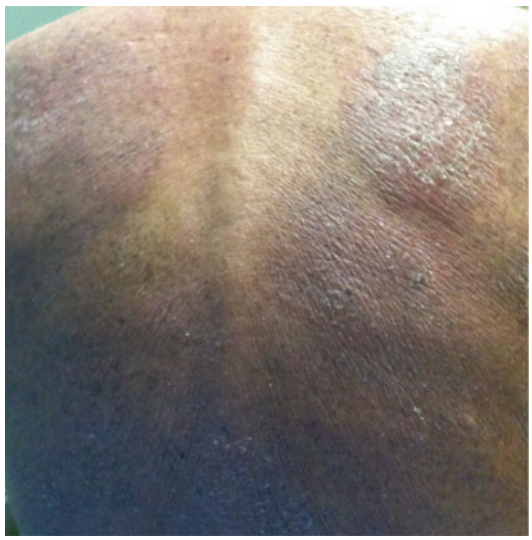


Fig. 14.1 Infiltrated, pseudolymphomatous patches and plaques on the back of a patient with severe chronic actinic dermatitis

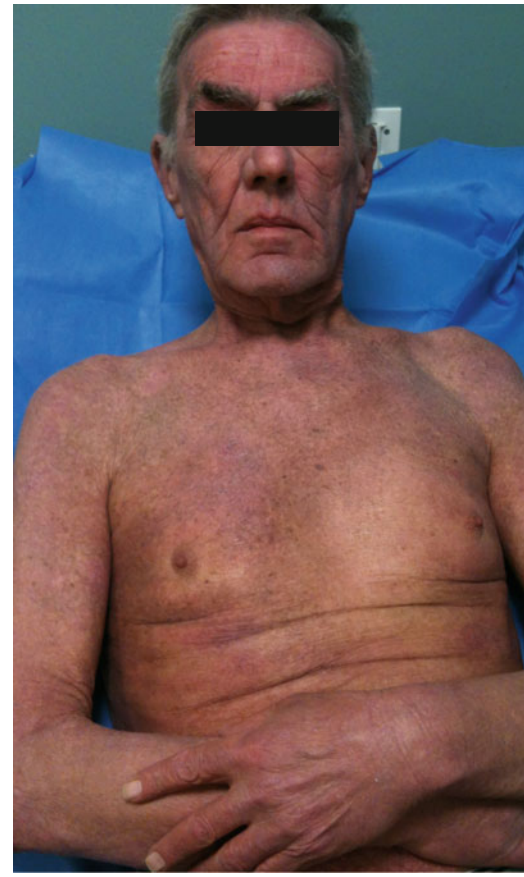


Fig. 14.2 Severe chronic actinic dermatitis and presented with erythroderma

Histology

Epidermal acanthosis, spongiosis, and a deep, dense, mixed, dermal, perivascular infiltrate are usually seen. Pseudolymphomatoid features, such as lymphocyte exocytosis, may also be seen in severe cases which may lead to suspicion of cutaneous T-cell lymphoma (Fig. 14.3). Further characterisation of the T-cell infiltrate, however, demonstrates predominantly CD8+ T cells, and T-cell receptor gene rearrangement studies are negative in chronic actinic dermatitis (Hawk et al. 2010).

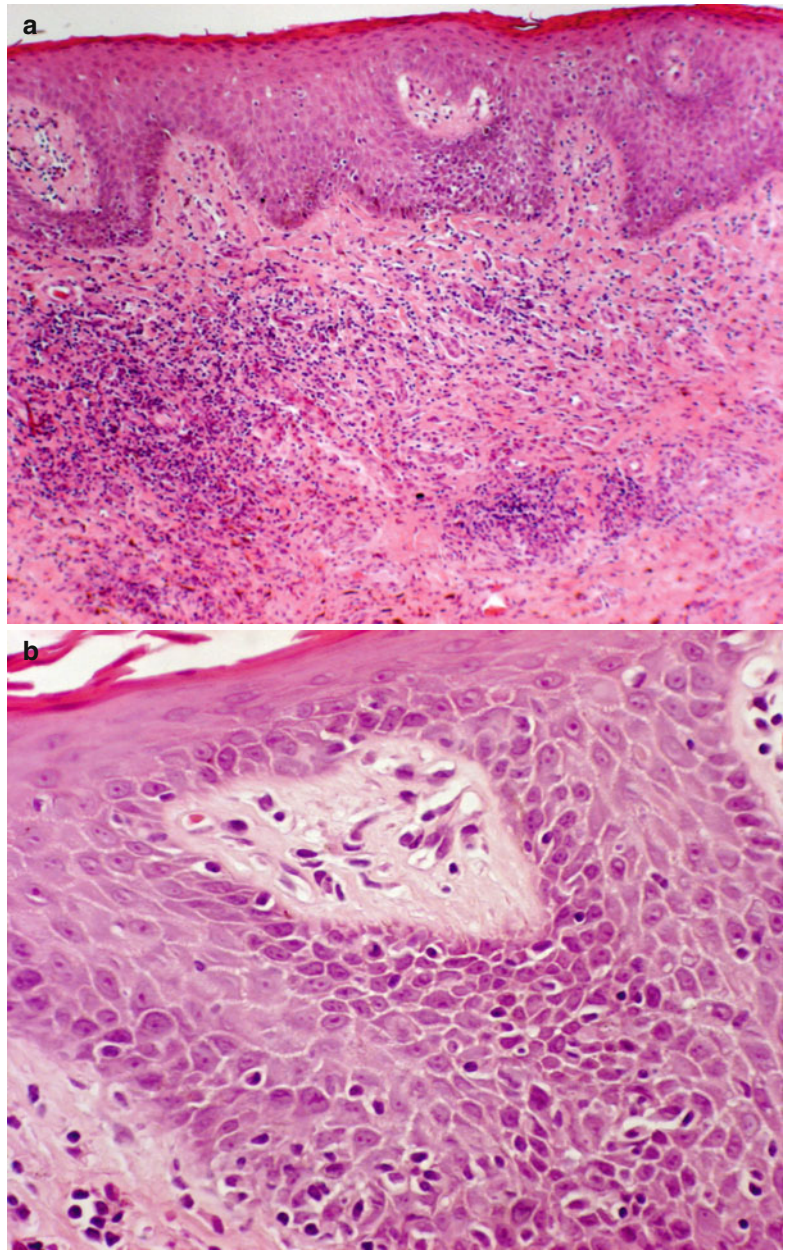
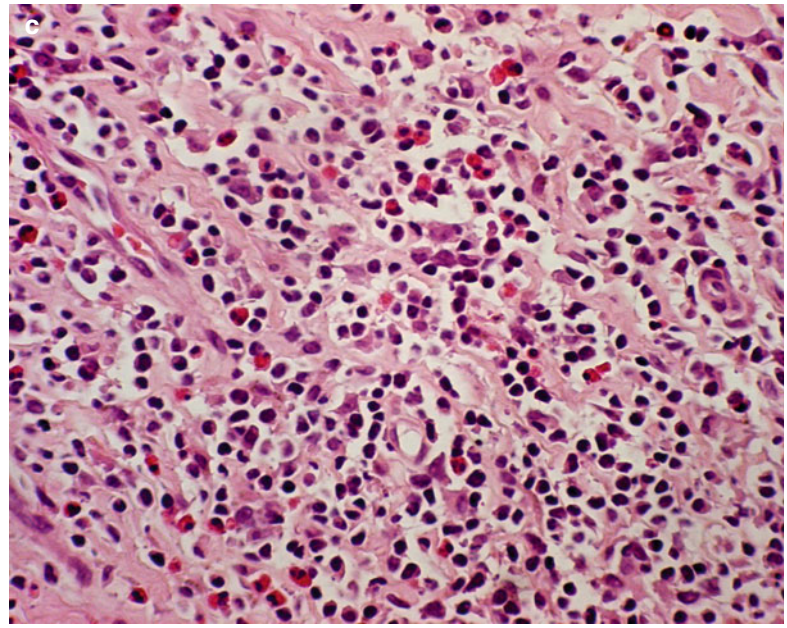


Fig. 14.3 (**a**) Low-power view shows intense dermal inflammation and fibrosis, epidermal acanthosis and parakeratosis. Haematoxylin and eosin, ×10 objective lens. (**b**) High-power view of epidermis highlights spongiosus as well as lymphocytic exocytosis. Haematoxylin and eosin, ×40 objective lens. (**c**) Mixed dermal inflammatory infiltrate composed of lymphocytes, histiocytes and many eosinophils. Plasma cells are also present. Haematoxylin and eosin, ×40 objective lens

Fig. 14.3 (continued)



General Principles of Treatment

All patients with chronic actinic dermatitis are counselled about strict photoprotection and allergen avoidance. (Please see reference 9 for a patient information leaflet). Sun block with complete UV spectrum protection is advised; these include those containing titanium dioxide and zinc oxide. Yellow blinds, which exclude UV and blue visible light energy, are also required. Museum film can be applied to windows, to minimise penetration by ultraviolet light. Bonwyke Dermagard is an example, although many brands exist.

Desensitisation with PUVA or TLO1 phototherapy can be considered. Other established treatment options include topical steroids, topical tacrolimus, azathioprine (Murphy et al. 1989), cyclosporine (Granlund et al. 1998) and mycophenolate mofetil (Thomson et al. 2005).

Systemic Treatments

Azathioprine, an imidazole derivative of 6-mercaptopurine, generates an immunosuppressive effect. It is generally prescribed at a dose of 1.0–2.5mg/kg/day. The exact mechanism of action remains to be elucidated, but it is thought to act by competitive binding of thionucleotide metabolites in a series of biochemical pathways. Its efficacy in chronic actinic dermatitis was first highlighted in a double-blind controlled trial, comparing azathioprine 50mg tds with placebo. After 6 months of treatment, five out of eight patients in the azathioprine cohort, compared with zero out of ten in the placebo group, achieved remission (Murphy et al. 1989).

Cyclosporine 3.5–5mg/kg/day results in rapid control of symptoms, but relapse upon weaning can pose a management problem.

Mycophenolate mofetil 25–40mg/kg/day is another alternative off-label treatment (Hawk et al. 2010). It exerts its effects, predominantly on lymphocytes, by inhibition of the enzyme inosine monophosphate dehydrogenase. This leads to depletion of guanosine nucleotides which results in impaired DNA, RNA and protein synthesis. Evidence supporting its use in the management of chronic actinic dermatitis relies mainly on case reports. Two male patients with recalcitrant disease noted symptomatic improvement within 16 weeks of treatment, with doses ranging from 500mg bid on a continuous regimen in one patient to 1g bid during spring and summer months only in the second patient (Thomson et al. 2005). The precise duration of treatment has not yet been determined.

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Cicatricial Alopecia

15

Antonella Tosti, Eric L. Maranda,
and Bianca Maria Piraccini

Key Points

- Cicatricial alopecia is a permanent condition that cannot be reversed by treatment.
- Early diagnosis of primary cicatricial alopecia is imperative and it should be treated aggressively to reduce permanent scarring.
- Dermoscopy may assist in selecting the optimal site of biopsy for pathological diagnosis.
- Improper lipid metabolism in lichen planopilaris leads to a toxic build-up of lipids in the sebaceous gland that may be initiating the inflammatory response.
- Peroxisome proliferator-activated receptor-γ, a master transcription factor that regulates the expression of genes involved in lipid metabolism, is aberrant in lichen planopilaris.
- Pioglitazone, a peroxisome proliferator-activated receptor-γ agonist, may be a novel means to effectively treat lichen planopilaris.
- In discoid lupus erythematous, autoreactive Granzyme B-positive CD8+ T cells are recruited to the hair follicles resulting in epidermal, dermal, and follicular destruction.
- Antimalarial drugs are the treatment of choice for discoid lupus erythematous.
- Retinoids may be used as an alternative treatment for patients with discoid lupus erythematous that do not respond to topical glucocorticoids, sunscreens and tacrolimus.
- Studies using field emission scanning electron microscopy and confocal laser scanning microscopy suggest that bacterial biofilm organization may play a role in the pathogenesis of folliculitis decalvans.
- Keratosis follicularis spinulosa decalvans is a rare, inherited or sporadically acquired X-linked disorder with a

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_15, © Springer-Verlag Berlin Heidelberg 2015

mutation in the MBTPS2 gene mapped to Xp21,13-p22.2.
- Global gene expression profiles in lichen planopilaris and pseudopelade of Brocq are distinct from one another and should be considered as separate conditions.
- Dysregulation of connective tissue metabolism in localized scleroderma leads to an excess deposition of collagen.
- Early stages of localized scleroderma are characterized by an elevation of Th1/Th17-associated cytokines and Th2-associated cytokines during the late stages of the disease.
- The downregulation of microRNAs, in particular miRNA let-7a, may perpetuate the fibrosis seen in localized scleroderma.
- Localized scleroderma usually resolves spontaneously in a few years.

Definition and Epidemiology

A large number of scalp disorders may destroy the hair follicles and result in cicatricial alopecia (Table 15.1). These include diseases that primarily affect the hair follicles as well as diseases that affect the dermis and secondarily cause follicular destruction. Once established, cicatricial alopecia is a permanent condition that cannot be reversed by treatment. The differential diagnosis between the diseases that cause cicatricial alopecia requires a pathological examination. The site of biopsy is crucial for pathological diagnosis and can be better selected using dermoscopy. Current treatment options of primary cicatricial alopecia are limited as the precise mechanisms that trigger the diseases are still unknown should be treated aggressively. Early diagnosis and treatment is necessary in order to avoid diffuse follicular destruction. When treating cicatricial alopecia, one must explain to the patient that hair that has been lost will not regrow. Surgical treatment of cicatricial alopecia includes excision of the scarring area after tissue expansion or hair transplantation. The latter technique is complicated by the poor recipient conditions due to the reduced blood perfusion present in scar tissue that may impair graft survival. There is also the possibility that grafting may precipitate relapses through a Koebner phenomenon. In many cases, the treatment selected is based on anecdotal and individual preferences, due to the limited number of double-blind, randomized studies completed and the small number of cases. This chapter discusses optimal management and treatment of some inflammatory scalp disorders that commonly cause primary cicatricial alopecia.

Table 15.1 Causes of cicatricial alopecias

Primary cicatricial alopecia
Lichen planopilaris
Frontal fibrosing alopecia
Fibrosing alopecia in a pattern distribution
Discoid lupus erythematosus
Keratosis follicularis spinulosa decalvans
Folliculitis decalvans
Central centrifugal scarring alopecia
Acne keloidalis nuchae
Secondary cicatricial alopecia
Traction alopecia
Bacterial or fungal infection
Localized scleroderma
Radiation
Pemphigoid
Chemical or physical injuries
Scalp metastases

Clinical Presentation and Treatment

Lichen Planopilaris

Lichen planopilaris (LPP) is the most common cause of cicatricial alopecia and is considered the follicular form of lichen planus. Microarray analysis has recently shown a reduction in the

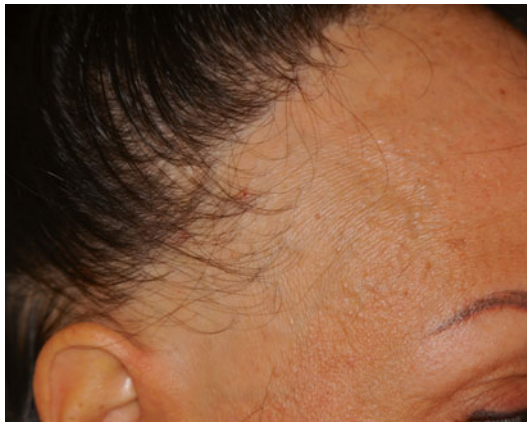

Fig. 15.1 Frontal fibrosing alopecia: hairline recession and loss of eyebrows. Also note prominence of temporal veins and papular lesions

expression of genes necessary for lipid metabolism and peroxisome biogenesis in LPP. Improper lipid metabolism in the sebaceous gland results in a toxic build-up of lipids that may be initiating the inflammatory response in this condition. It was hypothesized that peroxisome proliferator-activated receptor-γ (PPAR-γ), a master transcription factor that regulates these processes, is aberrant in LPP. To confirm the role of PPAR-γ in the pathogenesis of LPP, PPAR-γ was deleted in the follicular stem cells of mice, producing a phenotype similar to cicatricial alopecia. This finding supports the role of PPAR-γ in the pathogenesis of cicatricial alopecia and modulation of this pathway may be a new option to treat LPP.

The clinical variants of lichen planopilaris include classic lichen planopilaris, frontal fibrosing alopecia (Fig. 15.1), fibrosing alopecia in a pattern distribution and Graham-Little syndrome.

Classic lichen planopilaris presents as follicular destruction with a multifocal or central distribution and rarely involves the entire scalp. Patients usually seek medical advice once they have noticed one or several patches of hair loss. A certain degree of itching and burning is frequently reported. The pull test from these areas typically reveals anagen hairs with hyperkeratotic sheaths.

Frontal fibrosing alopecia causes progressive recession of the frontal hairline and loss of the eyebrows. The new hairline is uneven and lacks vellus follicles, while the alopecic area shows less signs of photoaging, compared to the skin of the forehead. This clinical variant most commonly presents in postmenopausal women. The pathogenesis of FFA is still unknown but the role of environmental toxins is suggested by epidemiology.

Treatment

Treatment results in complete remission of disease in about one-third of patients. Partial remission is obtained in another third, while the disease progresses despite treatment in the remaining patients.

Systemic Treatment

1. Steroids represent our treatment of choice. We utilize intramuscular triamcinolone acetonide at the dosage 0.5–1 mg/kg/month. Steroids are gradually tapered when active lesions disappear. This may require 6–12 months.
2. Azathioprine 100 mg/day is useful in association with systemic steroids in severe cases.
3. Systemic cyclosporine 3 mg/kg/day in our experience is scarcely effective.
4. Oral hydroxychloroquine at 200 mg, twice daily for 6–12 months is a second-line treatment. Dosage should not exceed 6.5 mg/kg.
5. Pioglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist is effective at a dosage of 15 mg daily. Liver function tests should be performed before starting therapy. Increased risk of bladder cancer has been reported in women taking the medication for more than 1 year.
6. Finasteride 1 mg/day in men and 2.5–5 mg/day for women or dutasteride 0.5 mg daily is useful in fibrosing alopecia in a pattern distribution and in frontal fibrosing alopecia.
7. Low-dose excimer 308-nm laser, two to three times a week, is useful in reducing the inflammation both in LPP and FFA.
8. We do not recommend retinoids for the treatment of LPP or FFA.

Topical Treatment

1. Topical 2 % or 5 % minoxidil may prevent fibrosis and is useful in association with systemic steroids. It also induces thickening of the remaining hair and allows better coverage of the alopecic area.
2. High-potency topical steroids can be prescribed in association with systemic treatment. However, they may aggravate skin atrophy, particularly in FFA.
3. Topical tacrolimus 0.1 % is useful as it does not cause skin atrophy. In lichen pigmentosus, topical tacrolimus 0.03 % twice daily can improve the pigmentation of the lesions.

Discoid Lupus Erythematosus

Discoid lupus erythematous (DLE) is the most frequent form of chronic cutaneous lupus erythematosus that leads to primary cicatricial alopecia. While it was previously shown that type 1 IFN production drives the inflammatory processes in DLE, new studies show that autoreactive Granzyme B-positive CD8+ T cells are recruited to the hair follicles, resulting in epidermal, dermal, and follicular destruction. Additionally, scientists have found a variant of a gene that may exert a strong genetic influence on the risk of developing DLE, independently from systemic involvement. It was found that the coding variant rs1143679 of ITGAM was highly associated with DLE patients without systemic involvement and with SLE patients that exhibited discoid rashes.

Diagnosis of DLE is strongly suggested by the presence of photosensitivity and "discoid" erythematous papules with follicular hyperkeratosis. As the disease progresses, the plaques enlarge and spread centrifugally and eventual atrophy with telangiectasia become evident. DLE may also present with cysts and comedones. Patients most commonly complain of single or multiple patches of hair loss, burning and scalp tenderness. Direct immunofluorescence is useful for the diagnosis and is often necessary for differentiating DLE from other primary lymphocytic cicatricial alopecias. All patients with discoid lupus erythematosus should be examined for systemic lupus erythematosus. Complications include the development of squamous cell carcinoma.

Treatment

DLE usually responds to treatment.

Systemic Treatment

1. Antimalarial drugs are the treatment of choice. Hydroxychloroquine 200 mg twice a day or chloroquine (200 mg/day) can be prescribed alone or in association with systemic steroids. Treatment lasts for at least 3 months and is then tapered to the lowest effective dose.
2. Quinacrine may be used in combination with other antimalarials in patients that have resistance or only partially respond to chloroquine or hydroxychloroquine. It may also be used as a monotherapy in patients with preexisting eye problems that contraindicate the use of chloroquine or hydroxychloroquine. The dosage of quinacrine as monotherapy or in combination therapy is 100 mg/day, for approximately 9 months.
3. Systemic steroids: initial dosages should be 40–60 mg/day of oral prednisone or 0.5–1 mg/month of intramuscular triamcinolone acetonide. Steroids are gradually tapered when active lesions disappear. This may require 3–6 months.
4. Thalidomide (100–300 mg/day) is a possible alternative. Low-dose thalidomide is an effective treatment for refractory DLE, but its benefits need to be balanced against the potential adverse effects.
5. Retinoids may be used as an alternative treatment for DLE patients that do not respond to topical glucocorticoids, sunscreens and tacrolimus.

Intralesional Steroids

Triamcinolone acetonide (5 mg/ml sterile saline solution) can be useful in localized lesions.

Topical Treatment

1. High-potency topical steroids can be utilized when the disease is circumscribed to a small area of the scalp.

2. Tacrolimus (0.1 %) ointment can be applied twice daily.
3. Topical 2 % or 5 % minoxidil may prevent fibrosis and can be prescribed in association with systemic steroids.
4. Topical tocoretinate 0.25 % ointment applied twice daily has been shown to improve erythema after 1 month. Improvements in skin pigmentation and atrophy can be observed after 12 months of treatment. Alternatively, topical tazarotene 0.05 % gel applied once daily at bedtime may show improvements.

General Measures

Patients should wear a hat to avoid sun exposure.

Folliculitis Decalvans (FD)

This term is utilized to include a spectrum of scalp disorders characterized by painful acute inflammatory changes with or without pustules (Fig. 15.2). Eventually, relapsing inflammatory episodes result in irregularly shaped areas of cicatricial alopecia and tufted folliculitis. Although *Staphylococcus aureus* may frequently be isolated from the pustules, FD is not an infective condition. Some cite local immunological deficits as a predisposition to this condition, while others propose the cause to be an abnormal host response against staphylococcal antigens or toxins. Recent studies suggest that bacterial biofilm organization may play a role in the pathogenesis. Biofilm presence in the root sheaths and on the hair shafts within the lesions was confirmed using field emission scanning electron microscopy and confocal laser scanning microscopy.

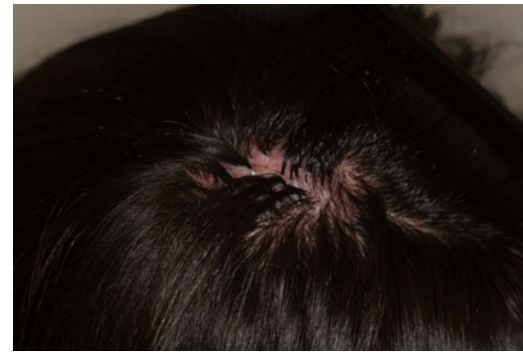

Fig. 15.2 Folliculitis decalvans: scarring alopecia and tufted folliculitis

Treatment

Although the inflammatory scalp lesions usually subside with treatment, the condition has a chronic course with frequent relapses.

Systemic Treatment

1. Oral antibiotics are the treatment of choice. Possible alternatives include erythromycin 1 g/day, clarithromycin 500 mg/day, cephalosporins or tetracyclines (minocycline 100 mg/day or hydroxytetracycline 200 mg/day). All of these are usually effective in arresting the inflammatory process, but relapses are common as soon as the treatment is interrupted. Combination therapy with fusidic acid 1,500 mg/day for 3 weeks and zinc sulphate 400 mg/day resulted in permanent remission in three patients (Abeck et al. 1992). The association of rifampicin 300 mg and clindamycin 300 mg taken both orally twice daily for 10 weeks is probably the most effective treatment (Powell et al. 1999, Powell and Dawber 2001). This may be due to the fact that rifampicin is an effective antistaphylococcal agent in addition to its immunomodulatory properties. This regimen produces long-term remissions in most patients. This particular association is required to avoid development of rifampicin resistance that is common when using this antibiotic alone.
2. Isotretinoin 0.5–1 mg/kg/day is effective in some patients but actually worsens the scalp inflammation in most cases.
3. TNF-alpha blockers are an option in recalcitrant cases. Infliximab at a dose of 5 mg/kg of body weight can improve symptoms after three infusions.

A short course of systemic and topical steroids, associated with oral antibiotics, can be utilized to suppress inflammation.

Topical Treatment

1. Shampoos containing antibacterial agents or 2 % ketoconazole may be helpful in preventing relapses.
2. Photodynamic therapy with methyl aminolevulinate has been shown to be effective in some cases.
3. Shaving of the scalp may improve the disease.

Keratosis Follicularis Spinulosa Decalvans (KFSD)

KFSD is a rare, inherited or sporadically acquired X-linked disorder with a mutation in the MBTPS2 gene, mapped to Xp21,13-p22.2. A more severe form of KFSD that is inherited in an autosomal dominant fashion has recently been proposed (Bellet et al. 2008). MBTPS2 codes for an intramembrane zinc metalloprotease necessary for the cleavage of sterol regulatory element-binding proteins (SREBPs). This genetic condition usually becomes evident in infancy and worsens into adulthood. Clinical diagnosis is suggested by the presence of follicular keratotic papules and pustules involving the vertex followed by progressive alopecia. Its severity considerably varies from patient to patient and may involve follicular papules on the eyebrows and cheeks. Due to the clinical and genetic heterogeneity observed in patients with KFSD, clear diagnosis is frequently challenging.

Treatment

In most patients the disease does not respond to treatment.

Systemic Treatment

1. Acitretin (0.5–0.75 mg/kg/day) may be effective in some cases. Isotretinoin 1 mg/kg/day is usually not effective.
2. Dapsone 100 mg/day can be tried in patients who do not respond to retinoids.
3. Oral antibiotics (tetracyclines, macrolides or rifampicin) as treatment for folliculitis decalvans are rarely effective.

Topical Treatment

1. Topical steroids and keratolytics may partially improve the symptoms.
2. Intense pulsed light (IPL) and pulse dye laser (PDL) has improved the condition in some patients.

Pseudopelade of Brocq

Pseudopelade of Brocq was classically thought of as not a separate entity but a representation of the final outcome of advanced lichen planopilaris. Yu et al. (2010), using significance analysis of microarrays, showed that the global gene expression profiles in lichen planopilaris and pseudopelade of Brocq are distinct from one another. This data suggest different etiologies accounting for these two disorders, which should be considered as separate conditions. The scalp presents multiple atrophic, irregular areas involving the vertex with little to no signs of inflammation. Mild pruritus and involvement of the beard area have also been reported. Clinicopathological features of classic pseudopelade of Brocq show nonspecific findings. There have been case reports of alopecia areata clinically mimicking this disease (Kittridge et al. 2010). The pull test from these areas typically reveals anagen hairs during active disease.

Patients with this diagnosis may fall into two possible categories:

- Patients in whom the disease has already spontaneously remitted
- Patients in whom the biopsy has been wrongly taken from an atrophic area

Currently, no established protocols exist for treating this condition.

Treatment

No chemical medical treatment is available.

Surgical autologous hair transplantation may be considered in patients with stable disease. Initial test transplantation of approximately 50 grafts should be done to exclude the possibility of reactivating the disease during the larger grafts.

Localized Scleroderma

Localized scleroderma (LE) is a connective tissue disorder in which a dysregulation of connective tissue metabolism leads to an excess deposition of collagen. Early stages of the disease are characterized by an elevation of Th1/Th17-associated cytokines and Th2-associated cytokines during the late stages of disease, resulting in fibrosis. Furthermore, microRNAs (miRNAs) may perpetuate the fibrosis seen in LE. Studies have shown that the miRNA let-7a, in particular, is downregulated in LE lesions (Makino et al. 2013; Etoh et al. 2013). Interestingly, miRNA injection of let-7a into the mouse model of bleomycin-induced dermal sclerosis improved the skin fibrosis. Insight into the role of miRNA in the pathogenesis of localized scleroderma may aid in the development of novel therapeutics to treat this disease.

Localized scleroderma of the scalp presents as a slowly progressing irregular patch of hair loss. The skin often shows a certain degree of erythema or pigmentation in the absence of follicular keratosis or scaling. The patch is often not completely bald but presents some vellus or intermediate hairs. Severe atrophy with involvement of the hypodermis and muscles is a feature of frontoparietal linear scleroderma ("en coup de sabre").

Treatment

Localized scleroderma usually resolves spontaneously in a few years.

Systemic Treatment

1. Systemic calcitriol at the dosage of 0.50–0.75 mg/day is effective in localized scleroderma of the scalp including frontoparietal linear scleroderma.
2. Oral methotrexate at 15 mg/m^2 (maximum 20 mg/week) for 6 months may be combined for the first 3 months with oral prednisone (1 mg/kg/day, maximum 50 mg/day) as a single morning dose.
3. Ultraviolet (UV) A1 phototherapy is a possible option.

Topical Treatment

1. Topical 2 % or 5 % minoxidil.
2. Calcipotriol lotion may be effective.
3. Tacrolimus 0.1 % ointment twice a day is a possible option.

Patients with frontal linear scleroderma ("en coup de sabre") can gain functional and aesthetic results from surgical volumetric restoration with fat grafting.

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Contact Dermatitis

16

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Abbreviations

ACD	Allergic contact dermatitis
AD	Atopic dermatitis
AZP	Azathioprine
CD	Contact dermatitis
CHS	Contact hypersensitivity
CSA	Cyclosporine
CU	Contact urticaria
ICD	Irritant contact dermatitis
OCD	Occupational contact dermatitis
PCD	Photocontact dermatitis
PD	Photodermatitis
SCD	Systemic contact dermatitis
SCS	Systemic corticosteroids
SNAS	Systemic nickel allergy syndrome
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
UV	Ultraviolet

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Key Points

- Contact dermatitis (CD) is used to describe a polymorphic pattern of skin inflammation in response to the contact with exogenous substances.
- It is one of the most common dermatoses that includes allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), photocontact dermatitis (FCD), systemic contact dermatitis (SCD), and contact urticaria (CU).
- Occupational contact dermatitis (OCD) refers to a dermatitis developed at workplace, and it represents a wide social and economical burden.
- The clinical history of a patient with CD has to be collected accurately.
- Patch test is an essential investigation in order to perform the proper diagnosis. Patients with persistent eczema and suspected ACD or not responding to conventional treatment should be patch tested with an extended standard series of allergens, including the risk-related series.
- The treatment should be effective and prompt in order to avoid the dermatitis of becoming chronic. The prognosis of contact dermatitis, especially occupational contact dermatitis, is poor if the trigger persists.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_16, © Springer-Verlag Berlin Heidelberg 2015

- The essential principle in the therapeutic management consists in:
  - Basic therapy, including explanation and comprehension of the diseases; recognition, avoidance, and protection from irritant or allergic substances; and proper use of cleansers and emollients.
  - Topical anti-inflammatory drugs (topical corticosteroids) and antipruritic drugs as a first line of therapy.
  - Systemic treatments (in particular oral corticosteroids) are reserved for chronic and severe cases.

Definition

The terms "dermatitis" and "eczema" are often used synonymously in order to describe a polymorphic pattern of inflammation. The clinical presentation of dermatitis ranges from acute phase with erythema and vesiculation to chronic phase with scales. Eczema rather reflects a later stage of inflammation with thickening and lichenification. Pruritus is almost always present.

Dermatitis is characterized by a spongiotic pattern, with epidermal spongiosis and perivascular lymphohistiocytic infiltrate in superficial dermis.

"Contact" dermatitis is commonly used to describe a skin inflammation in response to the contact with exogenous substances. It may be the result of external agents acting either as irritants or as allergens. In the last case, a T-cell-mediated immunity is involved, termed contact hypersensitivity (CHS).

Contact dermatitis (CD) can be divided in the following types:

- Irritant contact dermatitis (ICD)
- Allergic contact dermatitis (ACD)

Often ICD and ACD present simultaneously.

Moreover, both ICD and ACD can lead to a chronic eczema due to the repetitive exposure or the lack of treatment.

This chapter also includes the following:

- Phototoxic, photoallergic, and photoaggravated contact dermatitis
- Systemic contact dermatitis
- Protein contact dermatitis
- Immunological and non-immunological contact urticaria

Epidemiology

Few epidemiological studies address the prevalence of dermatitis in general population.

The prevalence of dermatitis, including also other types (e.g., atopic dermatitis), varies between 1 % and 20 %. An increase of its incidence has been registered in the last decades.

Contact dermatitis represents about 4–7 % of all dermatological consultations.

Irritant contact dermatitis (ICD) is more common than allergic contact dermatitis (ACD). The latter has a worse prognosis unless the allergen is identified and avoided. Among the most common allergens are nickel and chromate. Nickel contact dermatitis has become an epidemic disease in the industrialized world.

It has been estimated that in Europe about 65 million of people suffer from nickel allergy (54 million women and 11 million men). In Italy, the incidence in women is up to 20 %. Among teenagers, nickel is the most frequent cause of sensitization, and the incidence increases with age.

The high frequency of nickel ACD is related to its contact in both occupational and non-occupational settings. Due to its wide presence, nickel allergy is a lifelong condition and can be an important factor of chronic eczema.

European laws have led to a reduction of the nickel release from products over the years. The European Commission (EC) (Commission Directive 2004/96/EC of 27 September 2004) has established that the rate of nickel release from pierced parts of the human body must be less than 0.2 μg/cm^2/week.

National and European laws have led to a drastic reduction of prevalence of sensitized patients. In Europe, new cases have been linked to the

introduction of 1 and 2 euro coins made of nickel, brass, and copper. Yet, as the contact with coins is very short, coins are a very rare source of ACD.

Lastly, some concerns emerged from the nickel released from mobile phones and from some products made in China. So, the surveillance has to remain high.

Contact dermatitis represents a social and economical burden when it develops at the workplace (occupational contact dermatitis (OCD)). In Italy (Tuscany), about 10 % of all occupational diseases are skin diseases, with 97 % being contact dermatitis (85 % ACD and 12 ICD). ACD is usually more severe, and it is easier to identify ACD than OCD.

The professionals most frequently involved are construction and metalworkers, hairdressers, and health workers.

The main body sites involved are the hands, especially in OCD.

Basic Concept of Pathogenesis

The etiopathology of ACD is complex.

It is possible to distinguish two phases: induction phase (sensitization) and effector phase (elicitation).

The *sensitization* reflects the establishment of a T-cell-mediated memory response. The sensitization frequently occurs when skin damaged by ICD has contact with the allergen. It is complete when the individual is able of giving a positive ACD reaction.

The sensitization can be divided in the following steps:

- Binding of allergen to skin components
- Activation of allergen-presenting cells (APC), loaded with hapten
- Migration of hapten-loaded APC to the draining lymph node
- Recognition of allergen-modified dendritic cells (DC) by specific T cells
- Proliferation of specific interferon-producing T cells in draining lymph nodes
- Systemic propagation of the allergen-specific T-cell progenies

The *elicitation* is due to a renewed contact of healthy skin with the allergen. It results in clinical manifestation of ACD.

Irritant contact dermatitis (ICD) may be due to accidental exposure to strong irritants, as acids, or alcohols, causing severe wounding. However, it is much more common to face mild, repeated, and damaging insults to the skin that slowly cause visible damage by gradual denaturation of keratins, removal of horny layer lipids, and alteration of the water-holding capacity of the skin.

Individual susceptibility varies greatly: atopics and individuals with fair skin suffer more easily from irritant dermatitis.

The openly exposed areas of the skin are the most affected ones, e.g., the backs of the hands and the webs of the fingers. ICD can develop in numerous professions, especially in those that are performed in "humid" environment (the so-called wet workers), as:

- Catering
- Cleaning
- Construction work
- Medical (doctor, nursing, etc.)
- Engineering
- Gardening
- Hairdressing
- Housework
- Motor mechanics

Clinical Presentation

CD is characterized by a polymorphic pattern of skin inflammation, from acute to chronic.

ICD ranges from slight dryness, redness, to acute caustic burns, depending on the nature of irritant, the time of contact, and the area involved.

The first manifestation of ACD is often an acute eczema, although the severity ranges from mild to severe.

The polymorphic pattern of skin inflammation, characterized by erythema, edema, vesiculation, scaling to thickening, and lichenification, may be the result of combination of ICD and ACD, as well as the variable course of each type of dermatitis.

The prognosis of contact dermatitis is more problematic in atopic individuals and for people allergic to certain allergens, particularly nickel and chromate.

The clinical features of CD of the hand are reported elsewhere (→ see hand dermatitis chapter).

Other Types of Contact Dermatitis

Photodermatitis (PD)

Photodermatitis is an abnormal skin reaction to ultraviolet (UV) rays: from acute (sudden) to chronic (ongoing) skin reactions have been reported, with itchy erythematous rash, blisters, scaly patches, and hyperpigmentation. Several factors can increase the skin sensitivity to UV rays; individual factors mainly determine the sensitivity to UVB. The sensitivity to UVA is mainly determined by environmental factors, namely, topical or systemic drugs; exposition to certain plants, e.g., those belonging to the Apiaceae or Umbelliferae family; etc.

It is important to separate direct toxic mechanisms (phototoxic dermatitis) from allergic mechanisms (photocontact dermatitis (PCD)). As reported in an Italian multicenter study, the predominant groups of photoallergens were drugs, followed by organic UV filters and antimicrobial agents. Importantly, inappropriate UV irradiation can aggravate a preexisting contact dermatitis.

Systemic Contact Dermatitis (SCD)

Systemic contact dermatitis (SCD), or systemically reactivated allergic contact dermatitis, refers to a type of systemic contact hypersensitivity reaction (CHS) due to the ingestion of, or systemic exposure to, a contact allergen in an already sensitized person. Clinically significant SCD occurs only to certain allergens to which we are frequently exposed through a wide variety of routes.

Systemic nickel allergy syndrome (SNAS) is the most studied. It was highlighted some decades ago, and it still represents a common problem. Other potential allergens are balsam of Peru, neomycin, chromate, garlic, food colors, preservatives, and antioxidants.

A variety of clinical patterns have been reported in patients suffering from SCD: from focal flares of previous patch test sites to flares at sites of previous dermatitis, e.g., atopic eczema, diaper dermatitis, or drug rashes; to widespread eczema, sometimes associated with urticarial lesions; and to acral purpuric lesions, vasculitis, erythema multiforme-like lesions, "baboon syndrome," etc. Baboon syndrome refers to an acute SCD of the buttocks and upper inner thighs, with a pronounced erythema, reminding the red rump of a baboon.

A wide range of systemic symptoms can follow the dermatitis: from headache to asthenia, itching, intestinal, and respiratory symptoms.

Contact Urticaria (CU)

Contact urticaria (CU) is a rare condition characterized by itching wheals and flare response due to the relapse of histamine and other inflammatory mediators after the contact with proteins or with physical agents (cold) that either cause urticaria as an irritant reaction (frequently cold stress) or, rarely, as a type I allergic reaction (IgE mediated).

The skin manifestation ranges from wheals to anaphylactic shock.

CU can be distinguished in immune and nonimmune types. The first is IgE mediated and more common in atopics. The contact with latex proteins has to be always taken into consideration in case of surgical operation. In highly sensitized people or after extended exposure, the IgE response can lead to systemic response until anaphylactic shock.

Diagnosis

The clinical features frequently suggest the correct diagnosis. Yet, appropriate testing is mandatory for a definitive diagnosis. In some patients

with a clear history distinguishing ACD from ICD and atopic eczema, e.g., when the dermatitis is localized at the hands (→ see Hand Dermatitis), the diagnosis may be feasible without further tests. However, it is more frequent to face a more complex situation, where the role of an ICD, and ACD, and an atopic dermatitis can only be determined after testing.

Thus, following an accurate anamnesis, patch test represents an essential investigation to clarify the origin of an eczema that is unresponsive to topical treatment or immediately worsens after the end of the treatment. Testing is also needed if an ACD is suspected or cannot be ruled out. Patch test can or cannot confirm the nature and etiology of a contact dermatitis.

The most frequent sensitizers have been compiled to a "standard series" comprising 20–30 allergens in order to have a shared screening series.

The standard series should be revised on a regular basis.

Table 16.1 reports the European baseline series (Bruze et al. 2008) (28 allergens or better haptens).

The standard series usually varies from country to country. In fact, each national society board has approved its standard series according to the European recommendation. Table 16.2 reports the standard Italian series 2012, as suggested by SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) (25 haptens).

Importantly, dermatologists and dermatology centers adapt the spectrum of haptens/allergens to be tested by combining the European standard with allergens that may be of local importance.

The standard series of patch tests allow to detect approximately 80 % of the relevant sensitizations. Thus, it is worthy to emphasize the importance of using specific additional series, when the patient's history leads to a reasonable diagnostic hypothesis. This also includes testing products used by the patient; yet it is frequently difficult or impossible to standardize these procedures. Some Italian studies showed that not a small group (8.2 %) of patch-tested patients that is negative to standard series reacts positive to additional series.

Importantly, allergens may be commercially available in several additional series. Some examples are reported in Table 16.3.

Table 16.1 European Society of Contact Dermatitis (ESCD) and European Contact Dermatitis Research Group (EECDRG) standard series (2008)

Potassium dichromate 0.5 % in petrolatum
4-Phenylenediamine base (p-phenylenediamine) 1.0 % in petrolatum
Thiuram mix 1.0 % in petrolatum
Neomycin sulfate 20.0 % in petrolatum
Cobalt chloride 1.0 % in petrolatum
Benzocaine 5.0 % in petrolatum
Nickel sulfate 5.0 % in petrolatum
Clioquinol (chinoform and Vioform) 5.0 % in petrolatum
Colophonium (colophony) 20.0 % in petrolatum
Parabens 16.0 % in petrolatum
N-Isopropyl-N-phenyl-4-phenylenediamine 0.1 % in petrolatum
Wool alcohols 30.0 % in petrolatum
Mercapto mix 2.0 % in petrolatum
Epoxy resin 1.0 % in petrolatum
Myroxylon pereirae (balsam of Peru) 25.0 % in petrolatum
4-tert-Butylphenol formaldehyde resin (PTBP resin) 1.0 % in petrolatum
Mercaptobenzothiazole 2.0 % in petrolatum
Formaldehyde 1.0 % in water
Fragrance mix 18.0 % in petrolatum (it includes cinnamic alcohol, cinnamal (cinnamic aldehyde), hydroxycitronellal, a-amyl cinnamal (a-amyl cinnamaldehyde), geraniol, eugenol, isoeugenol, and evernia prunastri (oakmoss absolute))
Sesquiterpene lactone mix 0.1 % in petrolatum
Quaternium-15 (Dowicil 200) 1.0 % in petrolatum
Primin 0.01 % in petrolatum
Methylchloroisothiazolinone and methylisothiazolinone (Kathon CG_, 100 p.p.m.) 0.01 in water
Budesonide 0.01 % in petrolatum
Tixocortol pivalate 0.1 % in petrolatum
Methyldibromo glutaronitrile 0.5 % in petrolatum
Fragrance mix 214.0 % in petrolatum (it includes hydroxyisohexyl 3-cyclohexene carboxaldehyde, citral, farnesol, coumarin, citronellol, and a-hexyl cinnamal (a-hexyl cinnamaldehyde))
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5.0 % in petrolatum

From Bruze et al. (2008)

Table 16.2 Standard Italian series (2012)

Potassium dichromate 0.5 % in petrolatum
4-Phenylenediamine base (p-phenylenediamine) 1.0 % in petrolatum
Thiuram mix 1.0 % in petrolatum
Neomycin sulfate 20.0 % in petrolatum
Cobalt chloride 1.0 % in petrolatum
Benzocaine 5.0 % in petrolatum
Nickel sulfate 5.0 % in petrolatum
Colophonium (colophony) 20.0 % in petrolatum
Parabens 16.0 % in petrolatum
N-Isopropyl-N-phenyl-4-phenylenediamine 0.1 % in petrolatum
Wool alcohols 30.0 % in petrolatum
Mercapto mix 2.0 % in petrolatum
Epoxy resin 1.0 % in petrolatum
Myroxylon pereirae (balsam of Peru) 25.0 % in petrolatum
4-tert-Butylphenol formaldehyde resin (PTBP resin) 1.0 % in petrolatum
Mercaptobenzothiazole 2.0 % in petrolatum
Formaldehyde 1.0 % in water
Fragrance mix 18.0 % in petrolatum (it includes cinnamic alcohol, cinnamal (cinnamic aldehyde), hydroxycitronellal, a-amyl cinnamal (a-amyl cinnamaldehyde), geraniol, eugenol, isoeugenol, and evernia prunastri (oakmoss absolute))
Methylchloroisothiazolinone and methylisothiazolinone (Kathon CG_, 100 p.p.m.) 0.01 in water
Budesonide 0.01 % in petrolatum
Hydrocortisone 21-acetate 1 %
Methyldibromo glutaronitrile 0.3 % in petrolatum
Fragrance mix 214.0 % in petrolatum (it includes hydroxyisohexyl 3-cyclohexene carboxaldehyde, citral, farnesol, coumarin, citronellol, and a-hexyl cinnamal (a-hexyl cinnamaldehyde))
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5.0 % in petrolatum
Disperse blue 124 1 % in petrolatum

Table 16.3 Examples of additional series

Bakery[a]
Beautician
Cosmetics[a]
Corticosteroids
Construction workers
Dental technicians[a]
Dentists[a]
Eyelids[a]
Fragrance
Hairdressing[a]
Housewife[a]
Lips[a]
Medicament (including corticosteroids, antibiotics, local anesthetics, and ophthalmic)
Metal compounds
Metalworking/technical oils
Methacrylate and acrylate
Nails
Oral cavity[a]
Organic dyes
Prosthesis (dental, orthopedic)
"Para"-compounds[a]
Photographic chemicals
Plants, woods
Plastics and glues
Photoallergens
Printing (meth)acrylate
Resin (acrylic, epoxy, etc.)
Rubber chemicals[a]
Shoes and leather[a]
Sunscreen
Tattoos
Textile colors and finishes
Vehicles, emulsifiers

[a]In Italy, the composition of these series is recommended by SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology)

The Procedure of Patch Testing

An important aspect is the preparation of the patients. The skin on the back has to be free from dermatitis, and an eczema elsewhere has to be controlled as far as possible by local treatment. Patients have also to be instructed to not take oral corticosteroids, or other immunosuppressive drugs, the days preceding the patch tests. It is also important not to apply potent topical steroids to the back or to undergo a UV therapy. These factors are linked to a significant risk of false-negative results.

A diagnosis of acute or chronic irritant contact dermatitis is made by an accurate anamnesis that reveals a significant exposure to an irritant, the clinical manifestation, the course of the eczema, and negative results at the patch testing.

The most important causes of irritant contact dermatitis are as follows:

- Water
- Skin cleansers
- Detergents and solvents
- Acids and alkalis
- Cutting oils
- Chemicals
- Physical and mechanical factors
- Biological agents

The first three factors are the most common ones, causing irritant during the normal life, while the following three can have an important role in the occupational environment.

Special Conditions of Testing

Open Patch Test

Open patch test is useful when sensitizers, which may also cause irritant dermatitis, are assessed. It is useful in the investigation of ACD, contact urticaria, and protein contact dermatitis. It is usually performed on the forearm, and the site of investigation should be controlled for the first 30–60 min, to detect urticaria. A further reading should be made after 3–4 days.

Photopatch Test

When photoallergic dermatitis is suspected, photopatch test may be carried out.

It involves the application of the photoallergen series and any suspected materials (also patients' products) in duplicate on either side of the upper back. One side is irradiated with a dose of 5 J cm^2 of UVA after 1 or 2 days; the other is uncovered after 2 days. A final reading is taken for both sides after another 3 days. Importantly, in case of photoallergy an erythema is evaluated as "positive."

Differential Diagnosis

Other exogenous (such as tinea) and endogenous eczemas should be excluded.

Among the endogenous eczemas, atopic dermatitis, dyshidrosis, nummular eczema, or prurigo may be differential diagnoses. Moreover, endogenous and exogenous substances may cause other reactions such as erythema multiforme-like to lichenoid, purpuric, pigmented, and nodular reactions or granulomatous contact dermatitis.

Psoriasis and mycoses, especially when the dermatitis involves the hands, lichen planus, erythema multiforme, and prurigo nodularis have to be ruled out.

When the dermatitis involves the face or the scalp, psoriasis, seborrheic dermatitis, and rosacea are the most common skin diseases.

Prognosis

Several studies have confirmed that the long-term prognosis for contact dermatitis is often very poor. A Swedish study, which investigated a sample of patients with OCD, showed that only 25 % had the skin completely healed over a 10-year period. One half reported periodic symptoms and one quarter permanent symptoms. The overall prognosis of the disease was not improved in 40 % of the patients who had changed their occupation.

General Principles of Treatment

The essential principles in the management of contact dermatitis are as follows:

- Comprehension and explanation of the disease.
- Recognition, avoidance, and protection from irritants and/or allergens.
- Application of emollient and topical anti-inflammatory treatment (corticosteroids).
- Sedation of the itch.
- Rarely, in severe cases, a systemic treatment is needed.

The therapeutic strategies have to be realized promptly to avoid the dermatitis from becoming chronic.

A wide variety of local treatment modalities are available as reported in Fig. 16.1.

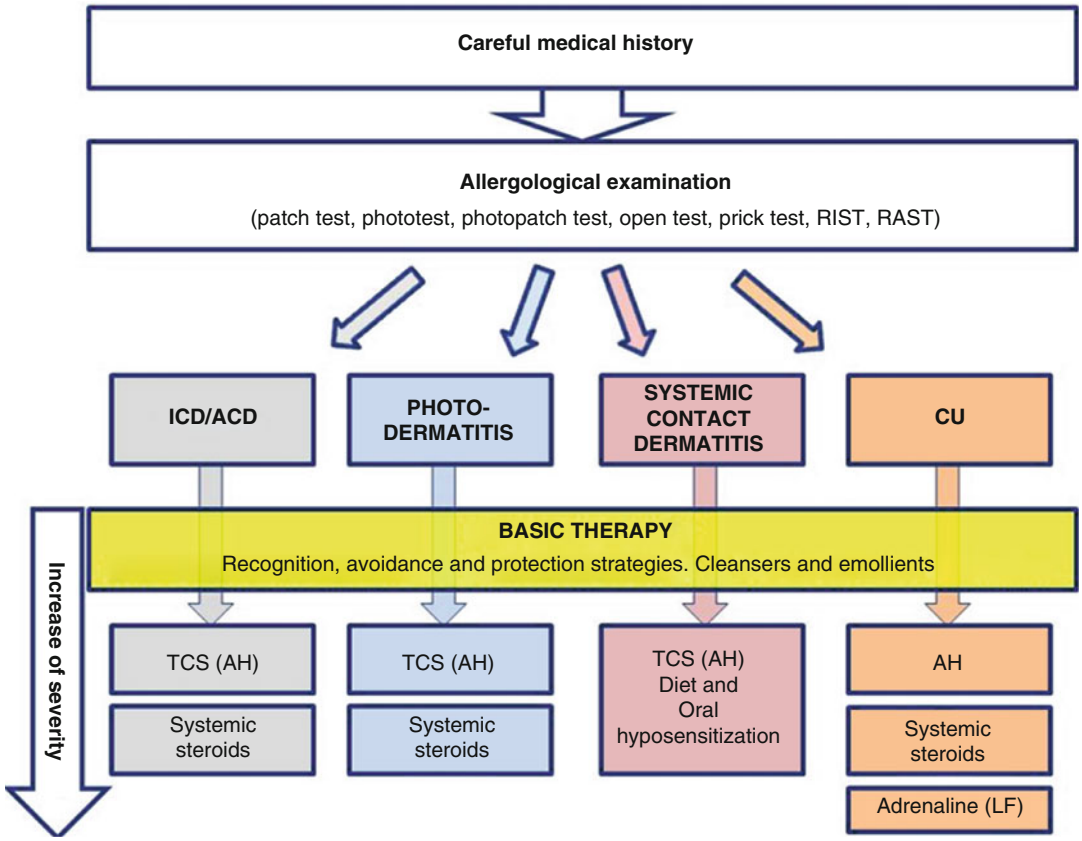

Fig. 16.1 Therapeutic algorithm in contact dermatitis. *ICD* irritant contact dermatitis, *ACD* allergic contact dermatitis, *CU* contact urticaria, *TCS* topical corticosteroids, *AH* (oral) antihistamines, *LF* life-threatening cases, *RIST* radio-immunosorbent test, *RAST* radioallergosorbent test

Basic Therapy

The first step in the management of irritant and allergic CD involves the explanation of the disease, followed by avoidance, protection, and substitution strategies. Educational programs are needed.

Avoidance

The recognition and avoidance of the exposure to all possible irritant and allergic factors from the domestic and professional environment has to be realized as consequently and as soon as possible. A careful investigation of the patients' habits together with a visit of the workplace may be necessary to identify all the potential skin irritants and allergens.

Protection

The protection is an essential step for the effective treatment. Its proper fulfillment depends on the nature of the irritant, the body area involved, and the environment where the contact is.

As many diseases involve the hands, gloves are the mainstay of protection. At home, rubber or polyvinyl chloride gloves, possibly over cotton gloves, should be sufficient. It is also important to educate the patient to properly use and remove gloves after their application. In fact, sweating and occlusion can trigger or aggravate the dermatitis. At the workplace, the choice of gloves to use depends on the work and the nature of the chemicals involved. Then, the choice of the gloves should be made carefully because many and different solvents and chemicals can

penetrate gloves with time, depending on the material. Table 16.4 reports the suggested types of gloves for different hazardous products.

The efficacy of barrier creams in the protection to irritants and allergens is questionable. They can be used, but their use should not be over-promoted. Their efficacy is not comparable to gloves, if used alone, and they may confer on workers a false sense of security. Emollients seem to provide some benefits in the treatment of irritant contact dermatitis.

Substitution

Some irritant agents, like soap, water, etc., can be substituted with nonirritating ones. Avoidance of an individual allergen is frequently difficult to realize.

Table 16.4 Gloves suggested for specific hazardous products

Hazard	Type of glove suggested
Microorganisms	NRL, thermoplastic elastomer
Disinfectants	NRL, PVC, PE, EMA
Pharmaceuticals	NRL (permeability time very short)
Composite materials	NRL (permeability time in minutes)
Solvents	PE, PVC, nitrile, NRL, neoprene, butyl rubber, Viton
Corrosives	NRL, PE, PVC, neoprene, butyl rubber, Viton
Detergents	NRL, EMA, PE, neoprene, PVC, nitrile
Machining oils	NRL, PVC, nitrile, neoprene

From Bourke et al. (2009) modified
NRL natural rubber latex, *PVC* polyvinyl chloride, *PE* polyethylene, *EMA* ethylene methyl methacrylate

Educational Programs

Educational programs have to be carried out to increase the knowledge of people and workers on this common disease.

Topical Treatment

The choice of the treatment depends on the severity and course of the dermatitis. A practical summary of recommendations is given in Fig. 16.1 and Table 16.5.

Cleaning and bathing are normally recommended if appropriately performed as in other diseases, e.g., atopic dermatitis. Yet, it is extremely important to investigate the patients' habits in cleaning and bathing to avoid misuse that can cause ICD and, in case of ICD, to modify them.

The vehicle of emollient or TCS is important and varies according to the clinical presentation. Cream is better for acute lesions, whereas ointment may be used in the case of lichenified and scaly thickened infiltrates.

Daily application of emollient is helpful in improving ICD and in preventing dryness. They should be used after wearing gloves at home or at the workplace and at the end of the work shift.

The soothing effects of paste bandage or wet dressing may help to improve the itch/scratch vicious circle.

Treatment should not be stopped until healing is complete. It is also important to explain to a patient that his/her skin will remain especially vulnerable for some weeks beyond the end of the

Table 16.5 Suggested treatment for different clinical manifestations

Therapeutic agents	Acute	Subacute	Chronic	Prophylactic
Wet dressing	++	+	–	–
Creams/lotion (emollients)	++	+	+	++
Pastes/ointments (emollients)	+	++	++	+
Topical corticosteroids (creams/lotion)	++	++	+	–
Topical corticosteroids (ointment)	+	++	++	–
Topical immunosuppressant	+	+	+	–
Polythene or bandage occlusion	+	+	+	–
Systemic steroids (and systemic treatment)	+	+	++	–

– Not recommended, +/– recommended in some clinical presentations, + sufficiently recommended, sometimes not as the first line, ++ recommended

treatment. Thus, an education in the daily skin care is mandatory to treat the skin and to prevent relapses.

Patients have to follow these basic recommendations for very long periods of time, often forever.

Topical Corticosteroids (TCS)

Topical corticosteroids (TCS) are widely accepted as the first-line treatment of established contact dermatitis. Studies regarding their use are present especially in allergic contact dermatitis. The choice of the potency of TCS depends on the severity of dermatitis, the area to be treated, and the age of the patient. Mild corticosteroids are usually preferred for sensitive areas (e.g., face and genital areas) and for children, whereas more potent molecules may be preferred on the other parts of the body and when the dermatitis is moderate to severe. Their use under polythene occlusion may be helpful: however, it has to be considered that the occlusion increases the TCS effects (both efficacy and side effects). TCS suppress the inflammation, but at the same time they make the epidermis thinner and can alter the barrier function. Thus, they have to be used properly.

It is worthy to remember that TCS can be an important cause of ACD even though rarely. ACD caused by TCS has to be suspected when the dermatitis persists and does not respond or worsens with the use of TCS.

TCS allergic contact dermatitis represents about 1 % of all ACD, and the patch test represents a mandatory step in the confirmation of the diagnosis. A late reading of the corticosteroids patch test reaction at day 7 is frequently necessary for the appropriate testing.

Corticosteroid molecules can be classified according to their allergological group, as reported in Table 16.6.

Cross-sensitivity among each group of corticosteroids is common and needs to be taken always into consideration. Patients, suffering from an ACD to a corticosteroid, can be treated with a corticosteroid of another group, but not with a corticosteroid of the same group. For example, a patient with contact sensitivity to a corticosteroid of class B (e.g., budesonide) can be treated with a corticosteroid of class D1 (e.g., fluticasone propionate).

Cross-reactivities between topical and systemic corticosteroids among each group have also been reported.

The sensitization to corticosteroids is linked to several factors. These are the following structures: the C(16)-methyl substitution and the C16-methyl corticosteroids (groups C and D1). The latter seems far less allergenic than the non-methylated molecules and may be preferred.

Topical Calcineurin Inhibitors (TCI)

Topical calcineurin inhibitors (TCI), especially pimecrolimus and tacrolimus, are frequently effective in the treatment of atopic dermatitis

Table 16.6 Classification of corticosteroids as allergens

A	B	C	D1	D2
Hydrocortisone 21-acetate	Budesonide	Desoximetasone	Mometasone furoate	Hydrocortisone 17-butyrate
Prednisone	Desonide	Dexamethasone	Betamethasone dipropionate	Methylprednisolone aceponate
Methylprednisolone acetate	Halcinonide	Betamethasone	Clobetasol 17-propionate	Prednicarbate
	Fluocinolone acetonide	Fluocortolone	Clobetasone 17-butyrate	
		Diflucortolone valerate	Alclometasone dipropionate	
			Fluticasone propionate	

(AD). Large-scale studies have been performed for AD, in children and adults, confirming their efficacy in a condition sharing many pathophysiological similarities with contact dermatitis (as eczema, itch, and the presence of inflammatory cell infiltrates in the skin). Studies have demonstrated the TCI to be effective in a model of allergic contact dermatitis to nickel. As compared to topical corticosteroids, TCI generally do not cause skin atrophy. However, their use in contact dermatitis is limited, and their recommendation is supported by few studies. They represent a second-line treatment of contact dermatitis: their use is suggested for sensitive areas (e.g., face, genital, etc.) and in cases who do not respond to TCS or in the case of sensitization to TCS.

Proactive strategies were not investigated in contact dermatitis.

Antimicrobial Treatments

Where secondary bacterial infection complicates an eczema, the combined use of topical corticosteroids together with topical antiseptic compounds may be useful, even if this approach is supported only by few studies.

In case of extended clinical skin infection, oral antibiotics have to be used that are effective against *Staphylococcus aureus*.

Systemic Therapy

Systemic Corticosteroids

Moderate to severe acute contact dermatitis may very rarely be required with a 14–21-day course of oral corticosteroids.

The initial dose of 25–50 mg of prednisone, daily, after breakfast should be decreased by 10 mg/day every 3–5 days according to the improvement of the dermatitis.

The oral therapy should be continued for at least 7–10 days after the clinical remission in order to avoid relapse. Importantly, all exogenous triggers, irritant or allergic, should be individualized and avoided; otherwise, the side effects of a steroid abuse become threatening.

Antihistamines and Antipruritic Measures

Pruritus has many causes, mediators, and treatment modalities (→ see Atopic Dermatitis).

Pruritus can be reduced by proper topical treatment, mainly TCS and basic treatment, and systemic treatment according to the severity.

Antihistamines are frequently used for their antipruritic effects in contact dermatitis. Yet, their efficacy is questionable. The efficacy of either first- or second-generation antihistamines has not been investigated deeply in contact dermatitis.

Patients suffering from pruritus that is severe or disturbs the daily life and sleep can benefit from first-generation antihistamines for their sedative effects.

Other Treatments

Phototherapy, with psoralen plus UVA (PUVA), UVA1, and broad- or narrowband UVB, is used either in moderate to severe AD or in chronic hand eczema.

Similarly, the use of cyclosporine A (CSA) and azathioprine (AZP) is supported by trials in these diseases. In contact dermatitis, these therapeutic strategies can be used with similar modalities.

Phototherapy, CSA, and AZP are second-line therapies for patients with moderate to severe contact dermatitis that does not respond to topical corticosteroids.

The use of one of these treatments depends on the severity of the dermatitis, the availability of the treatment, and the involved areas.

These treatments are discussed in detail elsewhere (→ see hand dermatitis, atopic dermatitis, psoriasis, phototherapy, immunosuppressive therapies).

The risk/benefit ratio of a treatment with CSA or with AZP should be considered before the start and during the treatment.

When the hands are involved, new therapeutic strategies are available in several European countries, such as alitretinoin (→see hand dermatitis chapter).

Summary of Recommendations at a Glance (Fig. 16.1, Table 16.6)

- The clinical history of a patient with CD has to be carried out accurately.
- Patients with persistent eczema, or not responding to conventional treatment, should be patch tested to at least an extended standard series of allergens.
- The treatment consists in basic therapy and use of TCS and antipruritic drugs as a first line of therapy. Systemic treatment is reserved for chronic and severe case.

(Nickel) Elimination Diet and Oral Hyposensitization

Nickel contact allergy is very common in Western countries, and the dermatitis may require prolonged treatment. The development of new strategies aims to improve the disease and the quality of life of affected individuals.

There are many evidences in supporting the benefit of low-nickel diet in some nickel-sensitive patients, in particular in those with wide and systemic manifestations.

In Table 16.6, the low-nickel diet is summarized.

High-nickel foods (forbidden)	Low-nickel foods (allowed)
Canned foods	Flour
Asparagus, mushrooms, onions, spinach, tomato, potatoes	Olive oil
Legumes, lentils, beans	Butter
Lettuce, carrots, broccoli	Eggs
Whole-wheat flour, oat, millet	Meat
Pear, plum, figs, apricot, kiwi, pineapple	Fish (with the exceptions signalized before)
Hazelnut, almond, peanuts	Milk and cheese
Dried fruit	Fruits and vegetables (with the exceptions signalized before)
Cocoa, chocolate	Wine
Margarine	Coffee
Herring, oyster, mackerel	Muesli
(Green) the	
Marzipan	
Licorice	
Vitamins and nutritional supplement	

Oral tolerance impedes or contrasts with the development of undesired immune responses toward dietary antigens. Oral hyposensitization with a daily dose of 50 μg (micrograms) of elemental nickel (given as $NiSO_4 \cdot 6H_2O$) has led in nickel-allergic individuals to a significant improvement of their cutaneous and systemic symptoms. This method is a promising approach for the management of cutaneous and systemic nickel allergy. Oral hyposensitization can be used also for the other systemic contact dermatitis.

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Cutaneous Vasculitis

17

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Key Points

- Cutaneous vasculitides (CV) are a group of clinical diseases characterized by angiocentric segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls.
- Usually they involve postcapillary venules. CV can be idiopathic, can be associated with an underlying chronic disease, or can be precipitated by infections or drugs.
- Although skin lesions of CV are various, palpable purpura is the most commonly described.
- Some patients may have also a systemic involvement of the small blood vessel.
- Evaluation of patient should include a thorough history, physical examination, laboratory tests, and histopathology studies. When it's possible, therapeutic approach to CV is to find out and to remove the causative agent.
- Otherwise, local and systemic treatments are necessary.

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Definition and Epidemiology

Vasculitis is a broad, poorly defined category of diseases, characterized by inflammation of the blood vessel that leads to various clinical manifestations depending on which organ systems are involved.

The clinical condition of dermatological interest is mainly related to "cutaneous vasculitis" (CV), a not uncommon disorder characterized by an inflammation and tissue damage of the blood vessel and skin lesions.

CV are a group of clinical diseases characterized clinically by palpable purpura and histologically by angiocentric segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls. On the basis of histopathological pattern, two major forms of CV are recognized: a leukocytoclastic form and a lympho-monocytic one. More recently, an eosinophilic vasculitis has also been described.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_17, © Springer-Verlag Berlin Heidelberg 2015

Usually, they involve small and medium blood vessels, especially postcapillary venules.

The disorder occurs equally in both sexes and at all ages. About 10 % of patients are children and suffer from the Henoch-Schönlein purpura.

An associated disease determines the age of the affected individual. Geographic variations in CV may reflect an environmental influence, although the seasonal variation may suggest an infectious etiology.

Cutaneous vasculitis may occur idiopathically or in association with chronic diseases, malignant neoplasm, and precipitating agents (Table 17.1).

The pathogenesis of leukocytoclastic vasculitis depends mainly upon immune complex formation. Immune complexes may activate complement system and lead to the generation of C5a anaphylatoxin. This one attracts neutrophils and degranulas mast cells. Finally, neutrophils produce lysosomal enzymes and reactive oxygen products that damage tissue.

A possible role of lymphocytes has been suggested by their presence in many skin biopsies. Lymphocytes may be activated by IC, by cellular immune mechanisms, and by primary activation in autoimmune disease. In the first cases, lymphocytes perpetuate CNV; in the other, they start the pathological process.

Time course analyses are evaluating the role of mast cells in CNV, especially in patient with urticaria. Eosinophils seem to be of less importance, except in eosinophilic vasculitis and drug-induced CNV. They increase vascular permeability and cause the release of mediators from mast cells.

Finally, there is ANCA-associated cutaneous necrotizing vasculitis. ANCAs are antineutrophil cytoplasmic antibodies, which can start the inflammation and the endothelial cell injury.

Clinical Presentation

Subtypes of Cutaneous Vasculitis

CV can be idiopathic, can be associated with an underlying chronic disease, or can be precipitated by infections or drugs (Table 17.1)

Many factors, such as infection, drugs, chemicals, and food, should be considered as a possible cause of CV. Really, most of the etiologic factors have been incriminated by the association rather than by direct demonstration.

Approximately 22 % of all cases of CV are associated with an infectious etiology, and maybe this prevalence is underestimated. The most common infection agents are β-hemolytic streptococcus, *Staphylococcus aureus*, *Mycobacterium leprae*, and hepatitis B and C viruses. More rarely, CV has been documented in other bacterial (e.g., *Neisseria meningitidis*, *Neisseria gonorrhoeae*), viral, fungal, protozoan, or helminthic infections. Cold, stasis, previous injury, or constitutional defects may predispose patients to the development of vasculitis. Biopsy usually reveals a mixed small- and medium-sized vessel vasculitis. The cutaneous features include hemorrhagic petechiae, purpura, blister, bullae, macules, or nodules.

Cutaneous vasculitis may be also a product of the exposure to many drugs (e.g., penicillin, hydantoin, thiazides, oral contraceptives, serum) and is considered as immune complex reactions. Usually, the interval between the ingestion of the drug and onset of the vasculitis varies from hours to days, more rarely years. The cutaneous manifestations vary from maculopapular, vesicular, or purpuric rash. Lesions can be localized or diffuse and may be associated to other systemic symptoms, like fever, malaise, arthralgias, nausea, and vomiting. Usually, the skin lesions resolve in few days, without sequelae.

CNV has been reported in association with coexistent diseases, most frequently with hyperglobulinemic states or cryoglobulinemia.

Connective-tissue disease vasculitis is an uncommon complication, which is described most frequently in association with systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. Usually, skin biopsy reveals a vasculitis of small- and medium-sized vessel. The clinical appearances can be many, but typically we describe purpura, vesiculobullous lesions, urticaria, and splinter hemorrhages. Ulcers, subcutaneous nodules, gangrene, livedo

Table 17.1 Classification of cutaneous vasculitis

Idiopathic disorders	Henoch-Schönlein purpura Urticaria vasculitis Erythema elevatum diutinum Nodular vasculitis Livedoid vasculitis Atrophie blanche Acute hemorrhagic edema of infancy Cutaneous polyarteritis nodosa Genetic complement deficiencies Idiopathic	
CNV associated with coexistent diseases	Chronic diseases	Systemic lupus erythematous Sjögren's syndrome Rheumatoid arthritis Behçet's disease Hyperglobulinemic states Cryoglobulinemia Ulcerative colitis Cystic fibrosis Primary biliary cirrhosis HIV/AIDS
	Solid tumor	Lung cancer Colon carcinoma Renal Prostate Head and neck cancer Breast cancer
	Lymphoproliferative disorders	Hodgkin's disease Mycosis fungoides Lymphosarcoma Adult T-cell leukemia Multiple myeloma
Precipitating factors	Viral infections (HAV, HBV, HCV, HSV, HTLV) Bacterial infections (β-hemolytic streptococcus group A, *Staphylococcus aureus*, *Mycobacterium leprae*) Fungal infections (*Candida albicans*) Protozoan infections (*Plasmodium malariae*) Helminth infections (*Schistosoma haematobium*, *Schistosoma mansoni*, *Onchocerca volvulus*) Drugs (insulin, penicillin, hydantoins, streptomycin, aminosalicylic acid, sulfonamides, thiazides, phothiazines, vitamins, allopurinol, phenylbutazone, quinine, streptokinase, tamoxifen, anti-influenza vaccine, oral contraceptive, serum, contrast media, methotrexate, drug additives, infliximab, etanercept, adalimumab, rituximab) Chemicals (insecticides, petroleum products) Foodstuff allergens (milk protein, gluten)	

Modified from Hautmann et al. (1999)

racemosa, and pyoderma gangrenosum can also be seen and represent arterial involvement.

Lupus vasculitis has been described in 20–40 % of patients with systemic lupus erythematosus, especially in young men. More rarely, it can be seen also in patients with subacute cutaneous lupus erythematosus. The most common cutaneous presentation is macules or depressed

punctuate scars and expression of skin infarcts. Lesions are mainly localized on the palms and on fingers. Other cutaneous manifestations include purpura, urticaria, and livedo.

Rheumatoid vasculitis is an uncommon complication of rheumatoid arthritis, which is described mainly in an adult man. RV is associated with high rheumatoid factor titer, joint erosion, rheumatoid nodules, and extra-articular symptoms (e.g., mononeuritis). The typical skin lesion is palpable purpura, localized on the lower extremities. Other cutaneous manifestations include maculopapular erythema, hemorrhagic blisters, nodules, ulcers, livedo, and atrophie blanche.

Patients with Sjögren's syndrome usually develop a systemic vasculitis. The most common skin lesions are palpable purpura, urticaria, and ecchymoses.

More rarely, CV can be seen in dermatomyositis, scleroderma, and polychondritis.

Occasionally, CV is associated with other chronic disorders, like bowel bypass syndrome, ulcerative colitis, primary biliary cirrhosis, and HIV/AIDS. Cutaneous vasculitis can be also described in lymphoproliferative disorders, such as Hodgkin's lymphoma, lymphosarcoma, adult T-cell leukemia, and multiple myeloma. More rarely, CV has been described in association with adenocarcinoma of the lung, prostatic carcinoma, kidney carcinoma, bladder carcinoma, or colon carcinoma.

In many patients the cause of CV remains unknown.

The Henoch-Schönlein purpura is the widely recognized one. It is a rare disorder, which occurs predominantly in children that are 4–8 years old. More rarely, it has been described in adults. The disease usually follows an upper respiratory tract infection, with a latency of 1–3 weeks. Clinically, it is characterized by a typical symmetric palpable purpura localized on the lower extremities, which regress in 10–14 days. Direct immunofluorescence studies show IgA deposits affecting small vessels. Most of the patients suffer arthralgias and arthritis and gastrointestinal (e.g., colicky pain, vomiting, melena) or renal symptoms (e.g., proteinuria, hematuria, glomerulonephritis). Central nervous system involvement may occur as diplopia and headaches.

Urticaria vasculitis is a chronic recurrent disorder, usually affecting young adult women in their fourth or fifth decades of life. Skin manifestations are pruritic, erythematous wheals that may contain foci of purpura. Lesions usually persist for 2–3 days. Occasionally, there could be macular erythema, livedo reticularis, nodules, bullae, or angioedema. Systemic symptoms (e.g., fever, arthralgias, abdominal pain) are usually present. The Schnitzler syndrome is a particular form of recurrent urticaria vasculitis, described in patients with monoclonal IgMκ M component. It's a rare disorder characterized by a systemic involvement (e.g., lymphadenopathy, hepatosplenomegaly, renal failure, neurological compromission) and by the risk of development of hematologic malignant conditions.

Erythema elevatum diutinum is a chronic cutaneous vasculitis. It's a rare disease, more frequent in female patient. The etiology is largely unknown; maybe there is an association between EED and connective-tissue disease, infection, and hematologic abnormalities. Clinically, EED is characterized by symmetric and persistent red or brown papules, plaques, or nodules on the extensor surface and over the gluteal area.

Behçet's disease is a chronic inflammatory disease, rarely described in Europe or North America, while it's more common in Asia. Typically, Behçet's disease affects young men who develop oral and genital ulcers and ocular defects. Patients may show also arthralgias and gastrointestinal or neurological symptoms. Cutaneous manifestations include erythema nodosum or purpura. Rarely, there could be hemorrhagic bullae, pyoderma gangrenosum-like lesions, or erythema multiforme-like lesions.

Nodular vasculitis affects women from 30 to 60 years of age. In some cases, it's associated with *Mycobacterium tuberculosis* infection ("erythema induratum"). Clinically, nodular vasculitis is characterized by a prodromal phase consisting of fever, malaise, and arthritis. After that, patients show the typical nodular skin lesions, localized on the posterolateral face of the legs. Lesions evolve slowly. The nodules that don't ulcerate may heal in 2–6 weeks, with residual scarring and hyperpigmentation.

Livedo vasculitis is characterized by a flat network of intersecting blue-red lines. Lesions are localized on the legs, arms, or lower trunk. Typically, patients develop painful ulcers of the lower extremities that resolve in sclerotic pale areas surrounded by telangiectasias ("atrophie blanche"). Livedoid vasculopathy is more common in women. It could be an idiopathic disorder or may occur in patients with connective-tissue disorder, thrombophilia, or malignant conditions. Sneddon's syndrome is a particular form of livedo, associated with ischemic cerebrovascular lesions, hypotension, and arterial and venous thromboses.

Acute hemorrhagic edema of infancy is another rare CV. It's characterized by edema and palpable purpura in infants younger than 2 years old. The disease has a short course, followed by spontaneous complete recovery.

Cutaneous polyarteritis nodosa is a limited form of polyarteritis nodosa which presents with skin lesions, fever, arthralgias, myalgias, and peripheral neuropathy. There aren't other systemic symptoms. The disease is more common in women that are 20–40 years old. The typical skin lesions are subcutaneous nodules localized on the lower extremities and on the buttocks. Other skin lesions include livedo reticularis with ulcerations, atrophie blanche, petechiae, purpura, or necrosis.

Rarely, CV has been described in young patients with genetic C2 deficiency. Also the deficiencies of C4A and C4B have been recognized in some adult patients with the Henoch-Schönlein purpura.

Finally, there are patients with CV that don't meet the criteria for recognized syndrome and are classified as idiopathic.

Clinical Features

The skin lesions of CNV are polymorphous; however, palpable purpura is the most common (→see also purpura chapter). It's characterized by erythematous papules that don't blanch when the skin is pressed. Initially, lesions might be only purpuric; as the process continues, they become palpable, ranging in size from pinpoint to several centimeters. Occasionally, subcutaneous edema can be observed in the same area.

Table 17.2 Systemic involvement in CNV

Kidney	Hematuria, proteinuria, glomerulonephritis, interstitial nephritis, acute and chronic renal failure
Gastrointestinal tract	Colicky pain, nausea, vomiting, diarrhea, hemoptysis, melena
Respiratory tract	Laryngeal edema; dyspnea; tracheal stenosis; chronic obstructive, restrictive, or interstitial pulmonary disease; hemoptysis; pleural effusion
Heart	Arrhythmias, valvular defects, congestive heart failure, myocardial angiitis, pericarditis
Nervous system	Headache, diplopia, hypo- or paresthesia
Joints	Arthralgia, arthritis
Eyes	Conjunctivitis, episcleritis, iridocyclitis, uveitis, retinal vasculitis, vasculitis of the optic nerve
Miscellaneous	Pancreatitis, hepatitis, lymphadenopathy, hepatosplenomegaly

Erythematous macules, wheals, papules, blister, nodules, ecchymoses, pustules, hemorrhagic vesicles, ulcers, and livedo reticularis are less common manifestations.

Lesions can occur anywhere, but they are most commonly found on the lower legs, where they are often distributed symmetrically. The mucous membranes are rarely involved (petechiae, hemorrhagic blisters, ulcers).

Lesional symptoms include pruritus, burning, or pain.

Usually, lesions persist from 1 to 4 weeks and resolve with hyperpigmentation and/or residual scarring.

The disease may be self-timing but can recur or become chronic.

Often, it's confined to the skin. In some cases, the cutaneous manifestations may be attended by fever, malaise, or signs and symptoms of a defined underlying disease. Some patients may have also a systemic involvement of the small blood vessel (renal, gastrointestinal, pericardial, neurological, and rheumatological) (Table 17.2).

Diagnosis

Evaluation should include a thorough history and physical examination with attention to possible etiological agents or associated diseases.

A complete history usually reveals risk factors and symptoms of systemic involvement. Drug or infection history, chemical exposure, food allergens, and travel histories are all essential. At the same time, it's important to investigate the presence of connective-tissue disease or other chronic disorders.

The clinical examination should follow a logical pattern beginning with the assessment of the primary clinical lesions (e.g., palpable purpura, livedo, urticaria) and of the secondary ones (e.g., ulceration, infection). A complete cardiopulmonary, abdominal, and neurologic examination must be performed in all patients, especially in whom systemic vasculitis is suspected.

The laboratory screening is always required to confirm the diagnosis of vasculitis, to find an associated disorder, and to determinate the extent of systemic involvement (Table 17.3). The laboratory's evaluation depends on the clinical history and physical examination of the patients.

Table 17.3 Evaluation of the patient with CV

History	Infections?
	Drugs?
	Chemicals?
	Foodstuff allergens?
	Underlying systemic disease?
	Systemic symptoms?
Physical examination	Primary clinical lesions
	Secondary clinical lesions
	Systemic involvement
Laboratory studies	Complete blood count
	Hepatitis surface antigen
	Rheumatoid factor
	Circulating immune complexes
	Complement components
	Antinuclear antibodies
	Antiphospholipid antibodies
	Cryoglobulins
	Antineutrophil cytoplasmic antibodies
	Urinalysis
Histopathological evaluation	Skin biopsy
	Muscle biopsy
	Renal biopsy
	Lung biopsy

The most common laboratory finding is an increased erythrocyte sedimentation rate.

In some patients with leukocytoclastic vasculitis, we can also find leukocytosis, anemia, and thrombocytosis.

Decreased levels of complement components are often noted in CNV associated with rheumatoid arthritis (C1, C2, C4), systemic lupus erythematosus (C1q, C2, C3, C4, C9, factor B), cryoglobulinemia, and Sjögren's syndrome. More rarely, a hypocomplementemia may be described in patient with urticarial vasculitis or idiopathic CV.

Autoantibodies to vascular endothelial cells are described in patients with urticaria or concomitant connective-tissue disease. In the Henoch-Schönlein purpura, serum IgA levels are elevated, IgA ANCA can be present, and urinary endothelin-1 can be increased.

Circulating immune complexes, rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies, antistreptolysin antibodies, and hepatitis surface antigens may be detected.

Also anticardiolipin antibodies occur in patients with various forms of CNV.

Cryoglobulins may be found in patients with idiopathic CNV and in patients with connective-tissue disease and lymphoproliferative disorders or infections.

In patients with systemic vasculitis, to test the antineutrophil cytoplasmic antibodies (p-ANCA, c-ANCA) can be diagnostically helpful. ANCAs have been demonstrated in Wegener's granulomatosis, the Churg-Strauss syndrome, microscopic polyarteritis nodosa, idiopathic glomerulonephritis, and many other leukocytoclastic CNV. The sensitivity of ANCAs to this group of disease is high when there is a renal involvement. However, the ANCA levels aren't correlated with the severity of vasculitis, an increase of their title may precede a relapse, and their disappearance is associated with the absence of disease activity.

Patients have only one of the two types of ANCA antibodies. c-ANCAs are specific for Wegener's granulomatosis and microscopic polyarteritis. p-ANCA occurs in idiopathic glomerulonephritis, the Churg-Strauss syndrome, polyarteritis nodosa with visceral involvement, and vasculitis overlap syndrome.

Urine analysis may reveal many abnormalities of sedimentation, such as proteinuria, hematuria, and cylindruria, caused by possible renal involvement.

Because significant morbility can result from systemic involvement of CV, careful evaluation of the patient should be done to define the type and severity of the involvement too. If the laboratory results are normal, further invasive studies (e.g., nerve, muscle, or lung biopsy) are warranted.

Skin biopsy is required for definitive diagnosis. The hallmark histopathologic pattern of CV is leukocytoclastic vasculitis. It's characterized by angiocentric segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls. A cellular infiltrate, largely composed by neutrophils, can be described around and within blood vessels. In the later phase lymphocytes and monocytes predominate in the infiltrate.

More rarely, we can describe a lymphocytic or an eosinophilic pattern.

Biopsy location, depth, and timing must be taken into consideration by the clinician to increase the diagnostic yield. Small vessels, for example, reside in the upper dermis, while medium-sized, muscular vessels are found in the deep dermis and subcutis.

Routine microscopy is best obtained from a newer primary lesion of 24–48 h duration if possible. Biopsies performed in that period can show a neutrophilic, eosinophilic, or lymphocytic infiltration, depending on the underlying process. After 48 h, lymphocytes replace the other inflammatory cells and the histological pattern becomes nondiagnostic.

In addition to routine microscopy, special stains for microorganisms, including the Gram stain, acid-fast stains, and methenamine silver stains, are recommended. In some cases, also the tissue cultures may be needed to rule out infection.

Direct immunofluorescence microscopy is usually helpful in selected cases of CV. DIF biopsies are best taken from a leading erythematous edge or perilesional in the recent lesions, better of less than 24 h duration. By direct immunofluorescence microscopy, fibrin deposition in venules is always identified, while the deposition of immunoglobulins and complement components varies widely. Immunoglobulin G, rather than IgM, is more likely to be present when there is an underlying collagen vascular disease. IgA are indicative of the Henoch-Schönlein purpura. C3 is the only complement protein which has been described with frequency in CNV.

General Principles of Treatment

Therapeutic approach to CNV is to find out and to remove the causative agent (e.g., infections, drugs, food allergens). This may be all that is required for the treatment because it's usually followed by the clearing of skin lesions. Interferon-α induces clearing of skin manifestations in patients with hepatitis C virus infection.

Otherwise, local and systemic treatments are necessary. In each case, the correction of local factors (e.g., trauma, cold stasis) may be important.

Local therapies (corticosteroids, antibiotics) are helpful only in some patients.

Better results are obtained with systemic therapy (Table 17.4).

Oral corticosteroids (prednisone 60–80 mg/day) are recommended in patients with a significant systemic involvement. Because of the risk of rebound effect, it's really important to reduce the dose slowly.

Patients with persistent or necrotic lesions may benefit from nonsteroidal anti-inflammatory drugs (e.g., acetylsalicylic acid, indomethacin). Chronic disease can also be treated with oral colchicines (0.6 mg twice or three times daily). This drug seems to be particularly useful in patients with erythema elevatum diutinum.

Table 17.4 Treatment of CV

Drug	Suggested dose	Suggested recommendation
Systemic glucocorticoids	60–80 mg/day	
Nonsteroidal anti-inflammatory agents		
Colchicines	0.6 mg twice or three times/day	Erythema elevatum diutinum
Dapsone	50–200 mg/day	Only skin involvement
H1 antihistamines		
Potassium iodine	0.3–1.5 g four times/day	Nodular vasculitis
Azathioprine	50–200 mg/day	
Methotrexate	10–25 mg/day	
Cyclosporine	3–5 mg/kg/day	
Cyclophosphamide	2 mg/kg/day	
Mycophenolate mofetil	0,6 mg twice/day	Severe and resistant CV
Intravenous gamma globulin		Severe and resistant CV
Plasmapheresis		Severe and resistant CV
Infliximab, rituximab		Severe and resistant CV

In patients with the only skin involvement, we can use dapsone (50–200 mg/day).

Potassium iodide (0.3–1.5 g four times daily) is useful in nodular vasculitis.

H1 antihistamines, eventually used in combination with H2 antihistamines, are helpful to alleviate pruritus and to reduce tissue deposition of circulating immune complexes. H1 antihistamines can be used also with nonsteroidal anti-inflammatory.

Fibrinolytic agents may be used in patients who have decreased fibrinolytic activity. Stanozolol (5 mg twice daily), heparin (5,000 U twice daily), mesoglycans (50–100 mg/day), and defibrotide (700 mg/day) have been used successfully in many hypofibrinolytic conditions.

On the other hand, aminocaproic acid (8–16 mg/day) is useful to treat patients with hyperfibrinolytic states.

Immunosuppressive agents, like cyclophosphamide (2 mg/kg per day or as a monthly intravenous pulse), methotrexate (10–25 mg/week), azathioprine (50–200 mg/day), and cyclosporine (3–5 mg/kg per day), are recommended in patients with CNV with a rapid course and systemic involvement, which aren't controlled with corticosteroids.

If there still is no therapeutic response, it is possible to treat the patient with plasmapheresis, intravenous immunoglobulin, mizoribine, infliximab, or rituximab.

Patients with urticarial vasculitis can be treated with the same therapeutic option. Intramuscular gold therapy, cyclophosphamide-dexamethasone pulse therapy, mycophenolate mofetil, thalidomide, PUVA therapy, anakinra, and cinnarizine have been reported to benefit some patients.

Patients with livedoid vasculitis can be treated with nonsteroidal anti-inflammatory agents, glucocorticoids, colchicines, dapsone, and low-dose heparin. Additional case reports exist on the treatment of patients with nifedipine, pentoxifylline, hyperbaric oxygen therapy, PUVA therapy, infusion of prostacyclin or prostaglandin E, intravenous immunoglobulin, or rituximab.

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Darier's Disease

18

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Key Points

- Darier's disease (DD) is an autosomal dominant disease induced by haplo-insufficiency with variable expressivity but with complete penetrance in adults.
- Lesions are hyperkeratotic, greasy papules, which are skin colored, yellow, or brown, that may coalesce into large plaques. Pruritus occurs in 80 % of patients and may be intractable. Nails, mucous, and folds can be involved. The disease usually has a chronic relapsing course.
- Diagnosis must be confirmed by histology, showing focal acantholytic dyskeratosis.
- Therapy is challenging and sometimes frustrating. It is based on topical and systemic retinoids or surgical procedures.
- Sun and heat avoidance, use of sunscreens, and maintenance of personal hygiene can be helpful. Clothing should be cool cotton and not too tight.

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Definition and Epidemiology

Darier's disease (DD) is an autosomal dominant genodermatosis belonging to the group of keratinization disorders that can affect the epidermis, the nails, and the mucous membranes. Darier and White first described the condition independently in 1889; although it is also known as "keratosis follicularis," this term should be avoided since it is inappropriate as the lesions are not follicular.

The prevalence ranges from 1 in 100,000 to 1 in 30,000, and it affects both males and females, of all ethnic groups. It has been reported that in women the disease shows a milder rash than in men. The disease is rarely observed before the age of 5, and it usually begins during the first two decades of life, although it may go unnoticed until aggravated by sweating, heat, or during summer.

Basic Concepts of Pathogenesis

DD is an autosomal dominant disease induced by haplo-insufficiency with variable expressivity but with complete penetrance in adults. Sporadic cases are not unusual.

It is caused by a mutation in the *ATP2A2* gene on chromosome 12q23-24.1. This gene encodes the sarco/endoplasmic reticulum Ca^{2+} ATPase type 2 isoform (SERCA/2) which transports Ca^{2+} from the cytosol back to the endoplasmic reticulum lumen.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_18, © Springer-Verlag Berlin Heidelberg 2015

The connection between molecular alterations and clinical expression is not completely understood. It has been hypothesized that abnormalities of SERCA2 in DD may alter cell signaling, and this induces the alteration of synthesis, folding, or trafficking of desmosomal components, causing interference with the adhesion and differentiation of keratinocytes.

Clinical Presentation

Considerable variation in severity as in clinical manifestation was found between families. In some patients with classic disease, no mutation was identified.

The distinctive lesions are firm, persistent, hyperkeratotic, greasy papules, which are skin colored, yellow, or brown (Fig. 18.1). The lesions may coalesce into large plaques or papillomatous masses, predominantly in the seborrheic areas of the trunk (Fig. 18.2a) and face (Fig. 18.2b), mostly the scalp margins (Fig. 18.2c), temples, ears (Fig. 18.2d), and scalp, symmetrically. In pigmented skin, flat and freckle-like lesions can be observed as pale macules.

The groin, axillae, and anogenital regions are also frequently affected and cause the major discomfort. These areas are prone to maceration; moreover, the lesions are often vegetating, infected, and malodorous due to secondary bacterial infections. Involvement of the hands is seen in the majority of patients. On palms and soles, small pits and/or punctuated keratoses, strongly suggestive of DD, can be observed. On the dorsa of the hands and feet, discrete papules are clinically identical to those of acrokeratosis verruciformis of Hopf (Fig. 18.3). Nail dystrophy is specific for the disease and it consists in nail fragility, red and white longitudinal ridging, V-shaped nick at the free margin of the nail, and subungual hyperkeratosis.

Although rarely, all mucous membranes can be involved. Oral lesions are asymptomatic and comprise multiple white papules in the buccal mucosa and the soft and hard palate, giving a cobblestone appearance. The non-affected skin is normal.

Clinical variants are papular-vesicular form, erosive-bullous form, vegetating form, acral form, and linear (localized) form.

The localized form is rare and it is characterized by keratotic papules unilaterally distributed in streaks or whorls following Blaschko's lines. It typically has a late onset and it is aggravated by sunlight. This form probably reflects genetic mosaicism.

Although DD is strictly confined to the skin, association with neuropsychiatric disorders (e.g., bipolar disorders, epilepsy, and learning difficulties) and other systemic involvement, including bone cysts, salivary glands obstruction, renal and testicular agenesis, cataract, and corneal opacity, have been reported. The high lifetime rate of affective disorders, mostly major depression, bipolar disorder, and psychosis with suicidal tendencies, in individuals with DD is probably due

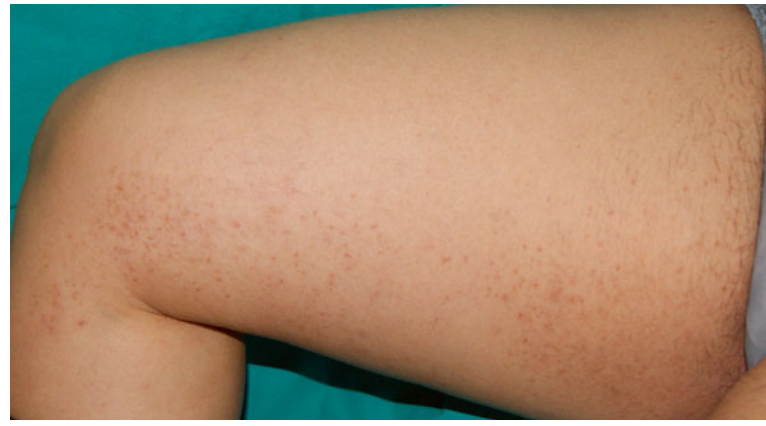

Fig. 18.1 Clinical appearance of Darier's disease: brown skin-colored papules

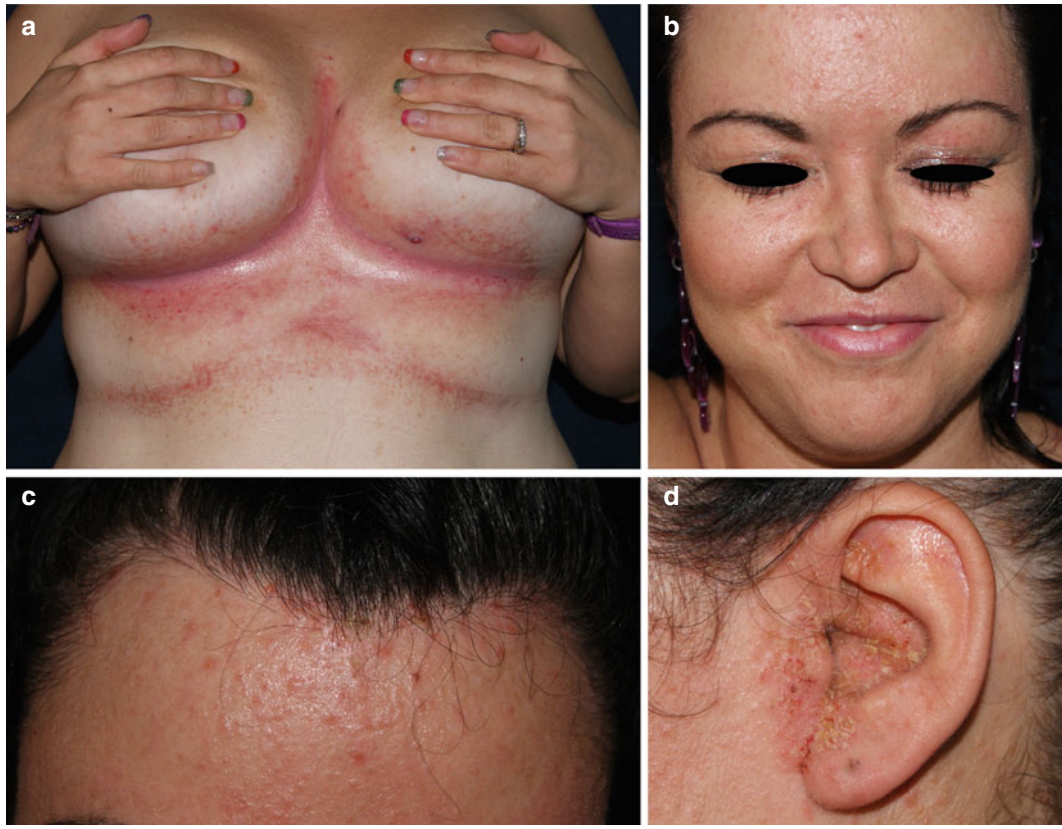

Fig. 18.2 Clinical appearance of Darier's disease: hyperkeratotic, greasy papules. (**a**) Trunk, (**b**) centrofacial, (**c**) hairline, and (**d**) ear

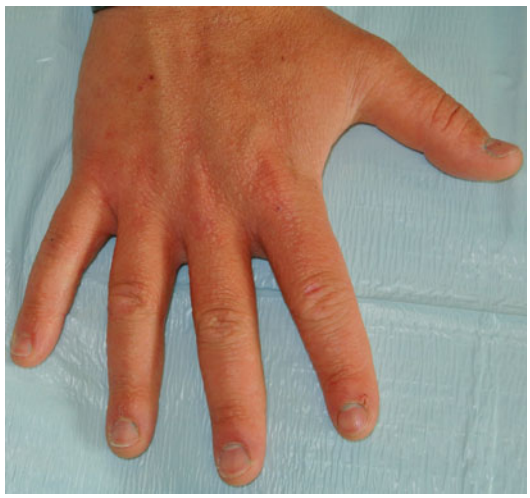

Fig. 18.3 Darier's disease with acrodermatitis verruciformis-like lesions on the back of the hands

to a susceptibility locus for affective disorders which is located adjacent to SERCA2 gene.

Pruritus is common, occurring in 80 % of patients, and may be intractable; pain is unusual.

The disease usually has a chronic relapsing course and may worsen with age, and general health is normally maintained. Patients with DD seem to have an increased susceptibility to herpes and bacterial infections but the exact immunologic relationship is not clear.

Diagnosis

Clinical manifestations are highly suggestive for diagnosis but the histological confirmation showing focal acantholytic dyskeratosis is mandatory. Direct and indirect immunofluorescence studies are negative.

The histological changes of DD, characterized by focal acantholytic dyskeratosis, are distinctive but not entirely pathognomonic.

Histological features of DD are as follows:

- Suprabasal lacunae resulting from suprabasal acantholysis
- Villi (irregular upward proliferation of dermal papillae lined with a single layer of basal cells)
- Corps ronds (small groups of cells around the lacunae separated from their neighbors; enlarged and presenting a darkly staining nucleus surrounded by a clear cytoplasm and a glistening ring; they occur in the upper stratum malpighii, particularly on the granular and horny layers)
- Grains (dyskeratotic small cells with elongated and often grain-shaped nucleus surrounded by shrunken cytoplasm; they are seen in the horny layer and in the suprabasal lacunae)
- Hyperkeratosis, acanthosis, and papillomatosis
- Chronic inflammatory infiltrate in the dermis

Acantholysis occurs first, dyskeratosis later.

Electron microscopy shows loss of the desmosomal protein attachments that normally link keratinocytes and perinuclear aggregation of keratin filaments. Also immunocytochemical study shows that desmosomal proteins are spread in the cytoplasm.

Differential Diagnosis

It includes seborrheic dermatitis, seborrheic keratosis, and candida infection, for the classic form; Grover disease for the papular-vesicular form; Hailey-Hailey disease, pemphigus vulgaris, Langerhans cell histiocytosis, and impetigo, for the erosive-bullous form; pemphigus vegetans for the vegetating form; verruca plana for the acral form; and epidermal nevus with acantholytic dyskeratosis for the linear (localized) form.

General Principles of Treatment

Despite the progress in understanding the pathophysiology of DD, a standardized real effective treatment is still lacking. Only one third of patients noted improvement with age. A good doctor-patient relationship to satisfied patients' emotional needs as well as medical requirements is necessary.

Sun and heat avoidance, use of sunscreens, and maintenance of personal hygiene can be helpful. Clothing should be cool cotton and not too tight.

Recommended Therapies

Treatment of DD can be challenging. In cases with mild skin involvement, a topical therapy can control the disease; however, in extensive cases a systemic therapy is necessary.

Topical Therapy

If skin lesions are limited, emollients containing urea, lactic acid, or salicylic acid, at low concentration, can be used to reduce crusting.

Topical retinoid acid (*TRA*) can reduce hyperkeratosis in a few months, but irritancy is often limiting, especially in patients with inflammatory disease. Topical adapalene and tazarotene have been also reported as effective. In particular, tazarotene 0.1 % gel is suggested as "short contact" therapy in linear DD.

*Steroids of m*oderate potency may help in reducing irritation.

Topical calcineurin inhibitors, *tacrolimus and pimecrolimus,* may be alternative agents in the treatment of DD, although the mechanism by which these agents improve this condition is not fully understood. *Other topical treatments* include the successful application of topical vitamin D as well as 5-fluorouracil. Vitamin E ointment can alleviate the symptoms.

Systemic Therapy

Retinoids

Retinoids are the conventional therapy for generalized or severe DD, because of their action on the disorder of keratinization. The rationale for their use includes the promotion of exfoliation. Their clinical response is good in up to 90 % of patients. We can start with 25–30 mg per day for 14 days–1 month.

Long-term therapy with retinoids has to be avoided because of mucosal dryness; nosebleeds; skin fragility; elevation of triglycerides, cholesterol, and serum liver enzymes; teratogenicity in women; possible depression; and suicide attempts. A topical antibiotic therapy is sometimes recommended in order to control infections of exfoliative, wet, and exudative lesions induced by retinoids.

However discontinuation of retinoid therapy is usually marked by relapse.

Cyclosporine

Several cases nonresponding to traditional therapy have been treated with cyclosporine (2.5 mg/kg/day) with controversial effects.

Photodynamic Therapy (PDT)

PDT has been described in a small number of patients as being a tissue-selective treatment for DD, although the mechanism by which PDT improves DD is not fully understood. Studies investigating photodynamic therapy with aminolevulinic acid have had variable results; in one case it has been reported a worsening of disease not only in the treated but also in adjacent areas after PDT treatment. Side effects of this treatment include pain, hyper-/hypopigmentation, and an inflammatory reaction in treated areas.

PDT should be used as a potential adjuvant modality for Darier's disease and should not be considered as a substitute for retinoids in patients who require systemic treatment.

Surgical Treatments

Dermabrasion can produce good long-term effects. There are recent reports of surgical treatment of DD, using electro- and cryosurgery.

Laser therapy: Er: YAG and CO_2 laser ablation have shown clinical efficacy. The treatment of DD with ablative lasers may induce complete remission after one treatment session, although some recurrences were noted: ablating the papillary dermis is recommended for successful treatment, because a too superficial treatment can cause early relapse. Potential problems of ablative procedures are scarring and hyperpigmentation. Also fractional photothermolysis has been used and is based on the injury of the dermis created by thermal columns. The intact stratum corneum aids in rapid healing and is associated with a low complication rate.

A case of unresponsive DD treated with electron beam has been reported.

Treatment with flashlamp-pumped pulsed dye laser has been shown to improve DD.

Despite the availability of many therapeutic weapons, treatment of DD is frequently very frustrating and several attempts are often necessary before the most effective therapy for the patient can be found.

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Dermatitis Herpetiformis

19

Ines Lakos Jukic and Branka Marinović

Key Points

- Dermatitis herpetiformis (DH) is a chronic, lifelong subepidermal autoimmune bullous disease associated with gluten sensitivity.
- It is most common in individuals of Northern Europe heritage.
- There is a strong association between DH and HLA-DQ2 and HLA-DQ8 antigens.
- Tissue transglutaminase (tTG) is a major autoantigen for celiac disease, while epidermal transglutaminase (eTg) is the dominant autoantigen in DH.
- There is an increased prevalence of other autoimmune diseases in DH, most commonly of thyroiditis.
- Enteropathy-associated T-cell lymphoma is a recognized risk in patients with DH.
- Classic clinical finding in DH are grouped "herpetiform"-arranged papules and papulovesicles on erythematous urticarial base, symmetrically located on extensor surfaces of the upper and lower extremities, elbows, knees, buttocks, nuchal area, and scalp.
- Lesions are intensely pruritic.
- Direct immunofluorescence (DIF) study of perilesional, normal-appearing skin with granular deposits of IgA within the tips of dermal papillae is pathognomonic.
- Demonstration of circulating antibodies against tTg and eTg is a useful serologic tool in confirming the diagnosis as well as in monitoring disease activity.
- Gluten-free diet is effective for both skin lesions and enteropathy.
- Pharmacological treatment of choice in DH is dapsone; it has no effect on small bowel damage.
- Regular screening for dapsone-induced side effects is mandatory.
- The prognosis of DH is usually favorable.

Definition and Epidemiology

Dermatitis herpetiformis (DH) is a chronic, subepidermal autoimmune bullous disease associated with gluten sensitivity, and thus it can be defined as a cutaneous manifestation of celiac disease (CD).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_19, © Springer-Verlag Berlin Heidelberg 2015

The prevalence of DH is different among ethnical populations; it is most common in individuals of Northern European heritage. Epidemiologic studies from Sweden and Finland reported prevalence rates of 39 and 66 per 100,000 people. Smith et al. have found prevalence of 11.2 per 100,000 in Utah, United States. In contrast to Caucasoid, DH is very rare among African Americans and Asians.

The onset of disease varies; it can start at any age. However, the second, third, and fourth decades are the most common. Although childhood DH overall is a rare disease, studies from Hungary and Italy have suggested DH is common among children in these countries. There is a slight male preponderance among patients with DH, which is opposite to higher female prevalence of celiac disease. In childhood, DH affects both genders equally.

These various prevalences and geographical distribution of DH may be dependent on genetic predisposition and environmental factors, such as diet. Genomic typing of patients with DH, as well as of patients with CD, has shown strong association with class II alleles DQA1*0501 and DQB1*02 in chromosome 6. These genes encode HLA-DQ2. Different studies have reported HLA-DQ2 in 86 %, 95 %, and 100 % of the patients with DH. Thus, HLA typing of class II region genes might be a diagnostic marker for CD and DH. The remaining patients with DH (5–12 %) presented with alleles DQA1*03 and DQB1*0302 encoding HA-DQ8. Ohata et al. in a study of 91 Japanese patients with DH have not observed association of these HLA antigens with DH.

Genetic factors, beside HLA genes, are important key in pathogenesis of DH. Association of genomic variants at interleukin-1 (IL-1) and interleukin-21 (IL-21) region in chromosome 4q27 and CD has been reported. There is a report of monozygotic twins, one with DH and the other with CD, suggesting the role of environmental factors in development of CD and DH. Hervonen et al. have reported that 18 % of patients with DH had a first-degree relative with DH or gluten intolerance. The practical use of these findings is to consider serologic screening for first-degree relatives of DH patient to identify silent or latent signs of gluten sensitivity.

Basic Concepts of Pathogenesis

As mentioned above, DH is multifactorial disease with genetic and autoimmune background, influenced by environmental factors. There has been a quite progress in understanding pathogenesis of DH since Marks et al. first described small bowel changes in 9 of 12 patients with DH in 1966. The next major advance was identification of antibodies to tissue transglutaminase (tTg) in sera of patients with DH. Subsequently, tTg was identified as a major autoantigen for CD. Three years later, Sardy et al. have demonstrated that epidermal transglutaminase (eTg) is the dominant autoantigen in DH patients. eTg is homologous but not identical to tTg. While tTg is ubiquitously expressed in many tissues, including the skin, eTg is found only in the epidermis, small intestine, brain, and testis. Transglutaminase plays a crucial role in pathogenesis of gluten intolerance. Gluten is a protein found in wheat, barley, and rye. Upon the digestion of gluten-containing food, gliadin, which is the alcohol-soluble fraction of gluten, elicits an immune response in predisposed individuals. After absorption of gliadin into the intestinal mucosa, deamidation of gliadin by tTg leads to formation of efficient antigen with high affinity for HLA-DQ2 on dendritic antigen-presenting cells. Gliadin antigen is then presented to sensitized helper T cells in lamina propria, resulting in T-cell proliferation, synthesis of proinflammatory cytokines, and matrix metalloproteinases resulting in inflammatory response, which is responsible for mucosal epithelial cell damage. T-helper cells can stimulate B cells to produce antibodies to tTg. These antibodies are predominantly of IgA class, directed against gliadin and gliadin cross-linked to tTg, tTg, or eTg. The production of antibodies directed against eTg is probably the result of intermolecular epitope spreading in patients who already have IgA anti-tTg antibodies. These IgA anti-eTg antibodies reach the dermis and form immune complexes with eTg in dermal papillae, resulting

in neutrophil chemotaxis. Degranulation of neutrophils releases proteases, which are responsible for proteolytic cleavage of the lamina lucida and formation of subepidermal blister.

Associated Diseases

Patients with DH have an increased prevalence of other autoimmune diseases. The most common associated disorder is thyroiditis, more likely with hypothyroidism then hyperthyroidism. Several studies have demonstrated that incidence of thyroid disorder ranged from 11 to 14 % in DH patients. An increased incidence of insulin-dependent diabetes mellitus (type I), in ranges from 2.3 to 5 %, has also been noticed in patients with DH. Association with pernicious anemia has been identified, with incidence ranging from 1.9 to 3 %. Other diseases, which have been reported in DH patients, with association weaker than that with thyroid disorders, are Addison disease, connective tissue disorders, Sy Sjögren, vitiligo, alopecia areata, and rheumatoid arthritis. Disorders associated with DH, due to malabsorption, are microcytic or macrocytic anemia, folate, B12 or zinc deficiency, and osteoporosis.

Lymphoproliferative disorders, not only enteropathy-associated T-cell lymphoma, but also B-cell lymphoma, are a recognized risk in patients with DH, with incidence less than 2 %. It is still unclear whether adherence to strict gluten-free diet is protective against lymphoma in this population.

Clinical Presentation

DH is a polymorphous, intensively pruritic, papulovesicular disorder. Classic manifestation of DH includes grouped "herpetiform" papules and papulovesicles on erythematous urticarial base, symmetrically located on extensor surfaces of the upper and lower extremities, elbows, knees, buttocks, nuchal area, and scalp. Secondary to scratching because of severe pruritus, patients usually present with erosions, crusted papules, and excoriations, and thus, DH only rarely manifests as a clear bullous disease. The lesions usually resolve with postinflammatory dyschromia, most commonly hyperpigmentation. Besides pruritus, patients often complain about burning and stinging; these symptoms can precede the onset of skin eruption. Uncommon presentations of DH are palmoplantar purpura, which is more common in children, isolated lesions on the face or in the scalp, or development of lesions mimicking prurigo pigmentosa. Although there are reports about mucosal involvement in DH, including vesicles, erythematous macules, or erosions on the oral mucosa or tongue, overall it is rarely seen. Since other DH-associated disease like CD or connective tissue disorders may cause oral lesions, direct immunofluorescence of the oral mucosa is "conditio sine qua non" for a diagnosis of mucosal involvement in DH. Patients with DH can present with tooth enamel abnormalities. The most common enamel defects reported in both childhood and adult DH, as well as in CD, are horizontal grooves, enamel pits, and discoloration.

Diagnosis

The diagnosis of DH is based on clinical findings, histopathology, immunofluorescence studies, and serology. Obtaining a good biopsy specimen is prerequisite to reach the correct diagnosis; an early papule, papulovesicle, or a small bulla with healthy appearing skin around it should be used for histopathologic study. The typical early finding in DH is characterized by superficial perivascular and interstitial lymphocyte and neutrophil infiltrates and edematous papillary dermis. With progression of the lesion, neutrophils are accumulated in some dermal papillae. Further accumulation of neutrophils leads to formation of abscesses in dermal papillae with subepidermal separation (Fig. 19.1). The fully developed lesion is characterized by subepidermal blister. Beside neutrophils, eosinophils can be also found in infiltrate as well as in papillary abscesses; their number increases with age of the lesion. Similar histologic findings can be found in other diseases, like in linear IgA disease, epidermolysis bullosa

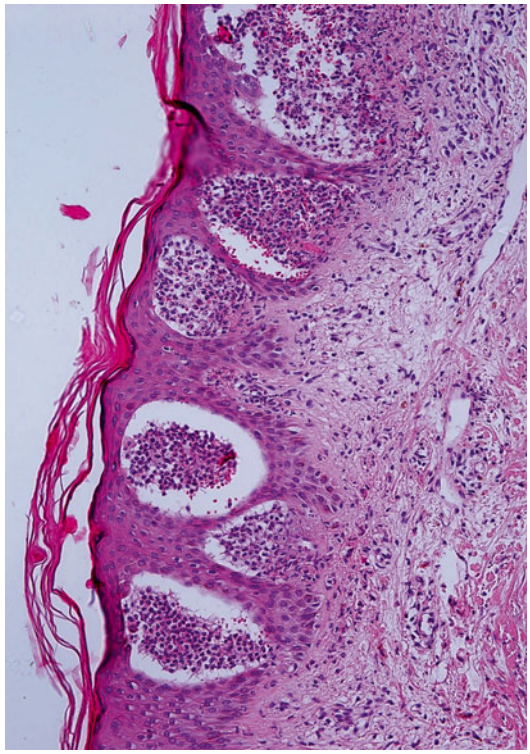

Fig. 19.1 Accumulation of neutrophils within tips of dermal papillae with partial subepidermal separation (HE X50)

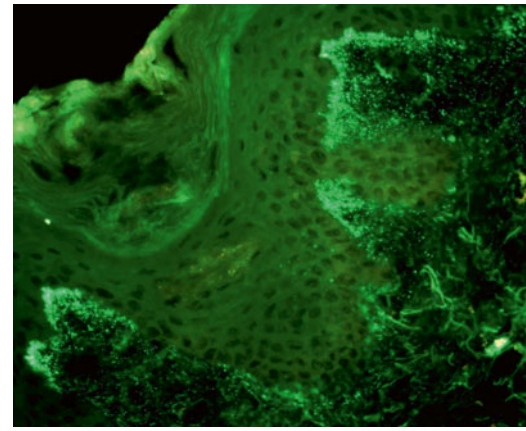

Fig. 19.2 Direct immunofluorescence of perilesional skin: granular deposits of IgA within the dermal papillae

acquisita, or in bullous form of lupus erythematosus, so histology is evocative, but it is not diagnostic. Therefore, direct immunofluorescence (DIF) study of perilesional, normal-appearing skin still remains the gold standard for diagnosis of DH. Typical, pathognomonic finding are granular deposits of IgA within the tips of dermal papillae (Fig. 19.2). Sometimes granular deposits along basement membrane zone can also be detected. In Japanese population of patients with DH, fibrillar pattern of DIF has been described; deposits of IgA present as linear streaks in the papillary dermis. This finding is usually associated with atypical clinical presentation of DH, like urticarial or psoriasiform lesions, absence of gluten-sensitive enteropathy, and without, for DH and CD, specific HLA antigens.

As mentioned above, patients with DH demonstrate circulating IgA antibodies against eTg and tTg, so serologic tests are useful tools in confirming the diagnosis as well as in monitoring disease activity. It is important to emphasize that patients with DH have no circulating antibodies against components of cutaneous basement membrane or to other adherent structures of the skin. Levels of IgA antibodies against tTg, detected by ELISA (enzyme-linked immunosorbent assay), correlate with bowel disease and adherence to gluten-free diet in patients with DH and CD. The sensitivity of this assay ranges between 47 and 95 % with specificity range up to 100 %. Antibodies directed against eTg are the most sensitive serologic marker in treated and untreated patients with DH, with specificity of commercially available ELISA up to 100 %. Endomysial antibodies (EMA) belong to the IgA1 subclass and are directed against endomysium – reticular connective tissue in smooth muscle. The endomysial antigen has been identified as tTg. These antibodies are detected by indirect immunofluorescence study on monkey esophagus as a substrate. EMA is a marker for small bowel damage, not for skin lesions, and it disappears with a gluten-free diet (47). Antigliadin and antireticulin antibodies are no longer considered as a sensitive and specific sign of DH. Today, the most reliable test to confirm gluten sensitivity in DH patients is detection of antibodies directed against deamidated gliadin-derived peptides.

Measurement of total IgA level is also included in serologic workup with patients with DH. Although selective IgA deficiency has an increased prevalence in patients with CD, no cases of IgA deficiency have been reported in DH patients. However, partial IgA deficiency has been documented in some patients with DH.

Because of the strong association between DH and thyroid dysfunctions, especially Hashimoto thyroiditis, thyroid-stimulating hormone and anti-thyroid peroxidase antibodies testing should be performed in patients with DH. Testing for serum level of glucose, antigastric parietal cells, and anti-nuclear antibodies should also be considered.

More than 90 % patients of DH have some degree of gluten-sensitive enteropathy. A milder degree of villous atrophy than that seen in celiac disease is typically seen in approximately two-thirds of DH patients with elevated intraepithelial lymphocyte counts in the remainder of DH patients' small bowel biopsy specimens. A biopsy of the small intestine is not necessary in patients with diagnosis of DH confirmed by DIF finding and positive serologic tests.

The differential diagnosis includes linear IgA dermatosis, bullous pemphigoid, scabies, atopic dermatitis, and arthropod bites.

General Principles of Treatment

Since DH is a cutaneous manifestation of gluten sensitivity, it is logical to expect that a cornerstone of therapy is lifelong gluten-free diet. A gluten-free diet is effective for both skin lesions and enteropathy, although intestinal symptoms tend to respond faster than skin. It is very important to motivate the patients to strict adherence to a gluten-free diet, which means complete avoidance of wheat, barley, rye, and their products. Besides gluten-containing food, exacerbation of DH may be induced by iodide, food additives in vitamin supplements, distilled white vinegar, malts, vegetable gum, and preservatives. Some patients may have long-term remission of disease, and gluten-free diet may be discontinued. It seems that gluten-free diet has protective effect against development of intestinal lymphoma. It usually takes from several months up to 2 years to control skin lesions with a gluten-free diet as a monotherapy.

Dapsone (4,4′-diamino-diphenyl sulfone) is pharmacological treatment of choice for DH. Dapsone has antimicrobial and anti-inflammatory effect. As an antibiotic, it inhibits the growth of microorganisms that are dependent of endogenous folic acid synthesis. Although the mechanism of action of dapsone in inflammatory diseases is not well understood, it seems that it may directly affect neutrophil function. Dapsone has a dramatic effect in DH patients; pruritus and skin lesions usually resolve within 48–72 h. In contrary, dapsone has no effect on small bowel damage, caused by gluten sensitivity. Most patients with DH may be maintained on 50–100 mg dapsone daily. However, some patients may need only 25 mg to control the disease, while others may have multiple skin lesions despite therapy with 300 mg. Overall, dapsone is well tolerated. It is associated with both pharmacological and idiosyncratic adverse reactions. Patients with pulmonary, cardiovascular, or hematologic disease as well as with glucose-6-phosphate dehydrogenase (G6PD) deficiency have an increased risk for the development of pharmacological side effects. Methemoglobinemia is the most common side effect of dapsone. Cyanosis, with brown pasty mucous membranes, is seen at 15 % of methemoglobin and it is often asymptomatic. The percentage above 45 is associated with acidosis, dyspnea, seizures, arrhythmias, and coma. Vitamin E, C, and cimetidine seem to have some protective effect against formation of methemoglobin. Hemolysis is also a common dose-related adverse event, and it occurs to some degree in all patients taking dapsone. Patients with deficiency of G6PD have been demonstrated to have a twofold increase in sensitivity towards dapsone-induced hemolytic anemia. The most serious, but very rare, idiosyncratic reaction to dapsone is agranulocytosis. Another rare, idiosyncratic adverse event of dapsone is hypersensitivity syndrome or "dapsone syndrome," clinically characterized by fever, cutaneous

eruption, and hepatitis. Patients usually have peripheral eosinophilia, too. Other side effects, as a single symptom or as a part of "dapsone syndrome," that have been reported to be associated with dapsone are peripheral neuropathy, hepatotoxicity, and renal toxicity. Considering adverse reaction associated with dapsone, patient should be regularly monitored. Baseline evaluation must include complete blood count (CBC), liver function panel, renal function test, and level of G6PD. Follow-up evaluation includes CBC weekly for the first month, then monthly for next 5 months, and later, semiannual while patient is taking dapsone. Liver and renal function tests should be checked every 3–4 months.

Once the diagnosis of DH has been achieved, the therapy with dapsone in combination with gluten-free diet is usually recommended.

In patients intolerant to dapsone, second-line pharmacological agents for treatment are sulfasalazine, in dose of 1–2 g/day, and sulphamethoxypyridazine with suggested dosage of 0.25–1.5 g/day. Both medications can cause hemolytic anemia, proteinuria, and crystalluria, as well as hypersensitivity reactions. Patients usually complain of nausea, vomiting, and anorexia.

Application of potent or very potent topical steroids and third-line antihistamines can be useful to decrease pruritus and itching. It is also important to recognize possible secondary bacterial infection.

Conclusion

Dermatitis herpetiformis, or, as Sarolta Karpati suggested, gluten-sensitive dermopathy, is a lifelong waxing and waning disease, most commonly clinically characterized by intensely pruritic papulovesicular eruption on extensor surfaces. The diagnosis is based on the correlation between clinical, histologic, immunological, and serologic findings. Granular deposits of IgA in dermal papillae on direct immunofluorescence assay are pathognomonic. Considering the fact that gluten is responsible for both enteropathy and skin lesions, it is most important for patients to understand that gluten-free diet is an essential part of the treatment. Dapsone is the only medicine approved by FDA (Food and Drug Administration) for therapy of DH. Regular screening for dapsone-induced side effects, as well as for associated diseases, is needed. The prognosis of DH is usually favorable. A multidisciplinary approach, involving dermatologist, nutritionist, and gastroenterologist, is required in the treatment and follow-up of patients with DH.

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Dermatomyositis

20

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Abbreviations

AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
AZA	Azathioprine
CMAS	Childhood myositis assessment scale
CP	Cyclophosphamide
CsA	Ciclosporin A
DLE	Discoid lupus erythematosus
DM	Dermatomyositis
ICAM-1	Intercellular adhesion molecule-1
IIM	Idiopathic inflammatory myopathies
IL	Interleukin
IVIg	Human intravenous immunoglobulin
JDM	Juvenile dermatomyositis
MAC	Membrane attack complex of complement
MMF	Mycophenolate mofetil
MMT	Manual muscle testing
MRI	Magnetic resonance imaging
MTX	Methotrexate
PM	Polymyositis
RCTs	Randomized controlled trials
SCLE	Subacute cutaneous lupus erythematosus
SLE	Systemic lupus erythematosus
TNF	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule-1

Key Points

- Dermatomyositis (DM) belongs to chronic idiopathic inflammatory myopathies (IIM), heterogeneous group of autoimmune disorders that predominately target the skeletal musculature and/or skin.
- Typical clinical symptoms are symmetrical proximal muscle involvement and typical cutaneous inflammatory lesions.
- Clinical examination and the histopathology analysis of the muscle are fundamental for the diagnosis.
- Therapy must be oriented in relation to the symptomatology and the severity of the disease.
- Pharmacological treatment is based on immunosuppressive agents, as glucocorticoids, azathioprine, or methotrexate.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_20, © Springer-Verlag Berlin Heidelberg 2015

Definition and Epidemiology

Dermatomyositis (DM) belongs to chronic idiopathic inflammatory myopathies (IIM), heterogeneous group of autoimmune disorders that predominately target the skeletal musculature and/or skin. Typical clinical symptoms are symmetrical proximal muscle involvement and typical cutaneous inflammatory lesions. DM affects approximately 5/1,000,000 population, twice more often in females.

Some following forms are distinguished (from Sontheimer and Costner, modified):

DM
Adult onset
Classic DM
Classic DM alone
Classic DM with malignancy
Classic DM as part of an overlap connective tissue disorder
Clinically amyopathic DM
Amyopathic DM
Hypomyopathic DM
Juvenile onset
Classic DM
Clinically amyopathic DM
Amyopathic DM
Hypomyopathic DM
Polymyositis (*PM*)
PM alone
PM as part of an overlap connective tissue disorder
PM associated with internal malignancy
Inclusion body myositis
Other clinical pathologic subgroups of myositis
Focal myositis
Proliferative myositis
Eosinophilic myositis
Granulomatous myositis

In childhood DM is not rare, and it is defined as juvenile dermatomyositis (JDM). In about 10 % of the patients, cutaneous symptoms are not associated with muscular involvement (amyopathic DM). Moreover, in about 30 % of the cases, DM is correlated with cancer (paraneoplastic DM).

Basic Concepts of Pathogenesis

The etiology is not clear. The inflammatory processes of the muscle and skin manifestations, followed by the cellular and humoral autoimmune abnormalities, have led to the hypothesis that DM results from a genetically determined, aberrant autoimmune response to environmental agents.

A genetic predisposition has been demonstrated in DM. This disease is linked to the 8.1 ancestral haplotype (HLA-A1, C7, B8, C4AQ0, C4B1, DR3, DQ2), in particular with HLA-B8, DR3, and DRw52.

The cutaneous manifestations of DM are exacerbated by environmental factors, as ultraviolet radiation and infections that could induce the loss of self-tolerance and the production of autoantibodies, immune complexes, and/or autoreactive T cells.

Several autoantibodies have been indentified to be specific of DM. Among those, we can remember 155 kd, 140kd, Jo-1, and Mi2.

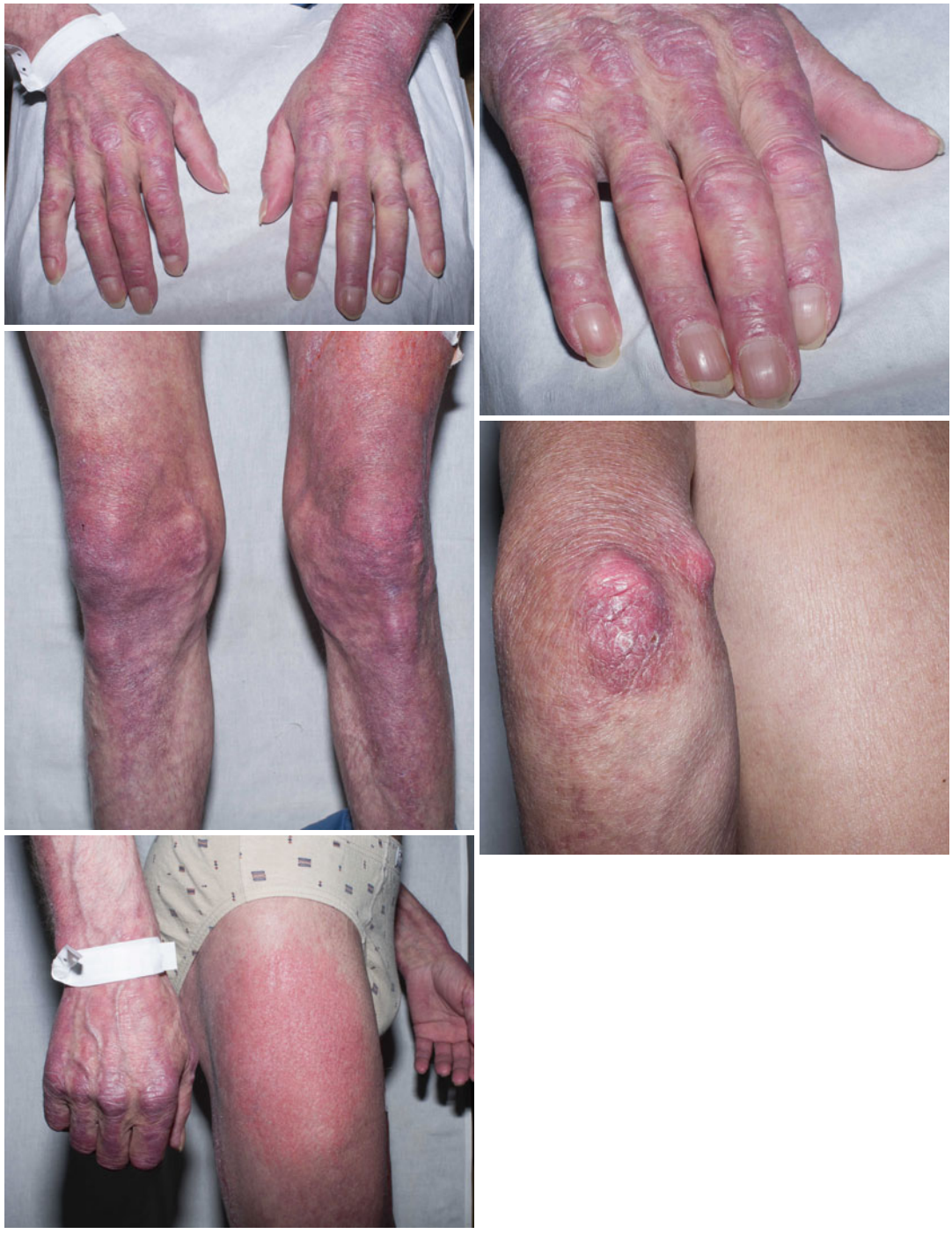
Predominately humoral autoimmune mechanisms targeting the microvasculature have been implicated in the pathogenesis of muscle injury in DM.

The vessel injury is linked with deposits in the intramuscular vasculature of autoantibodies that compose the membrane attack complex of complement (MAC), an increased expression of interleukin-1 (IL-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells of capillaries. The involvement of cellular immune response is demonstrated by the presence of activated lymphocytes in the inflammatory infiltrates. The cell-mediated response seems to be responsible for the muscle and skin injury.

Clinical Presentation

The principal cutaneous signs are:

Pathognomonic distinctive signs (Figs. 20.1, 20.2, 20.3, 20.4, and 20.5)



Figs. 20.1, 20.2, 20.3, 20.4, and 20.5 *Pathognomonic distinctive signs of dermatomyositis*: Gottron's sign and Gottron's papules

- Gottron's sign: symmetrical erythema overlying the knuckles, elbows, knees, interphalangeal, and metacarpophalangeal joints
- Gottron's papules in the latter location

Characteristic signs

- Edema and heliotrope periorbital erythema
- Periungual telangiectasia and erythema with or without dystrophic cuticles and cuticular hemorrhage
- Symmetric confluent macular violaceous erythema overlying on the extensor aspects of the arms and hands, deltoids, posterior shoulders and neck (shawl sign), V area of anterior neck, and upper chest (V sign)
- Mechanic's hand lesion: (keratotic plaques on the palms and the ventral and lateral sides of the fingers, with erythematous changes on the dorsal aspects)

Compatible signs

- Poikiloderma atrophicans vasculare (poikilodermatomyositis) (especially in the chronic cases) light hypersensitivity
- Alopecia
- Lipoatrophy in chronic cases
- Panniculitis (rarely)
- Calcinosis cutis

Cancer disease is strictly related to DM progression. Atypical presentation, most severe skin signs, like necrotic ulcerations over the elbows, knees, and malleoli, may emerge before paraneoplastic signs at visceral level. The diagnosis of cancer can be done before, simultaneously, or within 2 years after the onset of DM. The most common associated cancers are ovary, breast, and lung cancer, melanoma, mycosis fungoides, and lymphoproliferative malignancies.

Muscle Disease

The muscular activity deficiency is characterized by the weakness and possible tenderness of the proximal muscles, leading to muscle wasting in chronic cases. An elevation in the serum level of CK is the most sensitive and specific laboratory indicator of muscle disease activity in DM.

The Course of DM

The course shows significant variations. High level of Mi2 antibody can be associated with a chronic disease with milder skin and muscle symptoms. In rare case associated with anti-tRNA synthetase antibodies, the pathology affects pulmonary functionality (interstitial lung disease—ILD), and the symptoms are clearly visible. In chronic cases after the regression of cutaneous and inflammatory muscle changes, subcutaneous lipoatrophy, atrophy of muscles, and calcinosis are identifiable.

The reported mortality rates vary from 25 % to 80 %. In the past two decades, the mortality rate has decreased considerably because of the more aggressive use of glucocorticoids and other immunosuppressives and better supportive medical care (Sontheimer and Costner 2008).

Diagnosis

Clinical examination and the histopathology analysis of the muscle are fundamental for the diagnosis.

Some cutaneous lesions, as Gottron's papules/sign, are specific and distinctive of the disease and clearly direct the diagnosis even if the skin biopsy is usually not contributory. Muscle activity is evaluated by manual testing, functional performance, electromyography (preferably quantitative EMG), and muscle enzyme levels (creatine phosphokinase, aldolase).

The muscle biopsy, together with skin and muscular clinical signs, can confirm the diagnosis. Characteristic features of muscular involvement in DM are muscle fibers necrosis and regeneration, microinfarcts, perifascicular atrophy, inflammatory infiltrates of T cells, predominantly of CD4 type, and inflammatory vascular changes or capillary depletion.

In the severe cases, characterized by pulmonary fibrosis, pronounced Raynaud's phenomenon, arthralgia, and not infrequently scleroderma-like cutaneous changes, there is the need of respiratory function evaluation.

A nail fold capillaroscopy is indicated in all cases (which shows characteristic "bushy," highly enlarged capillaries of the subpapillary plexus and extravasations).

In adults over 40–50 years old, cancer screening is recommended (in females mammography and pelvic ultrasonography, and serological examination for the ovarian tumor with marker CA-125, and in all patients, lung and digestive tract studies). The follow-up of the patients is based on sensitive and noninvasive new methods for assessment of the muscle: magnetic resonance imaging (MRI) and P-31 magnetic resonance spectroscopy.

Differential Diagnosis

The diagnosis is quite simple when the clinical features of DM are typical. Pronounced photosensitivity should be exploited to differentiate from systemic lupus erythematosus (SLE) associated with myositis (differs by visceral and cutaneous involvement and by serological markers). JDM cases can be confused with SLE, since that pronounced vasculitis and photosensitivity are commonly in both the pathology. In these cases clinicians should refer to the serological markers of SLE. Cases of amyopathic DM should be differentiated, besides systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus (SCLE), and discoid lupus erythematosus (DLE), from polymorphous light eruption, lichen planus, seborrheic dermatitis (not infrequent scaling scalp lesions in DM), and erythema elevatum and diutinum.

General Principles of Treatment

Therapy must be oriented in relation to the symptomatology and the severity of the disease. Pharmacological treatment is based on immunosuppressive agents, as glucocorticoids, azathioprine, or methotrexate, even their benefit/risk ratio is not so clear. Randomized controlled trials (RCTs), confirming the value of immunosuppressants in inflammatory myositis, are not available. For this reason, it is important for physicians and patients to appreciate the precise benefit and risk of immunosuppressants in inflammatory myositis.

Additional considerations should be spent for the clinical assessment of juvenile DM. The evaluation of the involvement and severity of muscle inflammation has a significant importance in assessing disease activity and response to therapy in juvenile DM patients. Muscle strength is the primary clinical measure used to assess muscle disease. The manual muscle testing (MMT) and Childhood Myositis Assessment Scale (CMAS) are among the main tests exploitable. In JDM there is an imperfect correlation of serum muscle enzymes and myositis activity. Moreover health-related quality of life has been increasingly recognized as an important domain to be included in therapeutic trials and observational studies of patients with juvenile DM because it addresses aspects of disease that are not fully captured by other endpoints.

Therapeutic Ladder for Cutaneous Dermatomyositis

First Line
Photoprotection
Topical and systemic corticosteroids
Topical calcineurin inhibitors
Antipruritics
Antimalarials (single agent initially, consider combination if failed)

Second Line
Methotrexate
Mycophenolate mofetil
Human intravenous immunoglobulin IVIg

Third Line
Dapsone
Thalidomide
Azathioprine
Rituximab
Calcineurin inhibitors

Corticosteroids

Topical Corticosteroids

Topical corticosteroids are frequently used to manage the cutaneous inflammation and pruritus of DM. The application, in a vehicle most amenable to the patient and suitable for the area treated, should be once-twice daily. Appropriate breaks from use should be considered in order to prevent side effects as cutaneous atrophy, acneiform eruptions, striae, telangiectases, etc. For regions including the trunk, extremities, and scalp, a stronger (usually class 1 or 2) topical corticosteroid may be prescribed, whereas lower potency corticosteroids are suggested for the face. To increase potency and penetration, especially for hyperkeratotic refractory lesions, occlusion with a plastic wrap or steroid-impregnated tape is recommended.

In addition, there is a low risk of transient adrenal suppression and other effects from systemic absorption when large body surface areas are being treated. When prolonged use is anticipated, practice of cyclic therapy (e.g., 2 weeks of continuous therapy followed by 1–2 weeks treatment-free) is advised.

Systemic Corticosteroids

Systemic corticosteroids are the traditional first-line agent for management of DM. Normally the therapy consists of prednisone orally at 0.5–1 mg/kg per day. Some authors suggest giving methylprednisolone intravenously at 1 g daily for 3–5 days, followed by oral therapy, when muscle disease is severe. The well-documented adverse effects of corticosteroids as well as the known refractory nature of cutaneous DM lesions limit their use for the post-myopathic DM therapy. Some experts suggest short courses of prednisone 1 mg/kg/day tapered over 2–3 months for particularly symptomatic skin DM. Other experts prefer to avoid systemic steroids for skin-limited disease because the doses required to effectively treat cutaneous DM frequently result in steroid-related side effects. In JDM, both oral prednisone and intravenous methylprednisolone have been studied, particularly at the onset of disease, and efficacy has been demonstrated mainly for muscle disease as well as for prevention of calcinosis cutis.

Photoprotection

It is well known that sunlight can exacerbate or induce DM skin lesions. It is strongly recommended photoprotection year-round, based on the use of sun-protective clothing, wide-brimmed hats, and broad-spectrum sunscreen. A sun protection factor of at least 50 should be applied daily, with emphasis on reapplication every 3–4 h. Midday sun should also be avoided if possible, as well as tanning beds. Supplementation of vitamin D can be considered for patients with low levels of vitamin D.

Topical Calcineurin Inhibitors

They are T-cell-selective immunosuppressants, which mainly acts through inhibition of calcineurin and subsequent blockade of cytokine gene transcription (interleukin-2, interferon-gamma, and granulocyte-monocyte colony-stimulating factor). Particularly important is the blocking of interleukin-2, a cytokine essential in the T-cell activation pathway. Numerous case series and open-label studies have reported their efficacy in skin lesions.

Antipruritics

Topical Antipruritics

The management of pruritus associated to DM is an important therapeutic target for improving the quality of life of the patient. Clinicians can choose from the most simple bland moisturizers and emollients up to antipruritic formulations containing menthol, camphor, and/or pramoxine.

Systemic Antipruritics

Oral sedating antihistamines, such as hydroxyzine 10–50 mg given during the day and at bedtime, can be exploited for relief from the often-incapacitating pruritus and/or dysesthesia

caused by cutaneous lesions of DM. Doxepin and amitriptyline, long-acting tricyclic antidepressants with potent antihistaminic effects, given in doses of 10–50 mg at bedtime can be helpful for refractory pruritus. Other medications, such as gabapentin and pregabalin, may be considered.

Antimalarials

The antimalarials most commonly employed in dermatology are hydroxychloroquine, chloroquine (4-aminoquinolines derived from quinine), and quinacrine (yellow acridine dye compound). Their mechanisms of action are not clear, and their use is debated. They show immunomodulatory, anti-inflammatory, antiproliferative, and photoprotective properties. Normally they are considered for the treatment of cutaneous DM, and not for muscle disease. Monotherapy based on antimalarials appears to be less valuable in controlling cutaneous disease in DM than in cutaneous lupus, and additional medications are often needed.

Methotrexate (MTX)

This folic acid analog, competitively and irreversibly, inhibits dihydrofolate reductase, an enzyme that produces a necessary cofactor for the synthesis of purine and pyrimidine nucleotides. This blocking disrupts DNA and RNA synthesis and leads to inhibition of cell proliferation. The proposed mechanism of action in inflammatory cutaneous disorders appears to be related to its effect on adenosine, through inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase. The biological effect consists of an increase adenosine levels, a purine nucleotide with potent anti-inflammatory effects. MTX can be the first-line systemic therapeutic agent considered for cutaneous DM in a patient who fails to improve with diligent photoprotection, topical medications, and antimalarials. With MTX, the most commonly observed side effects include nausea, malaise, and fatigue, particularly following the weekly dose. Other more disabling adverse events include hepatotoxicity, hematologic disturbances including pancytopenia, ulcerative mucositis, and rarely pneumonitis or pulmonary fibrosis. Specific screenings, evaluating comorbidities that would prevent the use of this medication, alcohol consumption, and childbearing preferences that would impact the safe use of the drug, should be done prior to administrate MTX. The typical starting dose is 10 mg orally or subcutaneously per week with folic acid supplementation 1 mg daily. Follow-up laboratory studies are done at 2 weeks, and if normal, the dose is increased to 20–25 mg weekly. Like the antimalarials, it typically takes a minimum of 6–8 weeks of continuous therapy before a noticeable improvement can be appreciated.

Mycophenolate Mofetil (MMF)

MMF is a prodrug of mycophenolic acid, a lymphocyte selective immunosuppressive agent that inhibits inosine monophosphate dehydrogenase, reducing the novo synthesis of purine nucleotides. It reduces lymphocytic proliferations, suppress antibody production, and decrease lymphocyte migration and recruitment. The dose is typically titrated to 1 g twice daily after 2 weeks of therapy. The therapeutic effect is usually noted after an initial delay of 6–8 weeks. In patients transitioning from MTX to MMF, MTX may be continued at a lower dose (10–15 mg weekly) while starting MMF to prevent disease flares. Overall, MMF is a relatively well-tolerated medication. The most common adverse effect is dose-related gastrointestinal distress, especially significant when given at doses of greater than 2 g daily, which is often alleviated by taking the medication with meals.

Human Intravenous Immunoglobulin (IVIg)

Immunoglobulin (Ig) preparations are derived from pooled plasma collected from thousands of donors and are highly purified to contain mostly

Ig. The most common route of administration is intravenous Ig (IVIg), although subcutaneous and intramuscular products are also available. When used in autoimmune and inflammatory disorders, IVIg is considered an immunomodulatory agent and is usually administered at higher doses than when being utilized for replacement Ig therapy. In general, IVIg is reserved for patients who have failed, are intolerant of, or have contraindications to antimalarials and MTX. Generally, IVIg is well tolerated and appears beneficial for the skin disease of DM, including in patients who have failed other systemic medications such as MTX and MMF. It is generally given as monthly infusions of 1 g/kg on two consecutive days for an initial 6-month period and tapered thereafter according to skin response.

Dapsone

Dapsone, or 4,4′-diaminodiphenylsulfone, is a sulfone antibiotic and anti-inflammatory agent used to treat a variety of disorders, including Hansen's disease (leprosy), autoimmune bullous disorders, and neutrophilic dermatoses. It shows antibiotic properties through the inhibition of dihydropteroate synthetase, an important enzyme for the folic acid production. The mechanism of action of dapsone in cutaneous disorders is less well understood. The efficacy of dapsone in cutaneous DM is limited to a case report and two small case series. Known associated adverse events include hemolytic anemia (which correlates with the level of G6PD, which should be measured prior to initiating dapsone), agranulocytosis, peripheral neuropathy, hypersensitivity syndrome, and gastrointestinal disturbances. Treatment is usually initiated at 25–100 mg daily and may be increased to 200–300 mg daily as tolerated and according to response.

Thalidomide

The use of thalidomide was reportedly effective in controlling up to 60 % of the cutaneous disease activity in a case of drug-induced DM to gemfibrozil. It was also found to be beneficial in a case of JDM with extensive calcinosis accompanied by systemic inflammatory symptoms refractory to multiple therapies. In this child, thalidomide administered at 75 mg daily resulted in a reduction in pain and a decrease in inflammatory markers and symptoms; however, the existing calcium deposits remained.

Azathioprine (AZA)

AZA is a prodrug of 6-mercaptopurine, a purine analog. It is used in many autoimmune and inflammatory dermatologic diseases in doses ranging from 1 to 3 mg per kg daily. Its therapeutic success in skin disease is not clearly demonstrated, and the use in muscle inflammation shows mixed results. For this reason, the use of AZA in DM should be carefully evaluated. Known side effects associated with AZA include bone marrow suppression, hepatotoxicity, hypersensitivity reactions, and increased risk of nonmelanoma skin cancers. AZA is rarely used as a steroid-sparing agent in DM, and preference is usually given to MTX, MMF, or IVIg unless contraindications or comorbidities prohibiting their use.

Biological Drugs

DM shows elevated concentrations of proinflammatory interleukins (TNF, IL-1, IL-6) and increased expression of molecules related to costimulation of T lymphocytes. In this view the use of biologics in those conditions seems reasonable. Open-label studies are scarce, comprising mainly case reports and series. The most considered biologics are anti-TNF-α, anti-IL-6, and anti-CD-20. The latter has the most promising results.

Tumor Necrosis Factor (TNF)-α Inhibitors

TNF-α inhibitors have received attention in recent years for the treatment of refractory inflammatory myopathies with mixed results.

Increasing data on anti-TNF-induced cutaneous eruptions lend support to the consideration that cases of anti- TNF-induced DM do exist. With these potential adverse reactions and mixed results in the literature regarding the efficacy of anti-TNF agents in DM, it is difficult to formulate any formal treatment recommendations. Anti-TNF agents are usually reserved for refractory cases of DM that have failed treatment with multiple agents. Ideally, the results of upcoming controlled studies will provide more concrete data for therapeutic decision-making.

Tocilizumab

Tocilizumab is a humanized monoclonal anti-IL-6 antibody. Some reports have been published recently. It has been accepted in Castleman's disease.

Rituximab

Rituximab is a chimeric, murine-human, monoclonal antibody directed against the CD20 B-cell specific lymphocyte antigen expressed by pre-B and mature B cells. Data regarding the use of rituximab in the treatment of DM have yielded conflicting results. Case series and open uncontrolled studies have demonstrated efficacy in the treatment of both the myopathy and the cutaneous manifestations of DM. The skin changes that seemed to demonstrate the most improvement included the heliotrope eruption and the poikilodermatous photodistributed erythema. The doses used most frequently are 1,000 mg given as two intravenous infusions 2 weeks apart (which is the typical rituximab dosing regimen for rheumatoid arthritis) and 375 mg/m^2 given as four weekly intravenous infusions (the classic dosing regimen used in non-Hodgkin's lymphoma). Adverse events with rituximab infusions are generally rare; however, mild infusion-related reactions can occur, typically accompanied by fever, chills, nausea, and/or rash.

Sirolimus

Although similar to the systemic calcineurin inhibitors (CNIs) discussed previously, sirolimus (or rapamycin) inhibits the mammalian target rapamycin instead of calcineurin. It promotes the deactivation of T lymphocyte as well as the reduction of keratinocyte proliferation and vascular growth factors level. A recent case report documents its success in treating the skin and muscle disease in a refractory case of DM.

Tacrolimus

Tacrolimus, a macrolide immunosuppressant also acting via inhibition of calcineurin, has been used in the treatment DM. Its mechanism of action is similar to that of CsA, predominantly through interference with T cell activation, but it is 10 to 100 times more potent. A few case series have documented efficacy with this drug, particularly in cases of refractory muscle disease in JDM. In addition, a seemingly impressive resolution of skin lesions has been reported in several cases of JDM, including cutaneous calcinosis and vasculitis.

Plasma Exchange

Plasma exchange, the replacement of one volume of plasma with 5 % albumin in saline, could be considered for polymyositis or dermatomyositis that is resistant to corticosteroids. Significant clinical trials demonstrating its efficacy are not available.

Alkylating Agents

Cyclophosphamide (CP), administered orally or intravenously, has been mainly reported in patients with severe DM/PM associated with interstitial lung disease and in cases with rapidly progressive respiratory disease. Although chlorambucil, a nitrogen mustard-type alkylating agent, was reported to be well tolerated and successful in treating myositis in a series of patients with refractory DM, this medication did not seem to have much effect on skin manifestations.

Conclusions

The diagnostic tests, such as highly specific Mi2 antibody, the antisynthetase antibodies, and other myositis-specific antibodies should be done promptly for an early diagnosis and a correct choice of therapeutic regimen. Generally the outcome is positive if more aggressive is introduced at early stage of illness.

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Dermatophyte Infections

21

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Abbreviations

DLSO	Distal and lateral subungual onychomycosis
FDA	Food and Drug Administration
M.	*Microsporum*
OSI	Onychomycosis severity index
PDT	Photodynamic therapy
PSO	Proximal subungual onychomycosis
RCT	Randomized controlled trial
SO	Superficial onychomycosis
T.	*Trichophyton*
TDO	Totally dystrophic onychomycosis

Key Points

- Topical treatment with imidazoles is adequate for localized tinea corporis and tinea cruris.
- Widespread or follicular lesions of tinea corporis and tinea pedis require systemic treatment.
- Topical treatment with allylamines is indicated to treat most cases of tinea pedis.
- Systemic treatment with itraconazole, terbinafine, or fluconazole is necessary in cases of chronic tinea pedis, when topical therapy fails, or in "moccasin"-type tinea pedis.
- Controlling humidity and maceration is important in the prevention of recurrence of tinea pedis.
- Dermoscopy is a valuable tool in the diagnosis of tinea capitis.
- Tinea capitis usually requires systemic treatment.
- Tinea capitis caused by *Microsporum canis* is treated with griseofulvin, while terbinafine is used to treat tinea capitis caused by *Trichophyton* infections.
- The treatment of onychomycosis depends on the clinical type of infection.
- Superficial onychomycosis with patch infiltration and distal subungual onychomycosis with less than 50 % nail

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_21,

involvement can be effectively treated topically with nail lacquers.
- Distal subungual onychomycosis with greater than 50 % nail involvement, proximal subungual onychomycosis, and deeply infiltrating white superficial onychomycosis require systemic therapy, usually with terbinafine or itraconazole.
- Lateral nail plate involvement, dermatophytomas, and total dystrophic onychomycosis may require nail plate avulsion combined with topical or systemic treatment.

Tinea Corporis

Definition and Basic Concepts of Pathogenesis

Tinea corporis is an infective skin disease resulting from invasion and proliferation by the causal fungi in the stratum corneum. The fungi most commonly involved are *Microsporum* (*M.*) *canis*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. It most commonly involves exposed parts of the body, but can affect any site. Typical lesions are annular in shape, with a raised scaling erythematous edge. The presence of perifollicular granulomatous papules (Majocchi's granuloma) is a definite indication for systemic treatment.

General Principles of Treatment

Topical Treatment

In localized lesions of tinea corporis, topical treatment with imidazole derivatives, allylamines, phenylpropylmorpholine derivatives, tolnaftate, or cyclopiroxolamine is adequate. Treatment period varies between 2 and 4 weeks, except for allylamines that are effective after 1–2 weeks of therapy. Efficacy among the different classes is similar; however, butenafine may achieve faster mycological cure. Sertaconazole, a newer imidazole derivative, may be more effective at controlling symptoms of pruritus.

Systemic Treatment

Systemic treatment is required in widespread tinea corporis or when follicular lesions (Majocchi's granuloma) are present. Itraconazole (200 mg daily for 1 week), terbinafine (250 mg daily for 2 weeks), and fluconazole (150 mg weekly for up to 4–6 weeks) are currently preferred because time to treatment is usually shorter and they are better tolerated than griseofulvin.

Tinea Cruris

Definition and Basic Concepts of Pathogenesis

This infection mainly occurs in adult men and is usually caused *by Trichophyton rubrum* and *Epidermophyton floccosum*. Tinea cruris presents with an itchy scaling of the groin and insides of the thighs. The margin of the affected area typically presents with a raised erythematous border.

General Principles of Treatment

Topical Treatment

In localized lesions topical treatment, as for tinea corporis, may be sufficient.

Systemic Treatment

This is mandatory in long-standing lesions or when follicular granulomas are present. Itraconazole (200 mg daily for 1 week), terbinafine (250 mg daily for 2 weeks), and fluconazole (150 mg weekly for up to 4–6 weeks) are very effective.

Tinea Pedis

Definition and Basic Concepts of Pathogenesis

Tinea pedis is the most common dermatophyte infection and in most cases is caused by

Trichophyton (*T.*) *rubrum*, followed by *Trichophyton interdigitale*. *Trichophyton rubrum* usually produces noninflammatory lesions with different degrees of severity ranging from mild scaling to diffuse "moccasin-type" scaly rash. *Trichophyton interdigitale* usually causes interdigital or plantar inflammatory lesions that are often vesicular and pruritic.

General Principles of Treatment

Topical Treatment

Topical antifungals are usually used to treat tinea pedis. They are also commonly utilized to prevent reinfections. Generally, allylamines have been shown to be more efficacious than azoles. Usually, topical therapy lasts 1–4 weeks. Naftifine and terbinafine are the commonly used allylamine in tinea pedis. A new drug that has completed phase III testing, terbinafine film-forming solution, has shown to be safe and efficacious in preventing tinea pedis with only one application (Chauvin et al. 2008). Among the azole treatment options are ketoconazole, econazole, oxiconazole, miconazole, and clotrimazole. A newer treatment option is sertaconazole. Compared to miconazole, sertaconazole has a statistically higher complete clinical cure rate. Sertaconazole also provided patients with greater relief from erythema and desquamation. Sertaconazole has the added benefit of being effective with once daily application. Luliconazole is a new drug currently undergoing phase 2 testing (Jarratt et al. 2013). Flutrimazole and bifonazole are available as powders that can be applied twice daily for 2–4 weeks and may be effective in curing tinea pedis.

Alternative treatment options, including *Ageratina pichinchensis* extract (active ingredient encecalin), Brazilian green propolis extracts, green tea polyphenols, and tea tree oil, have shown some effectivity. *Ageratina pichinchensis* demonstrated similar cure rates to ketoconazole. Use of Brazilian green propolis extracts showed improvement of clinical features over petroleum jelly. Green tea polyphenols have been shown in one randomized controlled trial (RCT) to improve tinea pedis; however, the study design only had one physician making assessments and thus lacked interobserver validity (Ikeda et al. 2013). Tea tree oil shows significant promise as an alternative treatment for tinea pedis. In an RCT, tea tree oil demonstrated statistically significant improvement in mycological as well as clinical cure rates compared to placebo after 4 weeks of twice daily application (Satchell et al. 2002).

Systemic Treatment

Systemic treatment is indicated, if topical therapy fails, in chronic conditions, or in cases of moccasin-type tinea pedis. Itraconazole, terbinafine, and fluconazole are effective in the treatment of tinea pedis. Common treatment regimens include itraconazole at 100 mg/day for 2–4 weeks, terbinafine at 250 mg/day for 2 weeks, or fluconazole at 150 mg weekly for up to 6 weeks. However, clinically, there is some variance in the regimens. Terbinafine may be the preferred agent as it may be more efficacious, has lower recurrence rates, and requires a shorter treatment duration.

Prevention of Recurrences

1. Reduction of maceration and humidity can be obtained by regular use of talcum powders.
2. The demonstration that dermatophytes occur in shoes (up to 17 % in one study), flooring, and carpets (Muslim community) indicates that any treatment directed solely at the feet is inadequate to control the disease. Effective control measures must also include simultaneous eradication of the organisms (such as disinfection of shoes with 1 % 8-hydroxycholine sulfate, formaldehyde) and/or the environment to prevent reinfection. However, there is limited data which shows a correlation of such measures and the prevention of athletes' foot. In such circumstances, evaluating the preventative efficacy of these measures against athletes' foot remains guesswork.

Tinea Capitis

Definition and Basic Concepts of Pathogenesis

In Europe, tinea capitis is predominantly caused by *Microsporum canis* and increasingly by *Trichophyton tonsurans*, with *Microsporum canis* being the most common agent of tinea capitis in Italy. Other dermatophytes responsible for tinea capitis include *T. soudanense*, *T. violaceum*, *M. gypseum*, *T. mentagrophytes*, and *T. schoenleinii*. The most common causative agents vary significantly by geographic region. The clinical manifestations of tinea capitis range from mild scalp scaling to severe inflammatory reactions. Cervical lymph nodes are often enlarged.

Dermoscopy is an important and underutilized tool in the diagnosis of tinea capitis. It can be especially useful in African-American patients where erythema may be subtle and difficult to appreciate. Characteristic signs such as comma hairs and corkscrew hairs may help in making the diagnosis. In tinea capitis favosa, there is no significant hair structure abnormality, but large amorphous yellow areas and wax-colored perifollicular areas can be observed. Black dots and broken dystrophic hairs are also seen in tinea capitis but are not specific to the disease.

General Principles of Treatment

Topical Treatment

Although tinea capitis always requires systemic treatment, the use of adjunctive topical therapy is important. Periodic hair shaving prevents diffusion of the infection. Antifungal shampoos such as ketoconazole 2 %, selenium sulfide shampoo 1 %, and ciclopirox shampoo 1 % should be given to the patient and family members in order to reduce transmission of infection. Family members and primary contacts should be screened for asymptomatic disease. Family pets of patients with *Microsporum canis* infection should be treated. Fomites, including toys, phones, clothing, furniture, and hair care items, may contribute to spread of the infection and can be sterilized using high temperature or microwaves.

Systemic Treatment

Microorganism identification may be useful in the treatment of tinea capitis as the different species show varying susceptibilities. In tinea capitis due to *Microsporum canis*, griseofulvin is commonly prescribed. The drug should be administered at 10–25 mg/kg per day for 2–3 months. The azole antifungals fluconazole and itraconazole are effective in the treatment of *Microsporum canis* infection of the hair, with fluconazole being the only one available in a pleasant-tasting liquid formulation. The suggested regimen for fluconazole is 4–6 mg/kg per day for 8–12 weeks and may be administered on a weekly basis as well. Itraconazole can be administered at 5 mg/kg per day or as pulse therapy and is available in both capsule and oral solution. The length of treatment varies by organism, with *M. canis* requiring treatment for 6 weeks. Terbinafine is less effective in tinea capitis due to *M. canis* but may be more efficacious compared to griseofulvin in treating infection by the *Trichophyton* species. Dosages used in this setting are 3.125–6.25 mg/kg per day for terbinafine, 3–5 mg/kg per day for itraconazole, and 4–6 mg/kg once a week for fluconazole. Duration of treatment ranges from 2 to 6 weeks. Oral or topical steroids can be given in association with systemic antifungals to reduce pain, swelling, and inflammation.

Onychomycosis

Definition and Basic Concepts of Pathogenesis

Dermatophytes account for more than 90 % of onychomycosis, with T. rubrum being the most common pathogen. They may produce several different clinical types of onychomycosis, depending on the modality of nail invasion by the fungus.

Distal and Lateral Subungual Onychomycosis (DLSO)

DLSO (Fig. 21.1) is the most common of the clinical entities and involves invasion from the lateral or distal part of the nail plate. The affected

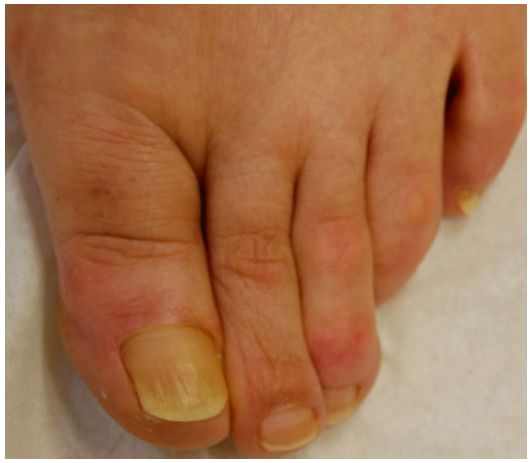

Fig. 21.1 Distal subungual onychomycosis due to *T. interdigitale* involving the distal 1/3 of the nail

nails usually show subungual hyperkeratosis, onycholysis, and white or yellow discoloration. Infrequently, brown, black, or orange discoloration may also be seen. In certain cases, longitudinal streaking of the nail, called dermatophytoma, can be seen. These infections are difficult to treat and may require excision of the area and systemic treatment rather than topical therapy. Since the skin of the palms and soles is the primary site of infection, DLSO is usually associated with tinea manuum or tinea pedis. This form of infection is seen with a variety of causative agents including dermatophytes.

Superficial Onychomycosis (SO)

SO can present with superficial patches or transverse striae and may arise from the superficial nail plate or emerge from the proximal nail fold. These bear clinical implications on treatment. In the classic form, previously known as white superficial onychomycosis, dermatophytes colonize the most superficial layers of the nail plate without penetrating it. The affected nail presents multiple friable white opaque spots in a patchy distribution that can be easily scraped away. This form is amenable to topical treatment. In contrast, in the striate form when the infection emerges from the proximal nail fold and with deep penetration of the nail plate, oral therapy is indicated.

Endonyx Onychomycosis

Endonyx onychomycosis is characterized by massive nail plate parasitization in the absence of nail bed inflammatory changes. Clinically, the affected nail may show lamellar splitting and a milky white discoloration. The nail plate is firmly attached to the nail bed and there is no nail bed hyperkeratosis or onycholysis. This type of infection is commonly seen with *T. soudanense* but can also be seen with *T. violaceum*.

Proximal Subungual Onychomycosis (PSO)

PSO is characterized by a primitive invasion of the nail matrix keratogenous zone through the proximal nail fold horny layer. Fungal elements are typically located in the ventral nail plate with minimal inflammatory reaction. The affected nail shows proximal leukonychia that progresses distally with nail growth. PSO can be divided into either patchy, striate, or secondary to paronychia. Among the dermatophytes, these infections are usually caused by T rubrum. PSO is difficult to treat and requires oral therapy.

Mixed Pattern Onychomycosis

Oftentimes, different patterns of infection may be seen in the same patient. DLSO may occur with superimposed SO or PSO and SO may occur with superimposed DLSO or PSO. The most common of these are PSO with SO or DLSO with SO. Mixed pattern onychomycosis often requires oral treatment.

Totally Dystrophic Onychomycosis (TDO)

TDO is the end stage of onychomycosis and can result from DLSO as well as PSO. The nail plate, in these cases, crumbles and the underlying nail bed is thickened.

Secondary Onychomycosis

In some cases of nail pathologies such as psoriasis or traumatic nail dystrophy, a secondary fungal infection can occur.

General Principles of Treatment

The treatment choice depends on the clinical type of the onychomycosis, the number of affected nails, and the severity of nail involvement.

The onychomycosis severity index (OSI) was developed in 2011 and provides a fast and effective way to evaluate the extent of onychomycosis and may provide an objective measurement on which to base treatment (Carney et al. 2011). Furthermore, the OSI scoring system demonstrates excellent interobserver reliability. The categories assessed when calculating the OSI are area of involvement, proximity of disease to matrix, and the presence of dermatophytoma or subungual hyperkeratosis greater than 2 mm. First, the area of involvement is determined as the percentage of the nail that is onychomycotic. Involvement is categorized as 1–10 %, 11–25 %, 26–50 %, 51–75 %, or 76 % or greater with scores ranging from 0 to 5, respectively. Next the proximity of disease to matrix is assessed by visualizing the leading edge of disease proximally. The nail is divided transversely into quarters. Scores of 1 through 4 are assigned, with 1 for only distal quarter involvement and 4 for proximal quarter involvement. If the proximal edge extends into the nail fold or if the lunula is involved, a score of 5 is given. The third step is to assess the presence of dermatophytoma, defined as the presence of a patch or a longitudinal streak, or subungual hyperkeratosis greater than 2 mm. If either of these is present, a score of 10 is given. The OSI is calculated by multiplying the score for the area of involvement by the score for proximity of disease to the matrix and adding 10 if necessary from the third step. Scores range from 0 to 35 with higher numbers correlating with increased severity. Scores of 1–5 indicate mild onychomycosis, scores of 6–15 indicate moderate onychomycosis, and scores of 16–35 indicate severe onychomycosis. A score of zero indicates a cured state.

Topical Treatment

Penetration of a topical antifungal through the nail plate requires a vehicle that is specifically formulated for transungual delivery. The two most commonly used agents are amorolfine 5 % nail lacquer and ciclopirox 8 % nail lacquer. However, agents such as miconazole, tioconazole, ketoconazole, tolnaftate, naftifine, and tea tree oil have been tested with varying success rates in the past. Amorolfine nail lacquer is applied once a week, whereas ciclopirox nail lacquer is applied daily.

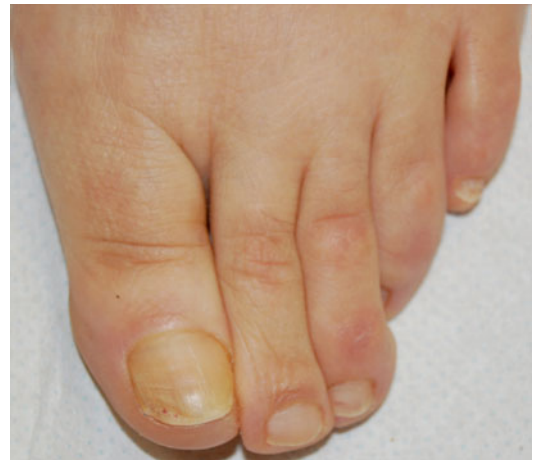

Fig. 21.2 Complete cure of the onychomycosis after 6 months of topical application of a nail lacquer containing ciclopirox with hydroxypropyl chitosan as vehicle

Nail lacquers are effective as monotherapy in the treatment of superficial onychomycosis, with patch infiltration, and of distal subungual onychomycosis, limited to less than 50 % of the distal nail (Hay and Baran 2011). Treatment duration should be 6–12 months (Fig. 21.2). Nail lacquers are also utilized in combination with systemic antifungals or nail avulsion in severe onychomycosis to reduce duration of treatment and increase cure rate.

Application of amorolfine nail lacquer once every 2 weeks after completion of treatment may be effective prophylaxis to prevent the recurrence of onychomycosis.

Recent studies on lipid diffusion enhancers and water-soluble biopolymers have shown promise (Baran et al. 2009; Hafeez et al. 2013). Terbinafine nail solution and a terbinafine spray using lipid-based vesicles currently under development, labeled TDT 067, may be viable treatment alternatives in the future (Elewski et al. 2013;

Table 21.1 New topical antifungal treatment options for onychomycosis

Drug	Nail involvement	Mycological cure	Clinical cure	Complete cure	Author
Efinaconazole	<50 %	53.4*–55.2 %*	–	15.2*–17.8 %*	Elewski et al. (2013)
Tavaborole 5 % and 7.5 %	20–60 %	Culture: 97 %, 94 % KOH: 63 %, 60 %	–	–	Beutner et al. (2009)
Urea, propylene glycol, and lactic acid (K101)	<50 %	27.2 %*	–	–	Emtestam et al. (2012)
Bifonazole after ablation with 40 % urea	<50 %	64.5 %*	86.6 %*	54.8 %*	Tietz et al. (2013)
Terbinafine nail solution	25–75 %	12.7–18.8 %*	2.3–3.5 %	1.2–2.2 %	Elewski et al. (2013)
Terbinafine spray (TDT 067)	–	90.1 %	–	–	Dominicus et al. (2012)
Terbinafine HCL with iontophoretic patch	25–75 %	84 %*	–	–	Amichai et al. (2010)

*Indicates statistically significant difference

Dominicus et al. 2012). Other formulations with terbinafine that are undergoing phase II trials include MOB-015 and TMI-358. Luliconazole has completed phase I and IIa testing for treatment of moderate to severe distal subungual onychomycosis with positive results (Jones and Tavakkol 2013). Refer to Table 21.1 for a comprehensive list of new topical antifungal treatment options for onychomycosis.

Treatments with photodynamic therapy (PDT) using photosensitizers may also prove to be effective treatment options in the future. Laser therapy is also currently being researched and may be effective in the treatment of onychomycosis. Food and Drug Administration (FDA)-approved lasers for onychomycosis include carbon dioxide laser, Nd:YAG laser, and the diode 870 nm, 930 nm laser. The carbon dioxide laser is the oldest laser and is infrequently used today. With the Nd:YAG laser, small clinical trials have demonstrated mycological cure rates as high as 87.5 % (Zhang et al. 2012). Similarly, the diode laser has shown some efficacy in small trials, with mycological cure rates as high as 38 % reported at 9-month follow-up (Landsman and Robbins 2012). Large randomized control trials need to be conducted to validate the efficacy of these lasers and PDT in the treatment of onychomycosis.

Systemic Treatment

Distal subungual onychomycosis that involves greater than 50 % of the nail, proximal subungual onychomycosis, and deeply infiltrating white superficial onychomycosis require systemic therapy. Systemic treatment with terbinafine or itraconazole produces mycological cure in more than 90 % of fingernail infections and in about 80 % of toenail infections. These success rates can be increased by associating a topical treatment with a nail lacquer to the systemic treatment. However, compared to itraconazole, terbinafine has a higher mycological and clinical cure rate and a lower rate of recurrence. Terbinafine can be administered as a continuous therapy at 250 mg per day for 12 weeks or an intermittent regimen of two pulses of 250 mg/day for 4 weeks on and 4 weeks off. Itraconazole is administered as pulse therapy at the dosage of 200 mg twice a day for 1 week a month. The treatment duration is 2 months for fingernails and 3 months for toenails.

Fluconazole is also used in onychomycosis but is less effective. The recommended dosage is 150 mg weekly for more than 6 months, especially for toenails. Posaconazole and albaconazole are newer drugs that could be alternative therapy options.

In cases of lateral nail plate involvement or dermatophytomas, surgical or chemical avulsion of the nail plate combined with topical or systemic treatment is indicated. Total dystrophic onychomycosis is an extremely recalcitrant entity. Surgical nail avulsion followed by topical therapy may not be enough to provide a cure in this situation; however, chemical avulsion with urea nail lacquer may be a viable treatment option. Sequential treatment with itraconazole and terbinafine has been utilized to increase cure rates: the suggested regimen is two pulses of itraconazole 400 mg/day for 1 week a month followed by one or two pulses of terbinafine 500 mg/day for 1 week a month.

Mycological cure can be evaluated at the end of treatment. Evaluation of clinical response, on the other hand, requires several months due to the slow growth rate of the nail. Recurrences and reinfection are not uncommon and vary with type of treatment (rates of 35.7 % reported with itraconazole). These may be prevented by the regular application of nail lacquers on the previously affected nails and topical antifungals on soles and toe webs.

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Drug Hypersensitivity Reactions

22

Andrea Szegedi and Eva Remenyik

Abbreviations

AGEP	Acute generalised exanthematous pustulosis
DiHS	Drug-induced hypersensitivity syndrome
DRESS	Drug reaction with eosinophilia and systemic symptoms
HSS	Hypersensitivity syndrome
LTT	Lymphoblast transformation test
MDE	Maculopapular drug eruption
NSAIDs	Nonsteroidal anti-inflammatory drugs
SJS	Stevens-Johnson syndrome
SSSS	Staphylococcus scalded skin syndrome
TEN	Toxic epidermal necrolysis

Key Points

- In the therapy of drug hypersensitivity reactions at the time of the acute symptoms, the main tasks are to state the correct diagnosis, classify the reaction, score the severity, withdraw the suspected drug, treat the symptoms and prepare the drug history documentation properly, which can help the allergological examinations in the future.
- After the resolution of the symptoms, the physician's next duties are the identification of the eliciting drug and the treatment of sequelae if needed.
- Since morphology and distribution of the rash does not help in determining the responsible drug, allergological investigations should be performed on the basis of the patient's history.
- Allergological tests are best prepared between 3 weeks and 6 months after the incident.
- A detailed history is one of the most important assessments when a patient presents with drug hypersensitivity reaction.

Definition and Basic Concept of Pathogenesis

Adverse reactions caused by drugs can be divided into two main groups, type A and type B reactions. Type A reactions represent nearly 80–85 % of these side effects and are caused by predictable pharmacological actions of the drug, while type B reactions develop on the basis of individual predisposition (idiosyncratic reactions, immune-mediated and nonimmune-mediated hypersensitivity

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_22, © Springer-Verlag Berlin Heidelberg 2015

Table 22.1 Pathogenesis and diagnostic steps in drug hypersensitivity reactions

Clinical manifestation	Potential pathogenesis	Diagnostic tests
Urticaria, angioedema	IgE mediated, pseudoallergy	Prick test, intradermal skin tests, specific IgE, basophil tests, LTT, provocation
Anaphylaxis	IgE mediated, pseudoallergy, rarely immune complex activation (C3a, C5a)	Prick test, specific IgE, basophil tests, serum tryptase measurement, LTT
MDE	T cell mediated (IVc)	Patch test, LTT
AGEP	T cell mediated (IVd)	Patch test, LTT
DRESS	T cell mediated	Patch test, LTT
	Viral reactivation?	
SJS and TEN	T cell mediated (IVc) and other nondrug-specific amplification mechanisms	Patch test, LTT (low sensitivity)

reactions) and account for 15–20 % of adverse effects. The skin is the organ most commonly, but not exclusively, affected in drug hypersensitivity reactions both in the immune-mediated (allergic) and in the nonimmune-mediated (pseudoallergic) forms; these reactions are observed in 2–3 % of hospitalised patients. Immune-mediated drug hypersensitivity reactions comprise a heterogeneous group of diseases which can be classified according to Gell and Coombs (antibody-mediated drug hypersensitivity reactions: type I, IgE; type II and III, IgG; and type IV, T cell mediated). After better understanding of T-cell functions and discovery of subgroups, the late type IV reaction has been further subdivided in the revised form of Gell and Coombs classification (type IVa, T helper 1; type IVb, T helper 2; type IVc, T cytotoxic mediated and type IVd). Nonimmune-mediated hypersensitivity reactions are the so-called pseudoallergic reactions, which usually imitate IgE-mediated reactions with wheal and oedema formation, but sometimes anaphylaxis can also develop. These pseudoallergic reactions tend to arise less rapidly than true IgE-mediated allergies, they require higher doses of the drugs and neither IgE nor T-cell reactions can be demonstrated later. Non-specific histamine release, arachidonic acid pathway activation, bradykinin pathway alteration and complement activation can be detected in the background. Nonsteroidal anti-inflammatory drugs (NSAIDs), plasma expanders and radiocontrast media are the most common causes of pseudoallergic reactions.

The therapy of drug hypersensitivity reactions comprises two fundamental steps. At the time of the acute symptoms, the main tasks are to state the correct diagnosis, classify the reaction, score the severity, withdraw the suspected drug, treat the symptoms and prepare the documentation properly, which can help the allergological examinations in the future. The second step is the identification of the eliciting drug and the treatment of sequelae if needed. Since morphology and distribution of the rash does not help to determine the responsible drug, according to data of the history, allergological investigations should be done between 3 weeks and 6 months after the incident in order to find the causative agent (see Table 22.1). The recommended test type depends on whether the diagnosis of the rash was an immediate- or delayed-type reaction.

This chapter will deal with the most common and severe forms of drug hypersensitivity reactions like urticaria and anaphylaxis, maculopapular drug eruption (MDE), acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Clinical Presentation

Urticaria, Anaphylaxis

Urticaria and anaphylaxis are the two most common immediate-type drug hypersensitivity reactions and urticaria is the second most common cutaneous manifestation of drug allergy after MDE. In

urticaria, disseminated wheals (oedema in the upper part of the dermis) are limited to the skin and can be accompanied by angioedema (tense, non-pitting oedema of the deeper skin layers and mucosa). Anaphylaxis has been defined as a severe, life-threatening generalised or systemic hypersensitivity reaction that occurs immediately after drug intake and affects more than one organ, whether or not accompanied by hypotension (anaphylactic shock). Urticaria can be caused by immune-mediated hypersensitivity reactions (type I, IgE-mediated reaction, or less frequently type III, immune complex-mediated reaction) or by nonimmune-mediated, so-called pseudoallergic mechanisms. In the pathogenesis of anaphylaxis, immunological reactions involving IgE or rarely immune complexes and also nonimmunological mechanisms are detected (called as nonallergic anaphylaxis or anaphylactoid reaction). Many different drugs can cause urticaria or anaphylaxis, most commonly beta-lactam and non-beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), radiocontrast media, general anaesthetics and latex.

Clinical Features

In drug-induced acute urticaria, symptoms appear usually within 1 h after drug intake. Rapidly emerging, migrating and extensively itching wheals occur on large body parts (see Fig. 22.1). The lesions typically disappear in hours in one location without leaving any remnant signs. Pruritus, urticaria and angioedema may also present as initial or partial symptoms of full-blown anaphylaxis. In anaphylactic patients, flushing, itching and pruritus of the palms and soles, together with generalised urticaria and angioedema, are followed by respiratory symptoms (in up to 70 % of patients) and by gastrointestinal symptoms (in up to 40 % of patients). Asphyxia due to laryngeal oedema is probably the main cause of lethal anaphylaxis. Laryngeal swelling

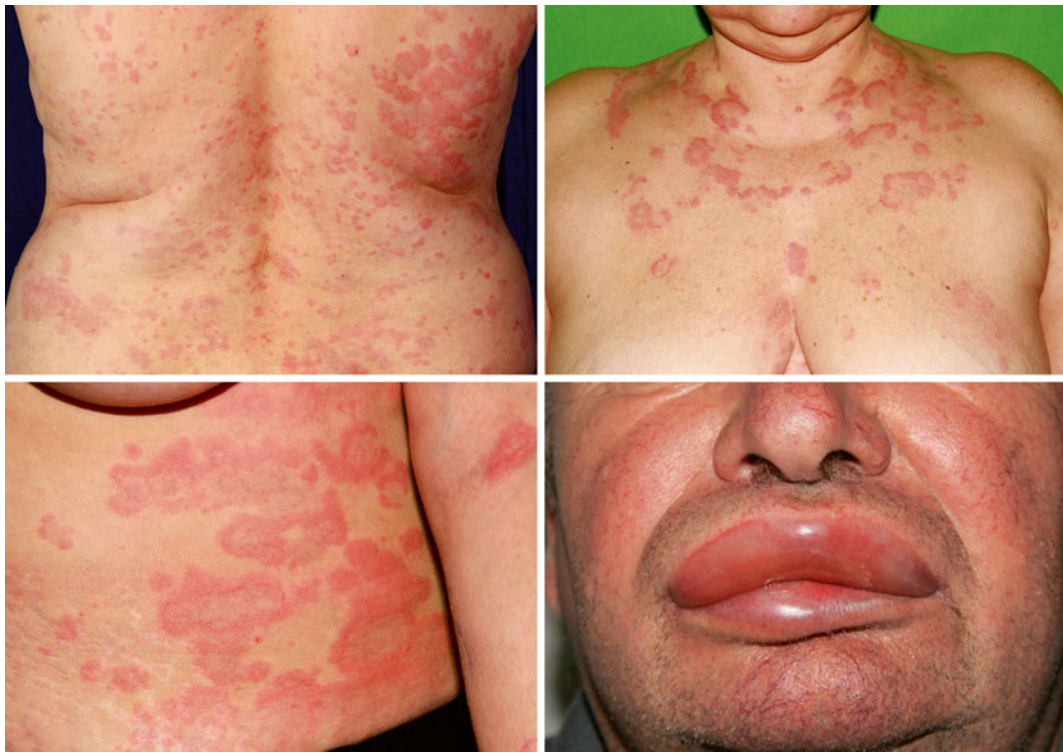

Fig. 22.1 Clinical signs of urticaria and angioedema

may be suspected in case of difficulty of speaking or swallowing and if the voice becomes hoarse. Hypotension, manifest as dizziness, tachycardia, shock and cardiorespiratory arrest, occurs in only 10–30 % of cases. Typically, anaphylactic symptoms start within minutes (seldom later than 20 min) after exposure to the causative drug. In the diagnosis, the physician should consider the wide spectrum of symptoms and the continuum of signs and symptoms.

Differential Diagnosis

The diagnosis of acute urticaria and anaphylaxis is based largely on history and physical findings at the time of the event. Usually skin biopsy is not needed, only if urticaria vasculitis has to be distinguished. Laboratory tests available to support the diagnosis of anaphylaxis have proved to be somewhat disappointing in the clinical practice. Transiently elevated plasma histamine level of >10 nM correlates with severity and persistence of cardiopulmonary manifestations or gastrointestinal manifestations, but as histamine needs to be measured within 1 h of the onset of anaphylaxis, this test is seldom used. Measuring serum tryptase level within 12 h is more widely used, although this method also has its limitations.

Treatment

Acute stage: In the majority of moderate drug-induced urticaria cases, stopping the causative agent and treatment with a non-sedative histamine H1 antagonist is sufficient. Locally corticosteroid-containing creams or lotions can be applied to decrease pruritus. In case of widespread lesions with oedema formation, oral corticosteroids provide symptomatic relief and attenuate the reaction. Patients with anaphylaxis should be lied down with their legs elevated and epinephrine should be administered at the first sign of respiratory failure or cardiovascular collapse. The intramuscular route for epinephrine administration is recommended when compared to the subcutaneous mode. The dose is usually 0.3–0.5 ml of a 1:1,000 dilution in adults and this dose can be repeated in every 5–15 min until symptoms improve. Intravenous epinephrine (1:10,000 dilution) should be reserved for extremely severe anaphylaxis with life-threatening hypotension because of the higher risk of cardiac arrhythmias, hypertension and myocardial infarction. The most common side effects of epinephrine are anxiety, tremor, palpitation and increased blood pressure. Beta-blockers may increase the severity of an anaphylactic reaction and antagonise the response to epinephrine; accordingly, the anaphylaxis of patients on beta-blockers can be severe and treatment resistant. Corticosteroids are often used to decrease the risk of recurrent or protracted anaphylaxis, but it is still not entirely clear how steroids work. If hypotension is severe or does not respond rapidly to therapy, 1–2 L of crystalloid fluid should be infused. Patients should be warned of the possibility of an early relapse and kept under observation for 8–24 h, particularly if the patient has asthma, has a history of biphasic response or may continue to absorb the drug. Oxygen should also be applied in respiratory or circulatory failure. In case of severe laryngeal oedema, in order to maintain the airway, endotracheal intubation or tracheostomy should be carried out.

Chronic stage: The main purpose is the identification of the eliciting drug. Since both urticaria and anaphylaxis can be the result of immune-mediated and also of nonimmune-mediated reactions, this often causes difficulties in the allergological investigations, which are recommended between 3 weeks and 6 months after the incident, when complete clearing of clinical signs and normalisation of laboratory values have occurred. In the case of acute urticaria, prick tests which are less sensitive but safer can be carried out if the intradermal skin test is negative. The negative result is not a guarantee that the drug is tolerated, because of the weak sensitivity of these tests. Whenever possible, one should carry out laboratory tests, such as drug-specific IgE measurements, basophil CD63 activation assay, basophil sulphidoleukotriene or histamine release assays or the lymphoblast transformation test (LTT). If these tests are negative, then a provocation test may be performed or in other words a graded challenge test. In the case of anaphylaxis, laboratory tests can be performed, whereas intradermal or provocation tests are usually not advised. Serum tryptase levels increase greatly after anaphylactic shock and anaphylaxis, but are

negative in anaphylactoid non-IgE-mediated reactions. The concentration of tryptase peaks 1–2 h after the onset of the reaction and remains elevated with a half-life of 1.5–5 h, so the samples for tryptase test should be collected within 6 h of initiation of anaphylaxis. In pseudoallergic reactions, skin tests and in vitro tests are also negative, since adaptive immune reactions are not involved to our present knowledge. Provocation tests can be informative but often negative suggesting that additional cofactors might be needed to develop clinical symptoms. Although it has been described with aspirin and penicillin, desensitisation is rarely performed, since the benefits are outweighed by the hazards. Patients may be advised to wear a MedicAlert bracelet and instructed on the use of a self-administration epinephrine device in the event of further episodes.

Maculopapular Drug Eruption (MDE)

The so-called exanthematous reactions, the MDEs, are the most common drug hypersensitivity eruptions affecting the skin and present 31 %–95 % of all drug-induced cutaneous reactions. Antimicrobials (beta-lactams, sulfamethoxazole, quinolones), anticonvulsants, NSAIDs, and allopurinol are the most frequently involved drugs, but it is important to know that any drug can play an initiating effect. There are a lot of cofactors in the development of MDEs, like viral infections, connective tissue diseases, older age and genetic factors. MDEs belong to the type B hypersensitivity reactions, so they are unpredictable and occur in individuals with personal susceptibility. Drug-specific, CD4+ cytotoxic T cells are the dominant effector cells, and MDEs are considered to be a Gell and Coombs type IVc, cell-mediated delayed-type hypersensitivity reactions.

Clinical Features

The clinical picture characteristic of MDEs consists of hyperaemic or pink-coloured papules and macules, which sometimes become confluent (see Fig. 22.2). The rash usually starts on the trunk and upper extremities and affects other body parts, like lower extremities, gradually. The palms, feet and mucous membranes are free and this can be an important differential diagnostic

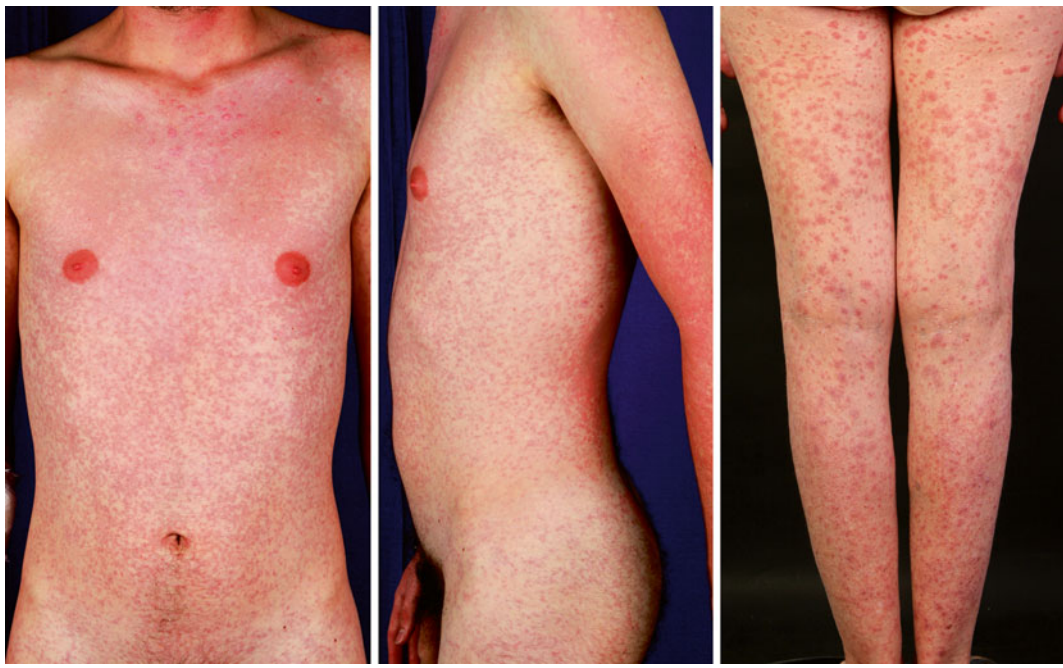

Fig. 22.2 Generalized erythematous morbilliform macules and papules of MDE

feature. Moderate to severe pruritus can occur. In the uncomplicated forms, the skin lesions usually begin to evolve 4–14 days after the patient starts to take the causative drug and disappear 1–2 weeks after discontinuation. MDE often heals with desquamation. On the other hand, in some cases the primary maculopapules can represent the beginning of more severe drug reactions, like erythroderma, SJS, TEN or DRESS, so all patients should be monitored for markers of severe reactions (see Table 22.2). In late-type reactions, including MDE, certain laboratory tests (complete blood count, liver function test, CRP, serum creatinine) are recommended to assess severity.

Differential Diagnosis

In the differential diagnosis of MDE, the dermatologist should consider acute viral infections, collagen vascular diseases, acute graft-versus-host disease and secondary syphilis (see Table 22.3). Usually skin biopsy is not needed; anamnestic data, clinical picture and some laboratory tests are enough to state the diagnosis.

Treatment

Acute stage: The suspected drug should be withdrawn as the first step of treatment. Sometimes it is not easy to identify the causative drug. In these cases, all drugs that are not essential and were started in the last few weeks should be stopped. In mild–moderate cases, topical corticosteroid creams and systemic antihistamines can be used; in severe cases, systemic corticosteroids can be initiated and then gradually decreased when the symptoms disappear.

Chronic stage: After the patient became symptom free, the next step is to identify the causative drug, if there are several suspected medications in the history. The patch test and the LTT can be performed after recovery and after stopping antihistamines and corticosteroids. Patch tests are recommended to carry out within 6 months after the MDE, and they are not well standardised so false-positive and false-negative results can occur. LTT validation is also not well organised in different laboratories. Provocation tests after MDEs are questionable since they need longer time period and hold the risk of inducing a more severe reaction. Desensitisation may be considered in those cases where the drug is mandatory without available alternative.

Table 22.2 Markers of severe reactions in patients with MDE

1. Skin pain or burning
2. Widespread eruptions (i.e. confluent erythema)
3. Affecting more than 60 % of the body surface area
4. Dusky red or purpuric macules
5. Atypical target lesions
6. Blisters or epidermal detachment
7. Positive Nikolsky sign
8. Involvement of mucous membranes
9. Facial oedema
10. Lymphadenopathy
11. Arthralgia
12. High fever (>40 °C)
13. Laboratory findings: eosinophilia, atypical lymphocytes and abnormal liver function tests

Acute Generalised Exanthematous Pustulosis (AGEP)

AGEP is a T-cell-mediated, late type IVd hypersensitivity drug-induced skin reaction with a rapid and dramatic appearance, but with a benign course. It is a rare disease with an estimated incidence equal to severe bullous skin diseases. The main causative medications are aminopenicillins, cephalosporins, macrolides, celecoxib, diltiazem and antimalarial drugs such as hydroxychloroquine or chloroquine, but there are reports on the role of sulphonamides and terbinafine. Usually the onset of the skin reaction occurs a few days (3–5 days) after the initiation of the suspected medication. In the pathogenesis, drug-specific T lymphocytes are supposed to migrate into the epidermis, where keratinocytes and T cells secrete IL-8, which attracts neutrophils, and neutrophil recruitment will result in the formation of subcorneal pustules.

Table 22.3 Differential diagnosis of MDE

	Clinical picture/histology	Laboratory findings
1. MDE	Polymorphous clinical picture, frequent confluence, elderly age group	Eosinophilia in peripheral blood
2. Acute viral infections (paramyxovirus, togavirus, Epstein-Barr virus, enterovirus, CMV, parvovirus)	Younger age groups, concomitant general symptoms, dermal haemorrhage	Serological test for infections are positive, laboratory signs of infections (CRP, leukocytosis)
3. Collagen vascular diseases	General symptoms differ, epidermal atrophy, focal parakeratosis, thickening of the basement membrane zone on histology	Immunological alterations, (autoantibodies, complement serology)
4. Acute graft-versus-graft reactions	Specific anamnesis, epidermal atrophy, parakeratosis, necrotic keratinocytes on histology	
5. Secondary syphilis	Palmoplantar lesions, plasma cell-rich mononuclear infiltration in histology	Specific serology

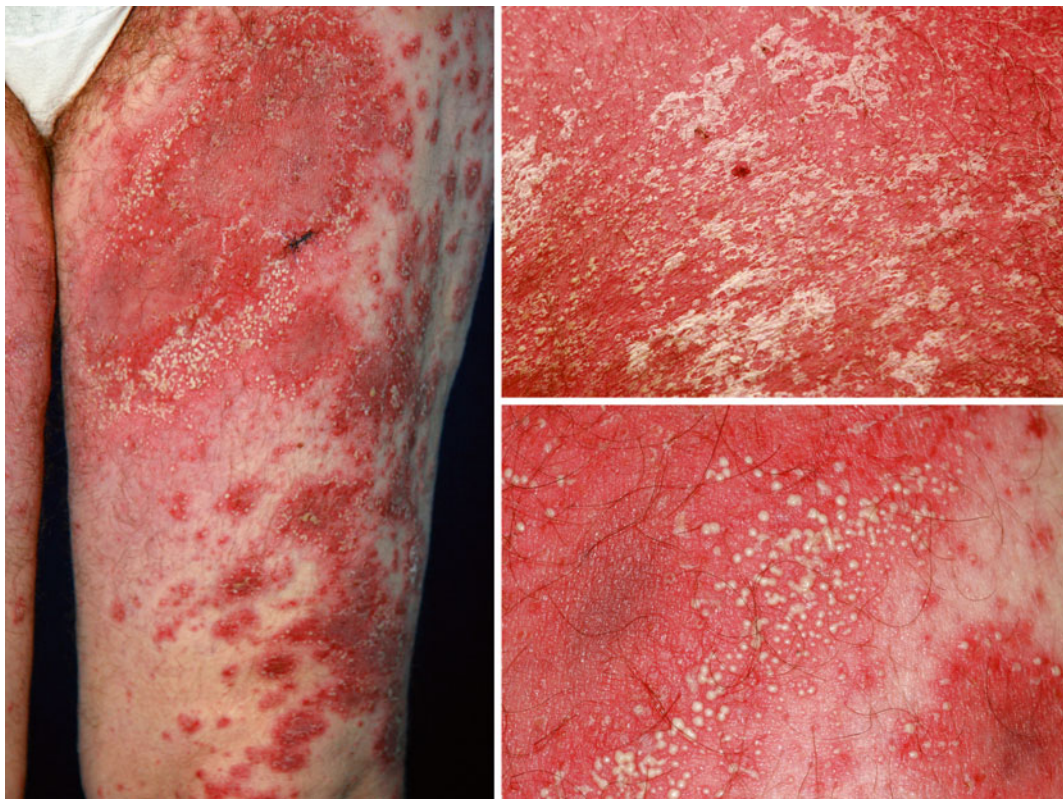

Fig. 22.3 Characteristic picture of AGEP with widespread small, non-follicular, sterile pustules

Clinical Features

In the course of AGEP, a widespread erythema suddenly occurs on the trunk and extremities, mainly affecting the flexural surfaces and skin folds. On the top of the erythema, a lot of small non-follicular sterile pustules develop rapidly (see Fig. 22.3)**.** Usually mucous membranes are not involved, but patients have fever and massive

neutrophilia. A diagnostic score for validation of AGEP was introduced and this system distinguishes definite, probable and possible AGEP diagnosis according to the final score. Spontaneous resolution in less than 15 days and post-pustular desquamation are also characteristics.

Differential Diagnosis

A pustular smear and culture should be taken to exclude infectious pustular disorders. A skin biopsy is also needed to differentiate other pustular skin diseases. Spongiform subcorneal and/or intraepidermal pustules and perivascular infiltrate of neutrophils with oedema of the papillary dermis are visible. Bacterial folliculitis, furunculosis, acne, acneiform eruptions, varicella, impetigo, Sweet syndrome and staphylococcal scalded skin syndrome (SSSS) are easy to differentiate from AGEP. On the other hand, psoriasis pustulosa generalisata and Sneddon-Wilkinson syndrome are rather difficult to distinguish. In the former, one history of psoriasis and histological signs of psoriasis can help; in the latter, one larger pustules with hypopyon formation and slower development are characteristics.

Treatment

Acute stage: Once the trigger was identified and discontinued, the disease has a self-healing resolution and symptomatic therapy is sufficient. In those cases with severe and widespread inflammation, a short course of systemic corticosteroids can be useful.

Chronic stage: During the latter allergological investigations patch test is recommended, since it is frequently positive in AGEP. The patch test reaction at 48 h imitates the early phase of the disease with T-cell infiltration; after 96 h pustules can be observed.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

The term DRESS has been suggested in place of hypersensitivity syndrome (HSS) or drug-induced hypersensitivity syndrome (DiHS) which has long been used to describe drug reactions with internal organ involvements. Drug-specific T cells play a role in the pathogenesis of DRESS, but it is also suggested that virus reactivation may be important in the development of the disease. It is not clearly revealed whether reactivation of latent herpes viruses (HHV-6, HHV-7 and EBV) may play a causal role or just can be considered as complications. In Europe, elevated HHV-6 IgG levels are not yet included in the diagnostic criteria of DRESS. After the initiation of the suspected drug symptoms that can start up to 12 weeks, the disease often persists for a long time even after stopping the indicated drug and introducing the correct treatment. Most commonly registered causative drugs in the development of this disease are aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), but there are reports on the triggering effect of minocycline, allopurinol, thalidomide and sulphonamides. Neurologists who often indicate anticonvulsants should be aware of DRESS as it might occur in 1:3,000 treated patients.

Clinical Features

The diagnosis of DRESS can be stated if at least three of the following criteria are fulfilled: skin rash, haematological abnormalities (marked eosinophilia, atypical lymphocytes in the peripheral blood), lymph node enlargement (minimum in two regions), hepatitis (liver transaminases show a more than twofold increase), interstitial nephritis (creatinine levels show more than 1.5-fold increase), interstitial pneumonia and carditis (CK, CK-MB and troponin levels are increased in these cases). In the beginning of the disease, the skin lesions have a morbilliform appearance, and facial oedema is quite common. As the disease progresses erythroderma develops with deeper infiltration, and purpuric lesions and sometimes exfoliative dermatitis occur. In the later stage, marked desquamation is visible. Fever accompanies the skin rash frequently.

Differential Diagnosis

During the development of DRESS, the initial rash has a maculopapular appearance, so MDE has to be excluded. In MDE, mild liver or kidney involvement can also occur, but prominent creatinine and

transaminase elevation and haematological abnormalities, which are characteristic to DRESS, cannot develop. As the skin lesions of DRESS progress, the infiltration become severe and erythroderma evolve. In this phase, lymphoma or pseudolymphoma should be taken into consideration. Acute viral infections should also be excluded in the differential diagnosis. During the diagnostic steps of DRESS, physicians have to keep in mind that skin changes and also histological findings are rather non-specific, the time period of the application of the causative drug is variable and the laboratory alterations can also develop in other diseases. Differential blood count, liver and kidney function tests and also serum CK, CK-MB, troponin and LDH levels should be determined.

Treatment

Acute stage: The first step in the management of DRESS is the immediate cessation of the offending medication. Systemic corticosteroid therapy in a minimum dose of 1.0 mg/kg/day is very effective both in the management of clinical and laboratory alterations. It is usually advised to decrease the systemic corticosteroid dose very slowly over 3–6 months in order to avoid relapse. Topical corticosteroids applied on the skin lesions can cause symptomatic relief. It is better to avoid empiric antibiotics or anti-inflammatory drugs, since they can exacerbate the symptoms. When DRESS is associated with severe exfoliative dermatitis lesions, the patients should be provided supportive care in an intensive care or burn unit. In some severe cases, other immunosuppressive medications should be considered (IVIG, plasmapheresis, cyclophosphamide, cyclosporine). Most patients recover completely, but chronic complications and mortality in about 10 % can occur, primarily from visceral organ failure.

Chronic stage: In order to determine the culprit drug in DRESS, patch test and LTT are used. Results of patch tests vary significantly based on the specific drug and the higher specificity was detected when antiepileptic medications (carbamazepine, phenytoin) were tested. In the case of LTT, positive values are more informative than negative ones.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN, the latter also called as Lyell syndrome, belong to the most severe drug-induced hypersensitivity reactions with a high mortality rate. SJS has a mortality of 13 % and TEN of 39 %. SJS and TEN are considered to be end points of a single disease, differing only by their extent of skin detachment. Acute and disseminated epidermal necrolysis on large skin areas and on the full thickness of the epidermis is the hallmark of this disease group together with a relatively mild inflammatory cell infiltration. SJS and TEN are rare diseases affecting approximately one or two cases per million inhabitants per year. SJS and TEN are specific drug hypersensitivity reactions in which cytotoxic CD8+ T lymphocytes play a crucial role in the drug-specific immune response (type IVc), but the relative paucity of these infiltrating T cells suggests that nondrug-specific amplification mechanisms should accompany the immune reaction and cause the massive apoptosis of keratinocytes. On the basis of extensive research, the co-expression of the membrane form of the death ligand (FasL) and its cognate death receptor (Fas) on keratinocytes and a recently identified secretory granulysin (a cationic cytolytic protein secreted by Tc, NK cells and NKT cells) are key players in the amplification of keratinocyte apoptosis. Most cases occur 2 weeks (range 4–30 days) after the first exposure to the suspected drug. Recently a very strong association of HLA-B1502 with SJS/TEN provoked by carbamazepine and allopurinol was proved in Chinese patients and also to a lesser extent in other populations.

Clinical Features

Typically unspecific initial symptoms characterise TEN and SJS, like throat pain, fever, malaise and stinging eyes. Skin and mucous membrane lesions occur in a few days. Cutaneous manifestations are located first on the face and presternal region of the trunk and soon rapid progression and involvement of large body parts develop as characteristic features. The palms and soles are

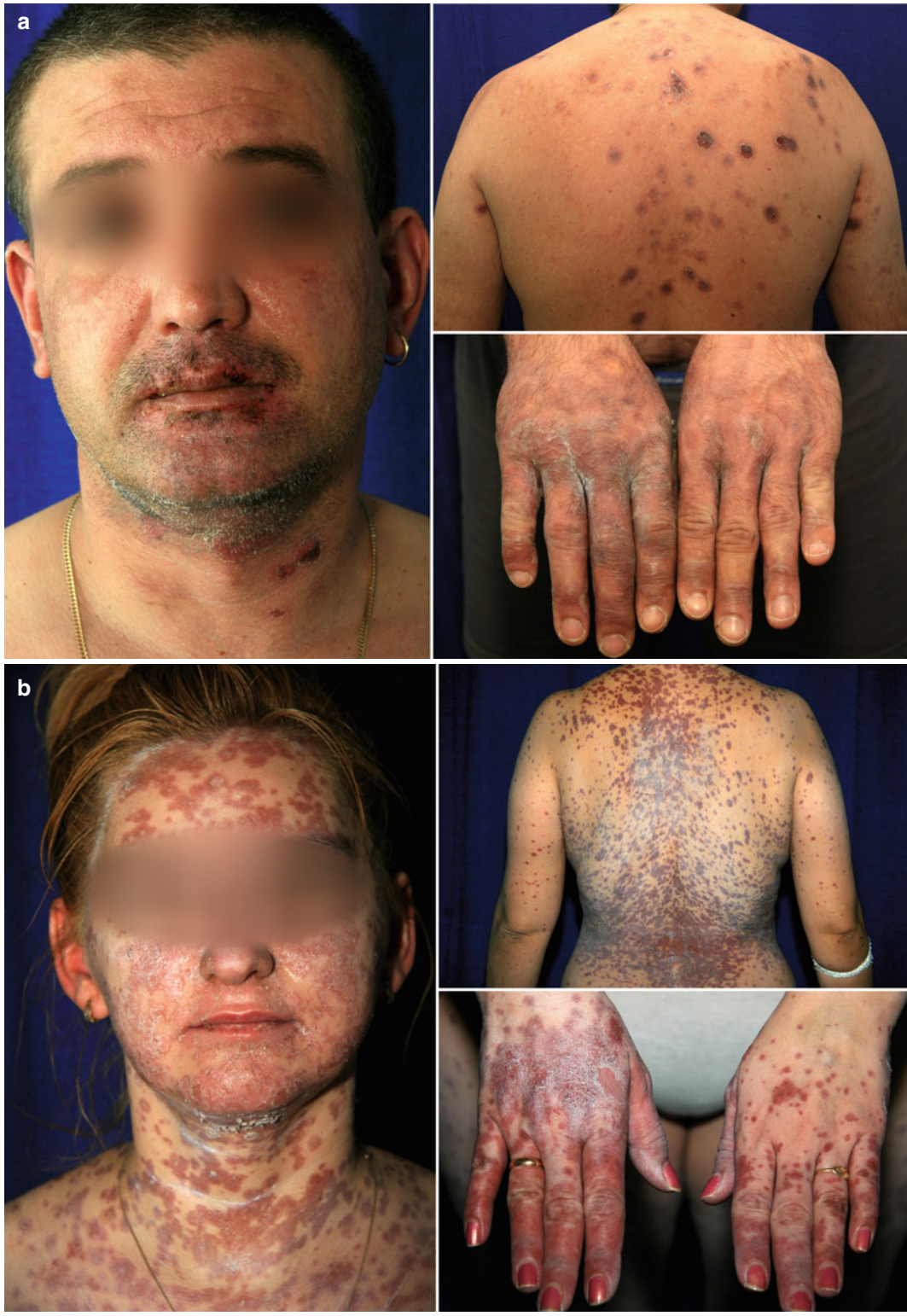

Fig. 22.4 Clinical manifestations of: (**a**) SJS with <10 % extent of skin involvement, (**b**) SJS/TEN overlap with 10 %–30 % extent of skin involvement, (**c**) TEN with >30 % extent of skin involvement

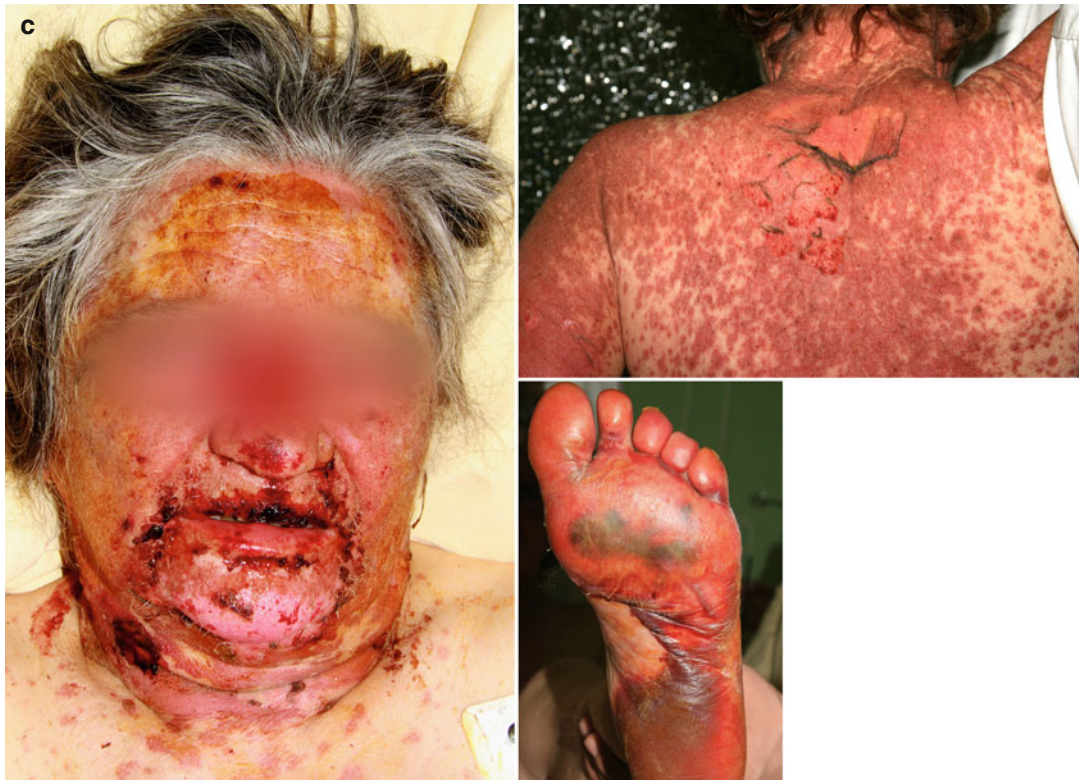

Fig. 22.4 (continued)

often affected. Erythematous macules, patches, flaccid blisters and erosions are visible, and the spots have a grey to violet colour. The Nikolsky sign is positive since tangential mechanical pressure on erythematous zones induces epidermal detachment (detachable skin). These regions together with already detached regions (blisters, erosions) should be included in the evaluation of the extent of skin involvement. According to the degree of epidermal detachment, we can distinguish SJS (<10 %) (see Fig. 22.4a), SJS-TEN overlap (10–30 %) (see Fig. 22.4b) and TEN (>30 %) (see Fig. 22.4c). The mucous membranes are involved in 95 % of patients, most commonly the buccal, genital and ocular mucosa, and in some cases the respiratory and gastrointestinal tracts are also affected. Early oral lesions may resemble aphthae, but pain, rapid progression, skin lesions and fever are important signs of a severe systemic disease. The lesions progress for 1 week as a mean, and then re-epithelialisation starts; sometimes the bullae formation is still progressing on lower parts of the body. The most common acute complications are hypovolaemia, sepsis, shock and multiple organ failure, but destruction of epithelium of the trachea and bronchial tree or other epithelial surfaces can also occur. The most frequent and severe sequelae are the ocular complications. On the skin, hyper- or hypopigmentation will remain, but can fade with years if the patient pays attention to sun protection. Nail dystrophies are also common and may result in persistent nail abnormalities.

Differential Diagnosis

The diagnosis relies on clinical symptoms and on histological analysis. Characteristic clinical signs are erythematous, grey to livid macules on the skin, rapid progression with bulla formation, Nikolsky sign positivity (although it is not specific for TEN/SJS), simultaneous mucosal involvement, pain, anxiety and fever. These severe signs should alert the physician and rapid diagnostic confirmation is needed with the help of

skin biopsy. Histological evaluation of cryosections or formalin-fixed sections demonstrates widespread necrotic epidermis involving all layers. In the differentiation of SJS/TEN from autoimmune bullous diseases, direct immune fluorescent staining is carried out, and neither immunoglobulin nor complement deposition is detected. The main diseases that should be ruled out are linear IgA dermatosis, paraneoplastic pemphigus, pemphigus vulgaris, bullous pemphigoid, AGEP, disseminated fixed bullous drug eruption and SSSS.

Treatment

Acute stage: In the acute stage, severity and prognosis of the disease should be evaluated; the suspected drug(s) should be withdrawn and supportive care and specific therapy should be initiated.

Evaluation of severity: The validated SCORTEN disease severity scoring system is generally used to determine the severity and progression of the disease and to define the further management.

It consists in attributing 1 point to each of the following:

- Age >40
- Detachment larger than 10 % of body surface area
- Recent malignancy
- Tachycardia
- Serum urea >10 mmol/l
- Serum glucose >14 mmol/l
- Bicarbonate >20 mmol/l

Patients with a SCORTEN score of 3 or above should be managed in an intensive care unit because of the high mortality rate. The risk of dying is about 3 % at a score of 0–1, but nearly 60 % when it reaches 4.

Withdrawal of culprit drug(s): To suspend the offending drug is a crucial step, since it has been shown that the earlier the pathogenic medication is withdrawn, the better the prognosis. Two data can help to identify the culprit drug, the chronology of drug use and the registered potential of the drug to cause TEN/SJS. The overwhelming majority of cases occur in patients with normal metabolic pathways, after taking a normal dosage of medication for the first time and the development of TEN/SJS is between 1 and 4 weeks (mean 2 weeks), in case of agents with a long half-life even up to 6 weeks (allopurinol and some antiepileptics). Medications with high risk of inducing TEN/SJS are the following: allopurinol, sulphonamide antibiotics, carbamazepine, phenytoin, phenobarbital, oxicam-type NSAIDs, lamotrigine and nevirapine. Some authors underline the role of aminopenicillins, cephalosporins and quinolones as well.

Supportive care: Since TEN/SJS is potentially a life-threatening disease with extensive skin and mucous membrane lesions accompanied by serious acute complications, patients are advised to be undertaken in specialised intensive care units or in burn units and the best management is to place the patient on air-fluidised bed or on Metaline sheet. The basic element of symptomatic therapy is the fluid and electrolyte supplementation. Patients with TEN/SJS usually require less fluid replacement than burn patients, about two-thirds to three-quarters as much. For the purpose of volume substitution, electrolyte solutions rather than colloidal infusion are preferred in the moderately severe cases; in severe hypotension, the colloidal and electrolyte solutions should be used simultaneously. Purely prophylactic antibiotic usage can increase the risk of another hypersensitivity reaction and is not advised, but in case of definite infection or sepsis, targeted antibiotics must be initiated. To treat the wounds, it is usually advised to leave the necrotic epidermis in place, without skin debridement, to promote re-epithelialisation. Antiseptic solutions and nonadhesive wound dressings are used, but sulphonamide-based medications should be avoided. Antiseptic solutions and creams or dexpanthenol-based ointments are recommended for oral mucosa or lip lesions and also to treat genital erosions. Aggressive nutritional support should be initiated promptly to minimise protein loss and it is important to pay attention on warming of the environmental temperature. Mechanical ventilation is necessary in case of hypoxaemia and correction of any organ failure if needed.

Specific Therapy

Systemic corticosteroids: There have been a lot of doubts on the use of systemic steroids considering the risks and benefits, but a recent retrospective monocentre study found that a short course pulse of high-dose corticosteroids (dexamethasone) can exert good effect (Kardaun et al. 2007). One year

later another large retrospective multicentre study also found positive effect on the outcome of the severe skin reaction if corticosteroids were given briefly at the beginning of the reaction in moderate–high doses (100–500 mg). In this study compared to supportive treatment alone, the death rate was importantly, but not significantly, reduced in those who received corticosteroids too.

High-dose intravenous immunoglobulins (IVIG): The main mode of action that is supposed in the background of IVIG usage in TEN/SJS is the presence of antibodies with anti-Fas potential that can block Fas-mediated keratinocyte necrosis. Numerous case reports and noncontrolled clinical trials studied the effect of IVIG in TEN/SJS and the results are contradictory. Nearly all studies confirmed the excellent tolerability and low toxic potential of IVIG when used with precaution in patients with potential risk factors, but the efficiency is not clearly proven yet, so definite conclusion cannot be drawn. In spite of this, many practising physicians, based on clinical and laboratory evidences and also on the favourable effects of IVIG on infections and on fluid balance, prefer its use.

Thalidomide: In a double-blind, randomised, placebo-controlled study, thalidomide, an effective TNF-α blocker, was shown to have harmful effects when used in the therapy of TEN. In the thalidomide-treated group, higher mortality was observed and therefore this drug must be avoided for this indication.

TNF-α antagonists: So far only case reports have been published in the literature about the effect of TNF blockers, so data are insufficient to draw a conclusion.

Plasmapheresis: Current data are not enough to support the use of plasmapheresis in the therapy of TEN/SJS, due to the small number of treated patients and the variable treatment regimes.

Cyclophosphamide: Larger studies are needed to gain clear-cut data on the efficiency and also on the potential side effects of this agent in TEN/ SJS.

Chronic stage: In this stage, treatment of sequelae and allergological testing are recommended. The treatment of sequelae is an interdisciplinary task, and since ocular complications can become serious, referral to an ophthalmologist is important. In a lot of cases, several medications are candidates to be the causative drug and after recovery allergological testing is needed to identify the most likely candidate. Patch testing is an option, but because of the low sensitivity, only positive test is relevant, while negative result cannot rule out a sensitisation. The sensitivity of LTT test is also very low in SJS/TEN. Intradermal testing and provocation are not recommended because of the risk of another hypersensitivity reaction.

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Drug Photosensitivity

23

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Key Points

- Clinical manifestations of drug photosensitivity are polymorphic.
- Acute exaggerated sunburn and eczema of photoexposed sites are the main presentations of systemic photosensitivity.
- Pseudoporphyria, photoonycholysis, dyschromia and subacute lupus erythematosus are forms of subacute drug photosensitivity.
- It is not always easy to distinguish phototoxicity from photoallergy and both mechanisms can be involved in the final reaction.
- Main topical drugs causing photosensitivity are the NSAIDs, particularly ketoprofen.
- Photopatch testing, indicated mainly for the study of photoallergic contact dermatitis, can also be useful in systemic drug photosensitivity.

Definition and Epidemiology

Drug photosensitivity is an abnormal skin reaction to light, usually ultraviolet (UV) light, in individuals exposed to a drug, who, tolerate the same amount of light exposure in the abscence of the culprit drug.

Drug photosensitivity can present under a wide spectrum of acute or delayed clinical patterns, which are important to recognize and distinguish from idiopathic photodermatoses, in order to remove the offending drug or take the adequate measures to reduce this adverse effect.

Some drug phototoxic reactions presenting as acute sunburn or acute photoallergic eczema on sun-exposed areas are well recognized, but other reactions are often misdiagnosed, as the relation between drug and sun exposure may not be so obvious. The involvement of drug is certainly underestimated in drug-induced lupus erythematosus (LE) or in actinic keratosis and nonmelanoma skin cancer (NMSC) in patients exposed to photoactive drugs (Placzek et al. 1999).

More than 300 drugs from different pharmacological groups can cause photosensitivity, namely systemic or topical drugs and, occasionally, drugs manipulated in an occupational setting.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_23,

Many photosensitizers have been recognized and removed from the market (benoxaprofen, chlorproéthazine); premarketing studies regularly performed prevent the release of potential photosensitizing drugs; and when photosensitizers are used (lomefloxacin, vemurafenib), sun avoidance/protection is recommended (Gelot et al. 2013). Nevertheless, with the constant development of new photosensitizers, namely, for therapeutic purposes (photodynamic therapy), the introduction of new drugs with distinct mechanisms of action, namely, new targeted therapies, and more severe patients with concomitant diseases (immunosuppression), it is difficult to avoid this adverse drug effect.

Photosensitivity is still a field of intense research, with new mechanisms of drug photosensitivity and new aspects of their clinical presentation being recognized, which may also be important to understand diseases that course with photosensitivity, like HIV infection. Moreover, different pathomechanisms underlying drug photosensitivity may explain their clinical expressions and orient the choice of the most adequate diagnostic tests and therapeutic and preventive measures.

Basic Concept of Pathogenesis

Classically, drug photosensitivity is divided into phototoxicity (the more frequent) and photoallergy, but there are many overlapping situations and other immune-mediated or nonimmune-mediated mechanisms can also be involved. Most reactions occur within the UVA wavelength, although some can extend to visible light or, also, to UVB.

Immune-mediated reactions are mostly T-cell-dependent reactions, responsible for photoallergic contact dermatitis and systemic photoallergy. Drug-induced or drug-enhanced autoimmunity with photosensitivity involves autoantibodies and an inflammatory response with involvement of T cells.

Drug phototoxicity, on the other hand, does not involve specific immune hypersensitivity reactions. Frequently, acute reactions can be associated with enhanced photoimmunosuppression, photocarcinogenesis and photoaging, responsible for late reactions (premature skin aging, lentigines, actinic keratosis, NMSC and, even, melanoma) (Gonçalo 2012).

Solar Light and UVR in Drug Photosensitivity

Artificial light can be involved in drug photosensitivity (UV lamps used for aesthetic or therapeutic purposes or UV sources in occupational settings), but natural sun exposure is usually the cause. From the solar spectrum that reaches the earth, UV radiation, particularly UVA (320–400 nm), is responsible for most cases of photosensitivity. Some chromophores absorb in the UVB (290–320 nm) and UVB is more energetic, but UVA penetrates the skin more deeply and, particularly for systemic drugs, this is certainly the most important part of the solar spectrum involved in drug photosensitivity. Only exceptional cases of exclusively UVB-induced drug photosensitivity have been documented (Fujimoto et al. 2009).

Mechanisms of Acute Drug Phototoxicity

Photosensitivity develops when an abnormal chromophore is present in the skin, when a normal chromophore is present in exaggerated amounts or when there is failure of normal defensive mechanisms. The drug or a drug metabolite may be the exogenous chromophore that is excited in the skin or the drug may increase the quantity of endogenous chromophores in the skin, and these are, finally, responsible for the inflammatory reaction.

When a chromophore in the skin receives the energy of a UV photon, the electrons in the outer orbits increase their energy, and the molecules enter a short-lived excited state, singlet state, or can undergo more long-lived modifications into biologically more active molecules, triplet state. Excited molecules react with

neighbouring molecules in a photodynamic reaction, involving oxygen (type I) or other molecules (type II), and, ultimately, induce changes in bioactive molecules (unsaturated lipids of cell membranes, aromatic amino acids of proteins and pyrimidine bases of DNA or RNA). Eventually, free radicals or reactive oxygen species (ROS) are formed and expand the reaction in a cascade of events that progress in the absence of effective repair mechanisms (antioxidative defence mechanisms). This will result in damage of cellular organelles (mitochondria, lysosomes and cell membranes), cell aggression or cytotoxicity (apoptosis) of keratinocytes, melanocytes, dendritic cells in the epidermis and, eventually, other cells in the dermis. Injured cells liberate inflammatory mediators (prostaglandins, leukotrienes, IL-1, IL-6, TNF-alfa, IL-8/CXCL8, other cytokines and chemokines), and inflammatory cells are recruited causing visible skin lesions.

Other Mechanisms of Drug Phototoxicity

In rare cases, the drug increases the concentration of endogenous photosensitizers. Elevated erythrocyte porphyrins, namely, zinc protoporphyrin, seem responsible for acute photosensitivity from vemurafenib. Actually, transient skin burning shortly after sun exposure followed by erythema and oedema clearly limited by protective clothing, lasting a few days, simulates the genetic erythropoietic porphyria. Other kinase inhibitors that interfere with porphyrin metabolism, namely, vandetanib and, less often, imatinib and sorafenib, also cause acute photosensitivity.

Protoporphyrins, elevated during treatment with docetaxel, may also be responsible for photosensitivity.

Other porphyrins, namely, uroporphyrins, were increased in a case of photosensitivity from voriconazole associated with porphyria cutanea tarda, although voriconazole induces mostly pseudoporphyria with normal porphyrin levels.

Increased endogenous retinoids were explored as a possible cause of voriconazole photosensitivity, but this was not proved, although exogenous retinoids increase photosensitivity from this antifungal.

A decrease in defensive mechanisms, with reduced vitamin PP (niacinamide), may also contribute to vemurafenib photosensitivity.

Drug Photoallergy

In photoallergy, the energy of the photon transforms the drug into a stable photoproduct or enhances its combination with an endogenous peptide, forming a hapten or an antigen. Dendritic cells will uptake this antigen and combine it with HLA molecules, and in an adequate environment in skin-draining lymph nodes (cytokines/chemokines and HLA and co-stimulatory molecules), they stimulate and, eventually, sensitize naïve T cells. As in allergic contact dermatitis, drug-specific T cells will be mostly responsible for the effector response.

Mechanisms to explain how drugs enhance cutaneous LE, particularly the subacute variant, are not completely understood. Drugs may enhance UV-induced expression of the Ro/SSA antigen on the surface of keratinocytes and may interfere with apoptosis or cytokine production, promoting photosensitivity and the development of skin lesions in susceptible individuals.

Drug-Induced/Drug-Enhanced Photocarcinogenesis

Apart from the capacity to generate free radicals and cell death responsible for acute phototoxicity, several phototoxic substances, like psoralens, chlorpromazine, fluoroquinolones and ketoprofen, also enhance chromosomal damage in the presence of UVR, as shown both in *in vitro* and *in vivo* studies (Ray et al. 2013). These drugs are, therefore, photogenotoxic, photomutagenic and, consequently, photocarcinogenic. Moreover, this type of DNA aggression is also usually associated with photoimmunosuppression which further enhances photocarcinogenesis.

Epidemiological studies, reported since 1999, called the attention to the association between actinic keratosis and the exposure to potentially photosensitizing drugs (Placzek et al.1999), and

recent reports reinforce this association, namely, for diuretics and cardiovascular drugs, even if patients do not develop acute signs of photosensitivity (Jensen et al. 2008; Traianou et al. 2012). Nonmelanoma skin cancer (NMSC) and melanoma are also increased in humans chronically exposed to photoactive drugs, namely, psoralens, voriconazole and vemurafenib (Miller et al. 2010; Rinderknecht et al. 2013; Stern et al. 2012).

DNA damage in the presence of UVR and drugs may not be the only mechanism of voriconazole- or vemurafenib-enhanced photocarcinogenesis. Activation of alternative oncogenic intracellular pathways due to BRAF inhibition in vemurafenib and previous immunosuppression in voriconazole-treated patients may also contribute to enhancing carcinogenesis.

Drug Photosensitivity: Phototoxicity Versus Photoallergy

Although mechanisms involving T-cell-mediated photoallergy and nonspecific acute phototoxicity are well individualized, their participation in each case of drug photosensitivity is often more complex. Except for a few drugs, as piroxicam, which do not have an intrinsic phototoxic potential and induce only photoallergy, most substances can induce both photoallergic and phototoxic reactions.

In theory, in the clinical setting, it is easy to differentiate photoallergy from phototoxicity, but there are many overlapping aspects.

Classically, photoallergy develops only in a limited number in individuals and needs previous sensitization but occurs also with cross-reactive chemicals. It is not dose dependent, develops on low UV dose and appears as eczema that can spread to non-exposed sites, and on skin biopsy, there are mainly T-cell infiltration, spongiosis and vesicles. Phototoxicity is more frequent, develops in every individual and, as long as enough photosensitizer and sun exposure are simultaneously present, it occurs on a first contact with no particular aggravation on further contacts. It is not associated with cross-reactions, presents mainly as well-demarcated erythema, exclusively on sun-exposed areas (mimicking sunburn), resolves with hyperpigmentation and apoptotic keratinocytes (sunburn cells) are abundant on histology (Table 23.1).

These are the two polar aspects of photosensitivity, but many molecules may induce both phototoxic and photoallergic reactions, and, in the same patient, aspects that resemble phototoxicity may coexist with others that suggest photoallergy.

The highly phototoxic furocoumarins, contained in plant extracts ingested or used topically in "folk medicine" or during photochemotherapy, can induce photoallergy in some individuals

Table 23.1 Distinction between phototoxicity and photoallergy

	Phototoxicity	Photoallergy
Frequency	High	Low
Latency period/sensitization	No	Yes
Doses of UV/photosensitizer	High	Low
Cross-reactions	No	Yes
Morphology of lesions	Sunburn, polymorphic	Eczema, erythema multiforme
Sharp limits	Yes	No
Covered areas	Not involved	Possibly involved
Resolution	Quick[a]	May recur, persistent reactors
Residual hyperpigmentation	Yes	No
Histology	Sunburn cells	Eczema
Pathomechanism	DNA/cell damage	Type IV hypersensitivity
	ROS/inflammation	Photoproduct

[a]This relates only to the acute phototoxic reaction, but late effects as photoaging and photocarcinogenesis may also occur

(skin lesions developing at very low concentrations of psoralens and UV light). Also, phototoxic drugs like promethazine and lomefloxacin can induce photoallergy.

Very probably, photoallergens, as photoactive molecules, may also have some inherent phototoxic potential, like contact allergens that have some "irritant" capacity. In allergic contact dermatitis, most contact allergens induce "danger signals" that are recognized by innate receptors in skin cells and awaken the adaptive immune system, promoting sensitization. An innate inflammatory reaction generated in skin, in the presence of photoactive molecules and UVR, can also act as the "danger signal" necessary to initiate the sensitizing process.

Although phototoxicity can occur on a first contact and photoallergy needs previous sensitization, individuals previously sensitized to a structurally similar molecule can develop the reaction on a first exposure. This occurs in individuals with contact allergy to thiomersal and its moiety, thiosalicylic acid, who develop photoallergy to piroxicam on the first drug intake. Upon UVA irradiation, piroxicam is photodecomposed into a molecule antigenically and structurally similar to thiosalicylic acid that is responsible for the photoallergic reaction (Serra et al. 2008).

Also, patients with contact allergy to perfumes (cinnamic alcohol), octocrylene or benzophenones may have photoallergic contact dermatitis from ketoprofen on a first exposure or vice versa, as there are conformational similarities between these molecules.

Phototoxicity is considered to occur in every patient, as long as enough chromophore and sun are present at the same time, but even in drug phototoxicity, there are particularly susceptible individuals, even though mechanisms underlying this susceptibility have not been characterized.

Clinical Presentation

The clinical patterns of systemic drug photosensitivity vary from urticaria through eczema or subacute LE up to vitiligo-like lesions or NMSC. They can be very typical as in acute exaggerated sunburn, but sometimes, the diagnosis or even the suspicion of drug photosensitivity is not so obvious (Table 23.2).

Skin reactions can occur immediately after sun exposure in vemurafenib-induced photosensitivity, but skin lesions may be delayed 1 or 2 days in most phototoxic or photoallergic contact dermatitis or systemic photoallergy, several days or weeks in pseudoporphyria or subacute LE or even years in skin cancers associated with a long exposure to the sun and the photoactive drugs.

In systemic drug photosensitivity, the reaction usually involves, in a symmetric distribution, the face and forehead, the V-shaped area of the neck and upper chest, dorsum of the hands and forearms. Shaded areas in the face (upper eyelids, upper lip, deep wrinkles) are usually spared (Fig. 23.1) as well as retroauricular areas, submandibular areas (Fig. 23.2) and areas covered by the beard or scalp hair. In more extensive sun exposure, large body folds, like the axillae, groins, finger webs and areas covered by clothing or other accessories (watch strip, shoes) are also usually spared. Involvement of the shaded areas suggests an airborne dermatitis, which may occur in occupational exposure to photoactive drugs, in nurses and caregivers who crash tablets or during drug manufacture.

A different pattern in the distribution of skin lesions can occur when sun exposure is asymmetric, as in car drivers who only expose the left

Table 23.2 Clinical patterns of photosensitivity

Predominant in phototoxicity	Predominant in photoallergy
Exaggerated "sunburn"	Urticaria in sun-exposed area
Pseudoporphyria	Acute or subacute eczema
Photoonycholysis	Cheilitis
Hyperpigmentation	Erythema multiforme-like
Hypopigmentation (vitiligo-like lesions)	Lichenoid reactions
Telangiectasia	Subacute or chronic lupus erythematosus
Purpura	
Pellagra-like reactions	
Actinic keratosis and squamous cell carcinoma	

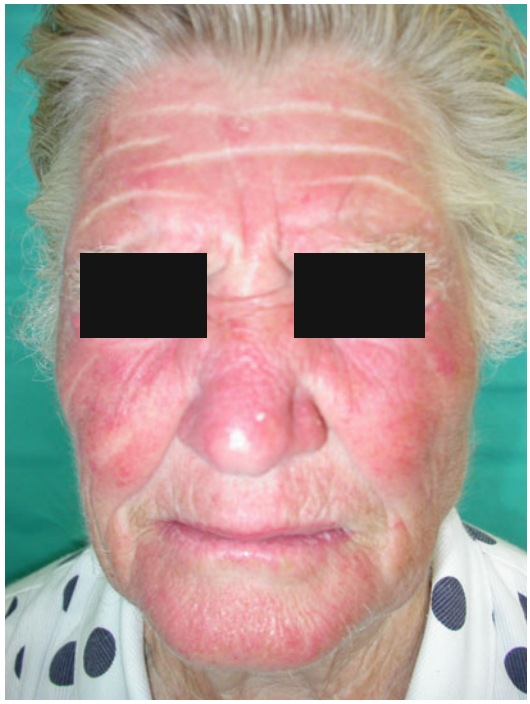

Fig. 23.1 Acute phototoxicity from amiodarone that mimics sunburn and spares the deep facial wrinkles

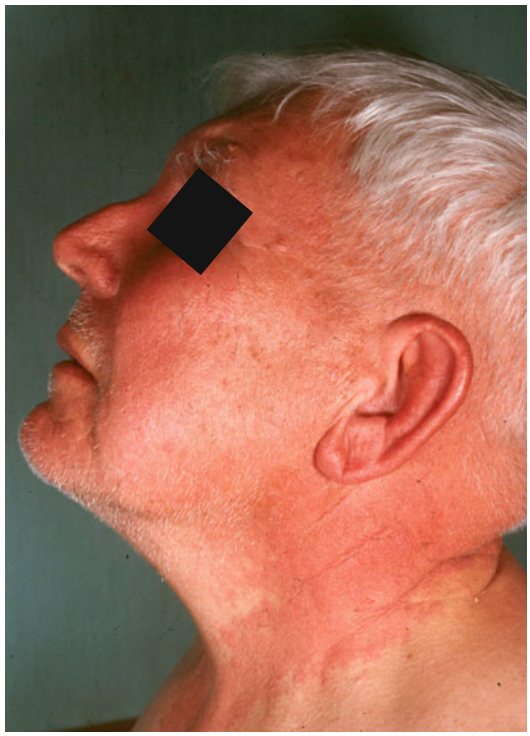

Fig. 23.2 Photosensitivity from systemic piroxicam, sparing the shaded submandibular area

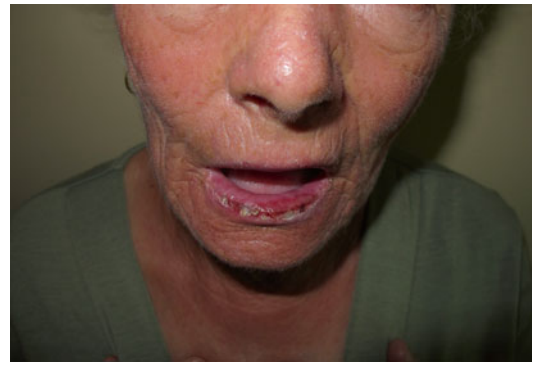

Fig. 23.3 Photosensitivity from voriconazole with severe cheilitis and lip erosions

arm. Sometimes, in systemic photosensitivity, the lower lip is mainly or almost exclusively involved (Fig. 23.3), because of its higher exposure and, very probably, because the corneal layer is thinner and, therefore, more prone to photosensitivity.

In photoallergic or phototoxic contact dermatitis from topical drugs, lesions are coincident with the area of drug application and concomitant sun exposure, but distant lesions can occur in areas of accidental contact, as in a contralateral limb (kissing faces of the legs), or in areas of inadvertent spread by the hands or contaminated objects. Cases of connubial dermatitis have been described, mainly for ketoprofen and benzydamine (Devleeschouwer et al. 2008. When used in the mouth these NSAIDs induce mostly lip and chin dermatitis (Conti et al. 2012). Some topical drugs can be considerably absorbed through the skin, and lesional distribution can be similar to systemic photosensitivity.

Acute Patterns of Drug Photosensitivity

Immediate Reactions

Immediate urticarial reactions, like photocontact urticaria, have been described with chlorpromazine (Lovell et al. 1986) and with 5-aminolevulinic acid used in photodynamic therapy (Kerr et al. 2007).

Some phototoxic drugs, like amiodarone and benoxaprofen (already removed from the market), induce immediate prickling and burning with transient erythema.

Immediate burning upon sun exposure followed by well-limited painful oedema and erythema during a few days, mimicking erythropoietic porphyria, is being described in more than 50 % of patients under vemurafenib treatment for metastatic melanoma (Rinderknecht et al. 2013). Photosensitivity can be highly limitative but can be prevented by sun avoidance or sun protection, extending to the long UVA.

Acute Photosensitive Dermatitis

Exaggerated sunburn that develops within 12–24 h of sun exposure is the main presentation of drug phototoxicity (Fig. 23.1). Non-pruritic erythema with sharp limits can be associated with vesicles and bullae and progress to desquamation in large epidermal sheets within the next days and, thereafter, to residual hyperpigmentation.

In acute drug photoallergy, confluent or non-confluent eczematous lesions or erythema multiforme-like lesions on photoexposed sites (Fig. 23.2), with frequent extension to covered areas, are mostly observed. In the case of photoallergy to piroxicam, pompholyx is often associated with non-confluent papular or vesicular facial lesions (Serra et al. 2008).

Subacute Patterns of Drug Photosensitivity

Photosensitivity may develop within days or weeks after exposure to the drug and the sun. Some clinical patterns evoke mainly a phototoxic reaction, like pseudoporphyria, photoonycholysis, hyper- or hypopigmentation, telangiectasia and purpura, whereas annular lesions may suggest a drug-induced cutaneous subacute LE.

Pseudoporphyria

Drug-induced pseudoporphyria resembles porphyria cutanea tarda or pseudoporphyria associated with haemodialysis, both clinically and on histopathology (bullae formation below the lamina densa). It develops within weeks to months as chronic skin fragility with flaccid bullae on non-inflamed exposed skin, occasionally progressing to milia. Pseudoporphyria occurs in individuals with no inborn error in porphyrin metabolism and no increase of endogenous porphyrins, although some drugs like voriconazole may transiently increase uroporphyrin levels.

Pseudoporphyria was initially described with nalidixic acid, furosemide and naproxen, predominantly in children (Ferguson 1999), but more recently, many other drugs have been associated with this phototoxic reaction: celecoxib (Cummins et al. 2000), ciprofloxacin (Schmutz et al. 2008), voriconazole, torasemide (Pérez-Bustillo et al. 2008), metformin (Lenfestey et al. 2012), finasteride (Santo Domingo et al. 2011) and imatinib (Timmer-de Mik et al. 2009). Pseudoporphyria represents a typical phototoxic reaction where the drug, as the uroporphyrin in the hereditary disease, probably induces phototoxicity through the production of singlet oxygen.

Photoonycholysis

Photoonycholysis is a typical pattern of phototoxicity. It presents as a half-moon distal onycholysis of one or several nails, most often as the single manifestation of phototoxicity (Fig. 23.4). It appears late (2–3 weeks after drug intake and sun exposure) and is sometimes preceded by pain in the nail apparatus. It occurs mainly with tetracyclines (demethylchlortetracycline or doxycycline), psoralens and fluoroquinolones (Baran and Juhlin 2002).

There is no definite explanation for the single involvement of the nail: the nail bed, relatively unprotected from sunlight with less melanin, and the nail plate, working as a lens to concentrate the

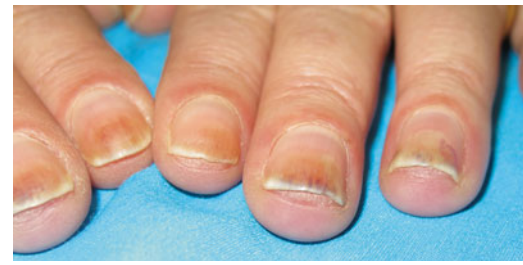

Fig. 23.4 Photoonycholysis from doxycycline

UVR, may enhance the inflammation and induce detachment of the nail plate from the nail bed.

Drug-Induced Cutaneous Lupus Erythematosus

In a recent multicentre database analysis of the European Society of Cutaneous Lupus Erythematosus, drug-induced cutaneous LE was shown to represent 6 % among 1,002 patients with cutaneous lesions and 13.2 % of those with the subacute variant of cutaneous LE (Biazar et al. 2013). This form of drug-induced subacute cutaneous LE is usually associated with photosensitivity and mild systemic manifestations of LE. More than 80 % of patients have anti-Ro/SSA autoantibodies, the hallmark of photosensitivity in LE.

Cutaneous lesions usually develop weeks or months after drug exposure (medium of 6 weeks) and can resolve on drug suspension, without scarring. They are annular or papulosquamous lesions, clinically and on histopathology similar to the idiopathic form of cutaneous subacute LE. Lesions are localized in photoexposed areas (face, neck, upper chest and arms) but also in usually UV-shaded areas. Erythema multiforme-like lesions or, seldom, chronic cutaneous LE with more infiltrated plaques on the face or V of the neck can also be related with drugs.

Subacute cutaneous LE was described initially in association with thiazide diuretics, calcium channel blockers, ACE inhibitors and more recently terbinafine, the drug associated with the highest odds ratio for this adverse event, and a long list of other drugs, namely, proton pump inhibitors, antiepileptics, TNF-alfa antagonists and anticancer taxanes, paclitaxel and docetaxel (Grönhagen et al. 2012; Lamond et al. 2013).

Dyschromia

Hyperpigmentation usually follows acute phototoxicity due to the residual melanocytic hyperpigmentation. In rare occasions, like in flutamide-induced photosensitivity, vitiliginous lesions with sharp limits occur after the acute reaction (Gonçalo et al. 1999). Dyschromia with solar lentigines and other signs of photoaging have been recently described with voriconazole and vandetanib (Malani and Aronoff 2008).

Dyschromia from the accumulation of the photoactive drug or its metabolites in the dermis occurs in a smaller percentage of patients after acute phototoxicity from amiodarone, minocycline or phenothiazines. Some patients with lower phototypes also develop a golden-brown, slate grey or bluish colour on sun-exposed areas that persists longer after stopping the drug than residual melanocytic hyperpigmentation.

Other Clinical Patterns of Subacute Photosensitivity

Telangiectasia as a manifestation of photosensitivity has been reported with calcium channel blockers. A telangiectatic pattern of photoaging with lesions mainly in the lateral folds of the neck, sparing the shaded skin under the chin, is frequently observed in patients chronically exposed to the sun and photoactive drugs. In rare cases, petechial purpura with sharp limits on the transition to the shaded areas was described with ciprofloxacin (Urbina et al. 2006).

Pellagra is associated with the prolonged use of isoniazid that needs niacin for its metabolism, and pellagroid reactions were reported with the anticancer agents, like 6-mercaptopurin and 5-fluoruracil.

Delayed and Late Effects of Photosensitivity

Patients that are chronically exposed to photoactive drugs can also develop accelerated photoaging, actinic keratosis and skin cancers, which, at least partially, can be explained by the photogenotoxic effect of some drugs.

Accelerated skin photoaging occurs with voriconazole, including in children, and presents as dyschromia, lentigines and actinic keratosis.

There is a consensual agreement on the dose-dependent increased risk of skin cancers after long-time therapeutic exposure to PUVA phototherapy. Apart from psoralens, drugs like naproxen, chlorpromazine and the fluoroquinolones, particularly lomefloxacin, augment DNA aggression induced in vitro by UV and increase epidermal neoplasia in animals

(Klecak et al. 1997). Also, in humans, potentially photosensitizing drugs, like diuretics and cardiovascular drugs, are being associated with increased cutaneous precancerous lesions, and recent reports correlate human short-term exposure (weeks/months) to voriconazole and vemurafenib with an increased risk of developing actinic keratoses, keratoacanthoma-like NMSC and, even, malignant melanoma.

Main Topical and Systemic Drugs Causing Photosensitivity

There is a large and increasing list of drugs inducing photosensitivity (Table 23.3), either when used topically or upon systemic exposure. Drugs, like piroxicam, induce photosensitivity both by topical and systemic exposure, whereas other drugs, like ketoprofen, frequently induce photoallergic contact dermatitis, whereas upon systemic exposure the cutaneous concentration is usually too low to induce photosensitivity.

Drugs manipulated in an occupational setting can induce photosensitivity: carprofen, an NSAID for animal use, induced photoallergic contact dermatitis in workers manufacturing the drug (Kiely and Murphy 2010), and photosensitivity has been reported in nurses and family members who smashed the tablets of chlorpromazine to give to their patients/relatives.

Topical drugs are, by far, responsible for most positive photopatch tests in studies from the south of Europe and in the recent European multicentre photopatch test study (The European Multicentre Study PhotopatchTest (EMCPPTS) Taskforce 2012). Main topical drugs that cause contact photosensitivity are the NSAIDs, namely, ketoprofen and other arylpropionic acid derivatives, etofenamate, benzydamine and phenothiazine derivatives used as antihistamines or muscle relaxants.

The main systemic drugs inducing photosensitivity are antimicrobials, particularly tetracyclines, fluoroquinolones, sulphonamides and antifungals, NSAIDs, phenothiazines and cardiovascular drugs.

Table 23.3 Main drugs causing exogenous photosensitivity

1. Antimicrobials
Tetracyclines[a] (doxycycline, minocycline)
Sulphonamides (sulfamethoxazole)
Fluoroquinolones (lomefloxacin,[a] ciprofloxacin[a])
Voriconazole,[a,b] griseofulvin[a]
Efavirenz, tenofovir
Faldaprevir
2. Nonsteroidal anti-inflammatory drugs (NSAIDs)
Arylpropionic acids:
Ketoprofen[c,d], tiaprofenic acid,[a] suprofen
Naproxen, ibuprofen, ibuproxam, carprofen[d]
Piroxicam[c,d], etofenamate[c,d]
Benzydamine[d]
Celecoxib, diclofenac[d]
Azapropazone, phenylbutazone, indomethacin
3. Phenothiazines
Chlorpromazine,[d] thioridazine
Promethazine,[c,d] isothipendyl chlorhydrate[d]
Chlorproethazine[c,d]
4. Targeted therapies
Vemurafenib[b]
Imatinib, vandetanib
5. Antidepressants
Clomipramine, imipramine, sertraline
6. Cardiovascular drugs
Amiodarone,[a] quinidine
Furosemide, torasemide and thiazide diuretics
7. Anticancer agents
Paclitaxel, docetaxel
Methotrexate, 5-fluoruracil
Dacarbazine
8. Miscellaneous
Psoralens[b]
Fenofibrate, simvastatin
Sulfonylureas, sitagliptin, metformin
Flutamide, finasteride
Pirfenidone
Porphyrin analogues for photodynamic therapy
Retinoids (isotretinoin)
9. Plants (used as drugs)[a]
Hypericum perforatum (St. John's wort)
Ruta graveolens (common rue)[d]
Kava extracts

[a]Mainly phototoxic
[b]An increase of actinic keratosis, NMSC and, occasionally, melanoma have been related with these drugs
[c]Mainly photoallergic
[d]Often also from topical exposure or airborne exposure, mainly in occupational settings

Antimicrobials

Tetracyclines

Systemic tetracyclines, particularly doxycycline and minocycline, are highly phototoxic, induce photoonycholysis and pseudoporphyria and, the latter, can also induce a bluish persistent pigmentation (Vassileva et al. 1998). A case of photoallergic reaction with positive photopatch tests was, nevertheless, described with doxycycline.

Quinolones

The fluoroquinolones induce phototoxic reactions, in some cases presenting as pseudoporphyria, as initially described for the first quinolone antibiotic, nalidixic acid. Ciprofloxacin was also responsible for purpura in photoexposed areas. Phototoxicity is particularly important and frequent (4–15 % of treated patients) with fleroxacin, lomefloxacin, sparfloxacin and pefloxacin and less frequent with ciprofloxacin, norfloxacin, ofloxacin and enoxacin (Ferguson 1999). The recommendation to take the drug by the end of the day, therefore reducing drug concentrations in the circulation and in the skin during midday, can reduce this phototoxic reaction.

Although in vitro and in vitro tests prove the high phototoxic potential of fluoroquinolones, photoallergy has also been reported with lomefloxacin and enoxacin. Reactivity in photopatch tests and in photoprovocation tests with very low UVA doses, cross-reactions with other fluoroquinolones (ciprofloxacin and flerofloxacin), positive lymphocyte stimulation tests and identification of drug-specific Th1 cells that recognize skin cells combined with UV-irradiated fluoroquinolone document photosensitivity is immune-mediated (Tokura et al. 2001).

Fluoroquinolones also photosensitize DNA and are, therefore, photomutagenic and photocarcinogenic. A young male patient from our hospital on long-term ciprofloxacin therapy for multiresistant tuberculosis developed chronic photosensitivity and highly aggressive recurring and metastatic squamous cell carcinomas of the face (personal experience).

Sulphonamide and Derivatives

Sulphonamide antibacterials, as well as sulpha drug analogues (thiazidic diuretics, hypoglycaemic sulfonylureas and celecoxib) and dapsone (diaminodiphenylsulfone), have been reported to cause photosensitivity within the spectrum both of UVB and UVA. This side effect is not so frequent with cotrimoxazole (Vassileva et al. 1998).

Antifungals

Griseofulvin is a known phototoxic drug and can aggravate lupus erythematosus, as the more recent antifungal, terbinafine, which induces subacute lupus erythematosus in patients with anti-Ro/SSA antibodies.

Voriconazole, used mainly in patients with invasive aspergillosis or refractory candidiasis, therefore with immunosuppression from an underlying disease or from immunosuppressive drugs, is associated with severe photosensitivity, an adverse effect that is not extensive to other azole antifungals. Photosensitivity develops in susceptible patients, including children. Apparently it does not depend on the highly variable individual pharmacokinetic profile of the drug and its main metabolite (n-oxide voriconazole), on the drug-metabolizing capacity or on increased levels of endogenous porphyrins or retinoids. Cutaneous reaction is dependent on the broad UVA, extends to the visible solar spectrum, develops within 1–16 weeks of treatment and manifests as a burning sensation soon after sun exposure, with a sunburn-like reaction, cheilitis and erosions of the lower lip (Fig. 23.3), or as pseudoporphyria (Riahi and Cohen 2011). On relative short exposures, photoaging with solar lentigines and actinic keratosis develops, and these soon progress to multifocal invasive squamous cell carcinoma (Morice et al. 2010). Malignant melanoma has also been described in these patients.

Antiviral Drugs

Photosensitivity from antiviral drugs used in the treatment of HIV or HCV infection has been reported. Efavirenz induced mostly photodistributed papulosquamous annular lesions within a few

days or weeks of treatment. The combination of faldaprevir and deleobuvir caused photosensitivity in more than a quarter of patients involved in controlled clinical trials (Zeuzem et al. 2013).

Nonsteroidal Anti-inflammatory Drugs

Benoxaprofen, marketed between 1980 and 1982, called the attention to photosensitivity from this class of drugs, and this adverse event was reported with other arylpropionic derivatives (carprofen, naproxen, suprofen, tiaprofenic acid, ketoprofen and ibuprofen) and NSAIDs from other groups (azapropazone, diclofenac, piroxicam, phenylbutazone, celecoxib, benzydamine and etofenamate). The in vitro and in vivo phototoxic potential has been documented particularly for tiaprofenic acid, with phototoxic reactions in more than half patients tested with tiaprofenic acid (5 % pet) and 5 J/cm^2 of UVA (Gonçalo et al. 1992), but in other studies tiaprofenic acid was typically photoallergic (Pigatto et al. 1996), therefore calling the attention to the concomitancy of both patterns of photosensitivity with the same drug.

Most topically applied NSAIDs are absorbed through the skin and can cause distant lesions, resembling systemic photosensitivity. Benzydamine, widely used in the oral or genital mucosa, causes photosensitivity at distant sites. When used in the mouth, benzydamine can induce cheilitis and chin dermatitis as a manifestation of photoallergy, and when used in a vaginal solution, hand dermatitis has occurred.

Ketoprofen

Ketoprofen, particularly when used topically in a gel formulation, is responsible for severe photoallergic reactions, often with oedema, bullae or erythema multiforme-like reactions, extending well beyond the area of application. Reactions may recur on sun exposure with no further drug application, as the drug or its metabolites persist in the skin for several days (>2 weeks) (Sugiura et al. 2000). There are also cases of connubial or by proxy contact dermatitis, namely, from the contaminated hands of the dance teacher, reactions induced by contact with contaminated objects, even clothes after being washed, or from exposure to cross-reactive chemicals, like benzophenones or octocrylene in sunscreens or benzophenones from magazine inks.

Although such a high frequency might suggest phototoxicity, the clinical pattern with erythema multiforme, positive lymphocyte stimulation tests with ketoprofen-photomodified cells, animal studies with absence of phototoxic potential, the capacity to photosensitize and transfer photoallergy by $CD4^+$ and $CD8^+$ T cells, in vitro activation and maturation of antigen-presenting cells by ketoprofen and UVA and characterization of a stable photoproduct – 3-hydroxy-ethyl-benzophenone – highly support a photoallergic reaction (Hino et al. 2008).

Cross-reactions occur between arylpropionic acid derivatives that share the benzophenone structure, namely, tiaprofenic acid and suprofen, and are not extensive to naproxen or ibuprofen. Cross-reactions are also common with the benzophenone UV filters, mainly oxybenzone, the UV filter octocrylene and the systemic hypolipemic agent, fenofibrate, that also induces systemic photosensitivity with cross-reactions with ketoprofen.

Patients with photoallergic contact dermatitis from ketoprofen have positive photopatch tests with 1 % ketoprofen, even if the patch is applied only for 1 h, and apart from the frequent cross-reactions in the photopatch tests (oxybenzone, octocrylene, fenofibrate), more than half of the patients also have positive patch tests to perfume mix I, particularly cinnamic alcohol (Pigatto et al. 1996). Moreover, many patients with contact allergy to cinnamic alcohol have positive photopatch tests to ketoprofen, a relation which is still not completely explained.

The analogues of ketoprofen, piketoprofen and dexketoprofen have a similar behaviour, in which concerns photosensitivity. A new topical formulation of ketoprofen, in plaster, may reduce the UV exposure of the drug but does not completely hinder this side effect of ketoprofen.

Piroxicam

Piroxicam is a known photosensitizer since the 1980s. Although there was some initial enigma around this photoallergy that usually developed with the first intakes of piroxicam, soon a relation was established with previous contact sensitivity to thiomersal (Cirne de Castro et al. 1991) and one of its main sensitizing moieties, thiosalicylic acid. Actually, upon low UVA irradiation, piroxicam decomposes and gives rise to a stable photoproduct structurally similar to thiosalicylic acid which is responsible for photosensitivity: in vitro UVA-irradiated solutions of piroxicam induce positive patch tests in patients with photosensitivity and individuals with positive patch tests to thiosalicylic acid, and animals sensitized by thiosalicylic acid develop positive photopatch tests to piroxicam.

Photoallergy from piroxicam can occur both from topical application and systemic use. It is becoming less frequent as this NSAID is replaced by newer drugs but it is still observed in Southern Europe (Cardoso et al. 2009), and a few cases were still found in the recent European multicentre photopatch test study.

Systemic photosensitivity develops within 24–48 h as an acute eczema involving diffusely the whole face or, often, as scattered erythematous papules and vesicles on the face and dorsum of the hands and pompholyx.

These patients do not react, neither on photopatch nor on drug rechallenge, to tenoxicam, meloxicam or lornoxicam, as these oxicams do not share the thiosalicylate moiety. Nevertheless, cross-reactivity between piroxicam and these oxicams occurs regularly in fixed drug eruption.

Other Drugs as Photosensitizers

Systemic phenothiazines (chlorpromazine and thioridazine), typically phototoxic, can induce lichenoid lesions with residual pigmentation, but most recent cases of photoallergy to chlorpromazine have been reported in caregivers who smash the tablets (Cardoso et al. 2009).

Promethazine, a highly phototoxic drug still used as a topical antipruritic, often induces photoallergic contact dermatitis. Another phenothiazine derivate, also used as a topical antipruritic, isothipendyl chlorhydrate, caused photoallergy with a positive photopatch test to chlorpromazine. Chlorproethazine, another phenothiazine marketed for some time in France and the UK as Neuriplege® cream for muscle pain (Genevrier, Antibes, France), was a frequent cause of photoallergic contact dermatitis in these countries.

The antiarrhythmic amiodarone induces erythema and a bluish-grey hyperpigmentation in sun-exposed areas due to the accumulation of drug metabolites in the dermis (Ferguson et al. 1985) The list of drugs causing photosensitivity is very large and always increasing, namely, with the recent inclusion of new kinase inhibitors in oncology, vandetanib, imatinib and, particularly, vemurafenib. With this drug more about 50 % of patients suffer burning and oedematous erythema on sun exposure (UVA) due to increased protoporphyrins and develop actinic keratosis, keratoacanthoma and squamous cell carcinoma, often as early as 8 weeks after initiating therapy for metastatic melanoma.

"Folk" Drugs as a Cause of Photosensitivity

Sometimes patients use "folk" medicines, mostly based on plant extracts, some of them rich in photoactive furocoumarins, which induce topical or systemic photosensitivity.

Since the antiquity, these substances have been used in the treatment of vitiligo and, more recently, in PUVA photochemotherapy.

Very occasionally, systemic photosensitivity develops upon oral exposure to furocoumarin-rich plants or their extracts, namely, to "homemade" infusions of St. John's wort (*Hypericum perforatum L.*) or to extracts commercialized in some European countries and used as a folk drug to treat depression (Fig. 23.5). Also, these infusions are occasionally used topically as a "folk medicine" with impressive adverse effects, as in a report where an infusion of *Ruta graveolens*, applied topically to relieve pain in fibromyalgia just before going into the sun, induced severe sunburn with bullae (Arias-Santiago et al. 2009).

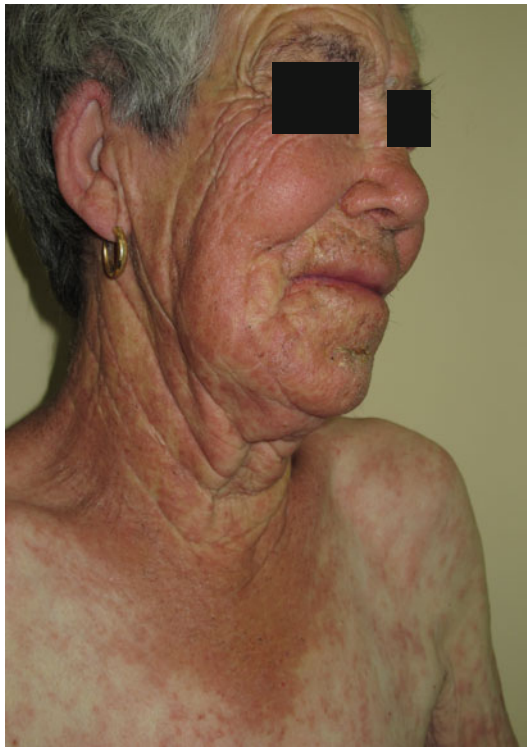

Fig. 23.5 Photosensitivity from consumption of infusion of *Hypericum perforatum* (St. John's wort)

Diagnostic Procedures in Drug Photosensitivity

Whenever a patient has a photosensitive eruption, a systematic inquiry for drugs should be conducted carefully.

Photopatch tests are indicated mainly for photoallergic contact dermatitis, but they can also be useful in the study of systemic drug photosensitivity. The recommended European baseline photopatch test series includes many drugs, namely, ketoprofen, etofenamate, piroxicam and benzydamine and also piketoprofen, dexketoprofen, ibuprofen, diclofenac, fenofibrate and chlorpromazine in the extended series (Gonçalo et al. 2013). Any other topical or systemic drug suspected of causing photosensitivity may be tested according to the general standardized procedures of photopatch testing. Briefly, allergens are applied in duplicate on the back, followed by skin irradiation of one of the sets of allergens at day 1 or day 2 with 5 J/cm2 of UVA, whereas the other set is shielded from light. Readings should be performed immediately after irradiation and also 48 and/or 72 h thereafter. Photopatch tests results have to be carefully interpreted. Positive reactions both in the irradiated and non-irradiated sites mean contact allergy that may be photoaggravated if the reaction is 1+ more in the irradiated site. A photopatch test is positive when erythema and papules covering the whole test area are observed only in the irradiated side. If the reaction is mainly erythema and oedema, without pruritus, exclusively limited to the test chamber area, with very sharp limits, begins shortly after irradiation, reaches its highest intensity by 24 h and regresses by 48/72 h (decrescendo reaction) with hyperpigmentation, it suggests a phototoxic reaction. A pruritic erythema with vesicles, diffuse limits extending beyond the chamber limit, increasing in intensity until 48/72 h after irradiation (crescendo reaction), suggests photoallergy. Often these patterns are not so typical, and the difficulties previously referred in the interpretation of clinical cases also occur in the interpretation of the photopatch tests.

In systemic photosensitivity, apart from photopatch tests, photoprovocation with irradiation after drug exposure or the calculation of the minimal UVA/B erythema dose when exposed to the drug and after drug withdrawal, may help identify the culprit.

In phototoxic reactions, both photopatch and photoprovocation tests are positive in the great majority of tested individuals; therefore, they are not particularly useful for confirming the aetiology of a phototoxic reaction, but they can disclose a hidden photoallergy.

General Principles of Treatment

Drug suspension and sun avoidance are recommended to resolve drug photosensitivity. When the drug is essential and life-saving, when there is no alternative drug or the alternative drug is not adequate, sun avoidance, protection from clothing and a broad-spectrum sunscreen that covers the UV spectrum of photosensitivity (mainly

within the UVA) may be adequate to improve photosensitivity. This protective effect of sunscreens can be helpful particularly in phototoxic reactions, as shown for voriconazole, vemurafenib and amiodarone. Broad-spectrum sunscreens may reduce both acute and long-term effects of photosensitivity, like photoaging and photocarcinogenesis, but they should always be associated with other sun-avoiding measures. Moreover, they should be recommended as preventive measures from the initiation of therapy with known photosensitive drugs. Nevertheless, it is important to recognize that chemical UV filters represent an important cause of contact photosensitivity, particularly in patients with previous dermatoses.

In cases of acute photoallergy from topical or systemic drugs, suspension of the culprit drug and sun avoidance will not resolve the skin lesions within a short time, and, therefore, active treatment may be necessary. Topical corticosteroids, in a formulation and potency adapted to the localization and severity of the dermatitis, may be prescribed for a few days. In severe reactions, as often observed with topical ketoprofen and systemic piroxicam, an additional short course of oral corticosteroids (24–32 mg of methylprednisolone, or equivalent, for a few days followed by a quick dose tapering) may be necessary to reduce acute symptoms and skin lesions.

In acute phototoxicity, presenting mainly as exaggerated acute sunburn, the efficacy of corticosteroids is highly questioned. Emollients and further photoprotection are advised for some time after resolution of acute photosensitivity.

Conclusion

Phototoxic, photoallergic and overlapping photosensitive reactions are still a frequent problem. They have a highly polymorphic clinical presentation, with different time courses and late consequences. Different responsible agents depend on geographic areas and, over time, depend on prescription habits. The dermatologist must be highly alert to search for a possible involvement of a drug in a photosensitive patient and try to confirm its contribution to photosensitivity. A correct questionnaire should be conducted and, although not so important in phototoxic cases, complementary tests including photopatch and photoprovocation tests may contribute to the final etiologic diagnosis. This is important in order to allow an adequate patient advice concerning further eviction of the photosensitizer and related chemicals.

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Epidermolysis Bullosa

24

Maya El Hachem, Mauro Paradisi,
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Key Points

- Epidermolysis bullosa is distinguished in:
  I. Inherited epidermolysis bullosa (EB)
  II. Acquired epidermolysis bullosa (EBA)
- Inherited epidermolysis bullosa (EB) is a heterogeneous group of genodermatoses, due to defects in epithelial adhesion and characterized by the development of mucosal and cutaneous bullous lesions, after minimal traumas.
- The new classification distinguishes four major groups, based on the site of blister formation: EB simplex (or epidermolytic: EBS), junctional EB (JEB), dystrophic (or dermolytic: DEB) EB, and Kindler syndrome.
- Many proteins are involved into the pathogenesis of all major EB types (plakophilin-1, desmoplakin, keratins 5 and 14, plectin, α6β4integrin, laminin-332, type XVII collagen, collagen VII, kindlin-1, etc.).
- Immunofluorescence and in some cases electron microscopy are necessary to identify the specific EB subtype.
- The prenatal diagnosis in families at risk of disease recurrence is possible through the molecular diagnosis; it could be performed when the mutation of the patient is already identified.
- The clinical pictures and course vary upon the EB type and subtype. The evolution is generally chronic; EBS, the evolution is chronic with improvement generally along the life; JEB, generalized severe (previously known as JEB-Herlitz), the clinical picture may be mild at birth and worsens dramatically in the first weeks/months of life; *severe generalized* recessive DEB (previously known as Hallopeau-Siemens RDEB) is the most important form because of multisystem involvement and the high risk to develop squamous cell carcinoma; other subtypes may be associated to extracutaneous abnormalities, e.g., *JEB with pyloric atresia* (JEB-PA), EBS-MD (EBS-muscular dystrophy).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_24, © Springer-Verlag Berlin Heidelberg 2015

- The treatment of EB patients requires a coordinated multidisciplinary approach. The management varies upon the age of the patient, the subtype of EB, the level of systemic involvement, and the complication.
- An adequate wound care is mandatory. The use of advanced dressings allows to delay the frequency of dressing change, in order to reduce pain and risk of infections and skin trauma. Caregivers should be trained specifically.
- Chronic wounds should be straightly followed in order to early detect carcinoma.
- Acquired epidermolysis bullosa (EBA) is a rare chronic autoimmune bullous disease of the skin and mucosa due to the formation of IgG autoantibodies directed against collagen VII.
- A genetic predisposition has emerged in some cases.
- The clinical diagnosis can be confirmed by ELISA, from IFD of salt-split skin and immunoelectron microscopy.
- Colchicine, dapsone, immunosuppressants, steroids, intravenous IgG and plasmapheresis, and rituximab are used as therapy with some success.

Definition and Epidemiology

Epidermolysis bullosa is distinguished in:

I. Inherited epidermolysis bullosa
II. Acquired epidermolysis bullosa

Inherited Epidermolysis Bullosa (EB)

Definition and Epidemiology

Inherited epidermolysis bullosa (EB) is a heterogeneous group of genodermatoses, due to defects in epithelial adhesion and characterized by the development of mucosal and cutaneous bullous lesions, after minimal traumas. Inheritance has a Mendelian pattern, autosomal dominant or recessive, depending on the forms. EB are rare diseases; epidemiological data are not homogeneous in all countries because of diagnosis and classification problems.

Table 24.1 The major epidermolysis bullosa types and subtypes

Major EB type	Major EB subtypes	Targeted protein (s)
EBS	Suprabasal EBS	Transglutaminase 5; plakophilin 1; desmoplakin; plakoglobin
	Basal EBS	Keratins 5 and 14; plectin; exophilin 5; bullous pemhigoid antigen 1
JEB	JEB, generalized	Laminin-332; collagen XVII; α6β4 integrin; α3 integrin subunit
	JEB, localized	Collagen XVII; laminin-332; α6β4 integrin
DEB	DDEB	Collagen VII
	RDEB	Collagen VII
Kindler syndrome	–	Fermitin family homolog 1 (kindlin-1)

From Fine et al. (2008, 2014)

Diagnostic criteria and classification of EB have been revised in 2008 and recently in 2014 by an international study group. These new revisions distinguish four major groups, based on the site of blister formation and proposed new nomenclature of some EB subtypes:

(a) EB simplex (or epidermolytic)
(b) Junctional EB
(c) Dystrophic (or dermolytic) EB
(d) Kindler syndrome

Each one is then subdivided into several subtypes as summarized in Table 24.1.

The major differences with the previous classification schemes are the inclusion of Kindler syndrome as a fourth major EB type, the subdivision of EBS into basal and suprabasal subtypes. In any case, this EB classification is not final and that further revisions are occurring.

Basic Concepts of Pathogenesis

Antigen mapping, ultrastructural images, and mutations identified until now, and their location contributed to understand that this group of

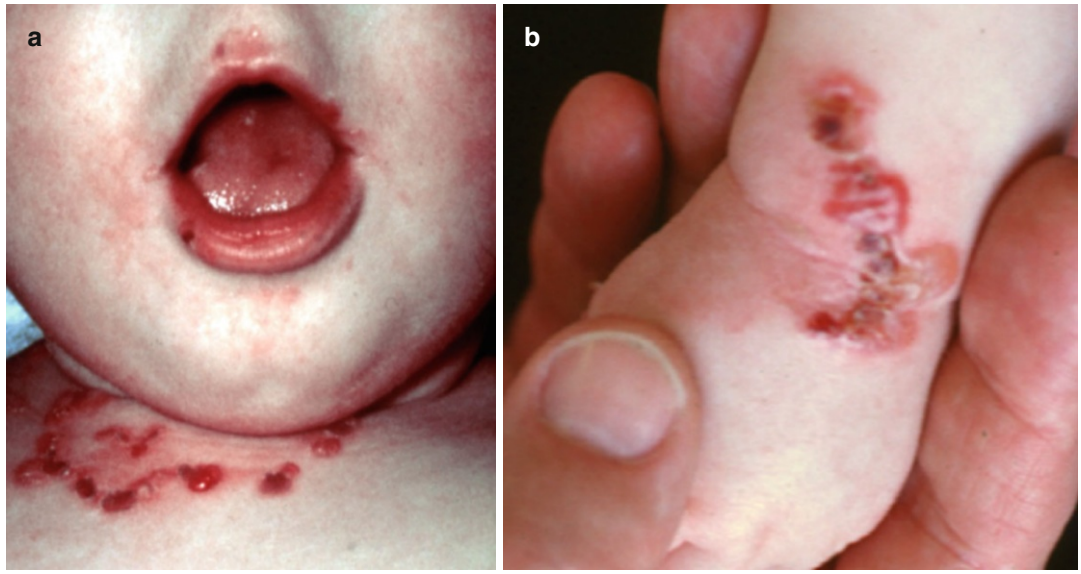

Fig. 24.1 (**a**, **b**) Hemorrhagic herpetiformis blisters in Dowling-Meara EB

diseases is the result of a defect in the adherence of the epithelium into the basement membrane zone. Although phenotype-genotype correlation is variable within the major EB types, the type of mutation, its location may suggest in some cases, even partially, the severity of different clinical manifestations. In Table 24.1 are listed the identified proteins involved into the pathogenesis of all major EB types.

Clinical Presentation

The clinical pictures and course vary upon the EB type and subtype.

EB Simplex (EBS)

Until now different subtypes have been identified. We limit the description to the particular or more frequent forms.

Localized EBS, known as EBS Weber-Cockayne, is the most common form of EBS. It is not present at birth and appears with the start of walking or during military service. The blisters are serious or rarely hemorrhagic and localized in particular at palms and soles; they usually heal without scarring. Teeth are normal; occasionally some nails may present dystrophies; oral mucosa involvement is transient. The association with hyperhidrosis is frequent, which contributes to the characteristic worsening of lesions in the summer.

EBS, generalized severe (previously known as EBS, Dowling-Meara) (Fig. 24.1a, b), known as EBS herpetiformis, appears at birth, and the blisters assume later on a characteristic herpetiform pattern, which are generally hemorrhagic affecting the entire body surface. The oral mucosa is frequently involved; in rare cases, it can spread to the tracheolaryngeal and esophageal mucosa. Nail dystrophy is usually observed. In the first year of life, the extensive involvement may, in rare cases, lead to systemic complications. Subsequently, there is a significant improvement of the clinical picture and development of palmoplantar hyperkeratosis. Patients with EBS-gen sev have a risk of developing basal cell carcinomas in adulthood.

EBS, generalized intermediate (previously known as EBS, Kobner), is characterized by blisters arising in particular at sites of friction. It appears usually at birth or in the first months of life. Nail dystrophies and lesions of the oral mucosa are mild and not constant; sometimes there are calluses and also palmoplantar keratoderma. The evolution is favorable, with an improvement in the clinical picture after puberty.

Table 24.2 Classification of EB simplex (EBS)

EBS major types	EBS subtypes
Suprabasal	Acral peeling skin syndrome (APSS)
	EBS superficialis (EBSS)
	Acantholytic EBS (EBS acanth)
	Skin fragility syndromes
	Desmoplakin deficiency (EBS-desmoplakin; skin fragility–wooly hair syndrome)
	Plakoglobin deficiency (EBS-plakoglobin; skin fragility–plakoglobin deficiency)
	Plakophilin deficiency (EBS-plakophilin; skin fragility–ectodermal dysplasia syndrome)
Basal	EBS, localized (EBS-loc)
	EBS, generalized severe (EBS-gen sev)
	EBS, generalized intermediate (EBS-gen intermed)
	EBS with mottled pigmentation (EBS_MP)
	EBS, migratory circinate (EBS-migr)
	EBS, autosomal recessive K14 (EBS-AR K14)
	EBS with muscular dystrophy (EBS-MD)
	EBS with pyloric atresia (EBS-PA)
	EBS-Ogna (EBS-Og)
	EBS, autosomal recessive-BP230 deficiency (EBS-AR BP 230)
	EBS, autosomal recessive-exophilin 5 deficiency (EBS-AR exophilin 5)

From Fine et al. (2008, 2014)

EBS with mottled pigmentation is rare; it is characterized by generalized bullous lesions associated with hyperpigmented macules, localized mainly at the trunk and extremities. Also, this form tends to improve spontaneously over time.

EBS with muscular dystrophy is characterized by an onset of generalized blisters at birth and associated with muscular dystrophy, which appears between the first year and the fourth decade of life and with a progressive clinical course. The cutaneous manifestation tends to resolve with atrophic scars and milia. Dystrophic nails and focal keratoderma of the palms and soles may be associated. Extracutaneous involvement is frequent: dental abnormalities, blistering in the oral cavity, inspiratory stridor, and breathing difficulties. The prognosis is related to the evolution of muscular dystrophy.

EBS, migratory circinate is very rare and characterized by migrating areas of erythema with multiple vesicles and small blisters at the advancing edge. The lesions heal with brown pigmentation without scarring (Table 24.2).

Junctional EB (JEB)

JEB, generalized severe (previsouly known as JEB_Herlitz) is characterized by the congenital presence of blisters and extensive erosions, on the skin and mucous membranes. The clinical picture may be mild at birth and worsens dramatically in the first weeks/months of life. Typical findings are exuberant granulation tissue formation in particular around nail folds and the involved site: perioral and periorbital areas, nose, shoulders, and buttocks. The involvement of mucous membranes may affect the entire respiratory, digestive, and less commonly genitourinary tract. The patients may require tracheostomy. The failure to thrive and severe infectious and respiratory complications are often responsible for the fatal outcome, occurring frequently within the first year of life.

JEB, generlaized intermediate (previously known as as JEB, non-Herlitz, generalized) is characterized by a clinical aspect similar to JEB, generalized severe but of lesser severity and therefore in most cases compatible with life. Skin blistering is generalized healing with atrophic scars or, less commonly, with exuberant granulation tissue. Nail dystrophy, hair loss, oral and nasal mucosa lesions, and teeth abnormalities are frequently present. Chronic anemia and growth delay are frequent. The course is relatively benign, with a gradual improvement up to adulthood. Adult patients with non-Herlitz JEB should be followed accurately for the increased risk of developing squamous cell carcinomas.

JEB with pyloric atresia (JEB-PA) appears generally at birth with widespread cutaneous and mucosal blistering and complete congenital pyloric. Congenital absence of skin (aplasia cutis congenita) is present in approximately 20 % of

cases. Nail dystrophy and dental abnormalities are constant features. This JEB type leads in most cases to early death; prognosis depends first of all on the prompt surgical correction of pyloric atresia. In some patients of this latter group, skins lesions improve gradually.

JEB, localized is characterized by localized disease, less severe than Herlitz and generalized JEB. It manifests at birth or soon thereafter with skin blistering on the hands, feet, lower legs, and face. Sometimes, mild nail dystrophy and dental abnormalities are associated (Table 24.3).

Dystrophic EB (DEB)

RDEB, generalized severe (previously known as Hallopeau-Siemens RDEB) is the most important form because of multisystem involvement. It appears at birth with widespread blisters and/or erosions of the skin and mucous membranes (Fig. 24.2). Nail involvement causes generally the permanent loss of nail plates of both hands and feet. The most affected areas are those subject to minimal traumas changing therefore with age. The recurrent lesions heal with milia formation and retracting scars: pseudosyndactyly, flexion contractures of the interphalangeal, metacarpophalangeal, and wrist joints, fusion of fingers and toes ("mitten deformities"), ankylosis of the limbs, scarring alopecia, chronic gingivitis, dental caries and enamel defect, microstomia, ankyloglossia, esophagus stricture, anal and perianal erosions, urogenital mucosa involvement, corneal opacity, and pannus formation (Fig. 24.3a, b). Most patients also present delayed puberty, osteopenia, osteoporosis, constipation, severe growth retardation, refractory anemia, hypoalbuminemia, and skin infections, which can cause post-streptococcal glomerulonephritis. Life expectancy and quality of life are significantly reduced. The most frequent cause of death remains squamous cell carcinomas that occur in areas of chronic skin wounds and scars and more often from the second-fourth decade of life, with frequent regional and distant metastases.

RDEB, generalized intermediate variant is the most common subtype of RDEB with onset at birth or in the first days of life and highly variable severity of the cutaneous and mucosal involvement. In some patients, the scarring phenomena can lead to a certain degree of pseudosyndactyly and loss of nail plates. Mucosal lesions are always present and affect the oral cavity, usually without the development of microstomia and

Table 24.3 Classification of EB junctional (JEB)

JEB, generalized	JEB, generalized severe (JEB-gen sev)
	JEB, generalized intermediate (JEB-gen intermed)
	JEB with pyloric atresia (JEB-PA)
	JEB, late onset (JEB-LO)
	JEB with respiratory and renal involvement (JEB-RR)
JEB, localized	JEB, localized (JEB-loc)
	JEB, inversa (JEB-inv; JEB-I)
	JEB-LOC syndrome

From Fine et al. (2008, 2014)

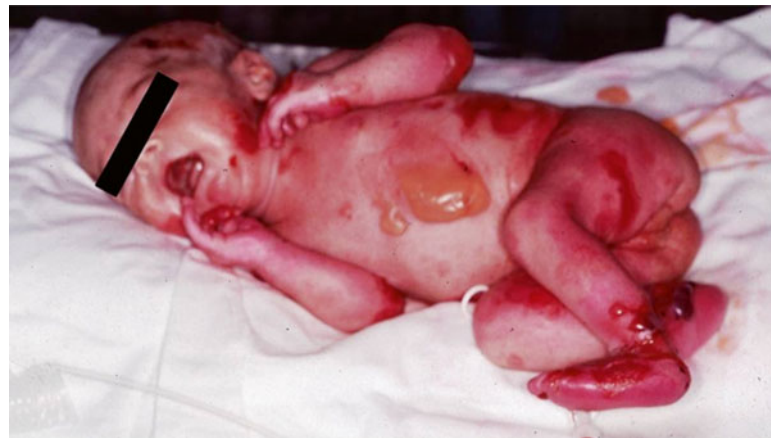

Fig. 24.2 A newborn with large, multiple, painful, and hemorrhagic blisters, affected by RDEB

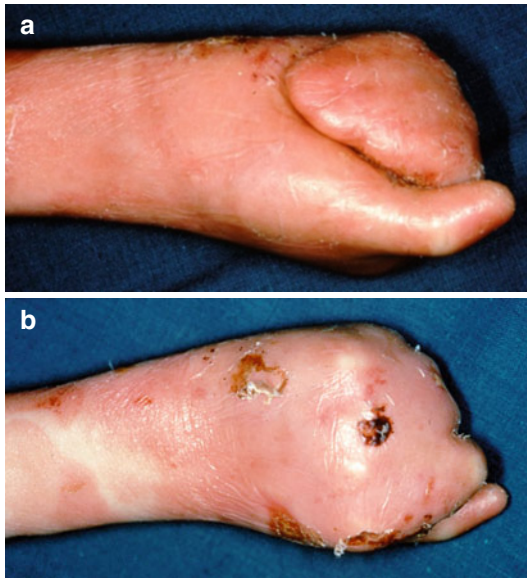

Fig. 24.3 (**a**, **b**) Digit fusion and pseudosyndactyly in a girl affected by RDEB

ankyloglossia; excessive dental caries are a common finding. The involvement of the esophagus, relatively frequent, is a major determinant of the severity of the clinical picture. In these patients too, chronic ulcerations, particularly of the limbs, are associated with an increased incidence of squamous cell carcinomas.

RDEB inversa is a rare but severe subtype of RDEB. After the first years of life, cutaneous lesions tend to localize mainly to folds. Nail dystrophies are typical but of variable severity. Lesions of the oral cavity, always present, can lead to microglossia and ankyloglossia, and esophageal involvement is often severe. Also common are lesions of the lowermost portion of the genitourinary tract, with possible development of vaginal strictures.

The *DDEB generalized* subtype manifests with blisters at the limbs and heal with formation of numerous milia and atrophic scars. Multiple papular and plaque lesions of ivory-white color, known as albopapuloid lesions, may occur and are most frequently localized on the trunk. Nail dystrophies and loss of nail plates are always present. Mucosal lesions are usually mild and limited to the oral cavity. Multiple dental caries are relatively frequent. The course is usually relatively benign, with improvement with age.

Table 24.4 Classification of dystrophic EB (DEB)

DEB, major subtypes	All subtypes
DDEB	DDEB, generalized (DDEB-gen)
	DDEB, acral (DDEB-ac)
	DDEB, pretibial (DDEB-pt)
	DDEB, pruriginosa (DDEB-pr)
	DDEB, nails only (DDEB-na)
	DDEB, bullous dermolysis of the newborn (DDEB-BDN)
RDEB	RDEB, generalized severe (RDEB-gen sev)
	RDEB, generalized intermediate (RDEB-gen intermed)
	RDEB, inversa (RDEB-inv; RDEB-I)
	RDEB, localized (RDEB-loc)
	RDEB, pretibial (RDEB-pt)
	RDEB, pruriginosa (RDEB-pr)
	RDEB, centripetalis (RDEB-ce)
	RDEB, bullous dermolysis of the newborn (RDEB-BDN)

From Fine et al. (2008, 2014)
DDEB dominant dystrophic EB, *RDEB* recessive dystrophic EB

The DDEB and RDEB pruriginosa variants are characterized by severe itching which appears frequently at adolescence or even adulthood. The characteristic features are the aspect and linear distribution of the lesions which may be papules, nodules, lichenoid, or hypertrophic at the extensor surfaces of the limbs.

DDEB and RDEB, bullous dermolysis of the newborn are characterized by generalized lesions with oral cavity involvement. The blisters heal within the second year of life with atrophic scars and milia. Nail dystrophies and mild skin fragility can persist in adulthood (Table 24.4).

Theresa Kindler Syndrome (KS)

KS is a rare autosomal recessive genodermatosis characterized by skin fragility and photosensitivity caused by recessive mutations in the *FERMT1* gene encoding for kindlin-1.

Clinically, KS is characterized by trauma-induced blisters localized most frequently at the

extremities, photosensitivity with erythema and photo-induced blisters, progressive poikiloderma, predominantly localized to the face and neck, partial pseudosyndactyly, and generalized skin atrophy. Additional features include oral, anal, urogenital, ocular, and laryngeal mucosa involvement, esophageal strictures, and an increased susceptibility to develop squamous cell carcinomas.

Diagnosis and Prenatal Diagnosis

Diagnosis of EB is generally clinical and easy for expert; however, the identification of specific subtype requires electron microscopy and/or antigen mapping in immunofluorescence, on a biopsy of a recent blister or, preferably, of one mechanically induced. Furthermore, specific monoclonal or polyclonal antibodies and immunofluorescence techniques are used to demonstrate the defective expression of specific protein components, which are altered in individual subtypes of EB.

Molecular diagnosis is possible by searching for mutations in different gene, such as the COL7A1 for DEB, LAMB3, LAMC2, COL17A1, and, less frequently, LAMA3 for JEB and allows to perform prenatal diagnosis in families at risk of disease recurrence.

General Principles of Treatment

The treatment varies upon the age of the patient, the subtype of EB, the level of systemic involvement, and the complication. In this chapter, we develop only the skin care.

General Measures

The care of EB requires a coordinated multidisciplinary approach; it should take into account the treatment of mucocutaneous lesions and systemic manifestations. Therefore, many specialists are involved (dermatologist: case manager, neonatologist/pediatrician, gastroenterologist, plastic surgeon, dentist, pain relief doctor, specialist nurse, dietitian, psychologist, etc.). An efficient treatment of EB patients encompasses information about the existence of patient association (DEBRA) and the advantages to become a member. DEBRA contributes to improve patient access to information, reference centers, and social services.

Management of EB Patients Since Neonatal Age

The fragility of the skin requires specific attention:

- Caregiver and patient education should be gradual and adapted to the sociocultural level of the family.
- Whenever possible, skin-to-skin contact with the mother and breast feeding should be encouraged.
- The baby should not be placed in an incubator unless needed.
- Handling and bathing the baby with extreme attention.
- There is no contraindication to immunization for infectious diseases.
- In case of hospitalization, a venous access should be guaranteed. Whenever required for a long term, an indwelling central venous catheter can be used for blood sampling, fluid/electrolytes, drug administration, etc.
- Whenever electrodes are needed, they should be of small size.
- Choosing clothes without seams and tags made by soft material and easy to put on and remove.
- Hard shoes with internal seams should be avoided.
- Toys should be in soft material without traumatic angles and frequently cleaned.
- Hobbies and sports should be at the lowest risk of skin trauma.
- Vulnerable skin sites, such as knees and elbows, should be protected when the child begins to walk and during sport activities or hobbies.
- Patient compliance and adherence to therapy should be regularly checked and if necessary supported by psychologist.
- Monitoring of EB requires periodically complete clinical examination and evaluation of nutrition status and infection through blood test and swabs for culture which should be taken from infected and critically colonized wounds.

- In recessive DEB patients, specific dressings of fingers and toes are required in order to prevent digit fusion and development of pseudosyndactyly. The separation should be performed by using easily modeled dressings such as soft silicone foams (e.g., Mepilex® or Mepilex Lite®, Mölnlycke®). in order to delay.

Wound Care

- The use of advanced dressings such as polymeric membranes, hydrogels, and hydrofiber allows to delay the frequency of dressing change, in order to reduce pain and risk of infections and skin trauma.
- New blisters should be lanced and drained in order to prevent their enlargement; the blister roof should be left in place
- Mechanical debridement, when necessary, should be performed gently with previous analgesia.
- Chronic wounds should be straightly followed in order to early detect carcinoma; in suspected lesions, biopsy is mandatory
- Topical antibiotics should be used only to treat infected lesions.
- The choice of dressings varies upon the availability and the type and site of the lesions.
- An adequate dressing retention should be provided in order to prevent slipping and further trauma (e.g., Elastomull®, Tubifast®, or Self-fix®).
- If available, Dermasilk® or other specifically designed garments, without silver, can also be useful to retain the dressings in place.

Exuding Wounds

- Nonadhesive soft silicone or lipido-colloid contact layers (e.g., Mepitel®, Adaptic® touch, Urgotul®), thin polyurethane foam-soft silicone (Mepilex® Lite), and hydrogels (Intrasite® Conformable) appear to be the most suitable in these types of lesions. Hydrogel dressings should be changed daily or as soon as they become dry. Others could be changed every 3 days. Hydrofiber dressings (e.g., Aquacel®) or soft silicone foam with super absorbers (Cutimed®Siltec) able to absorb the abundant exudates should be preferred. Soft silicone foam (Mepilex®, Mepilex®transfer) and polymeric membranes (PolyMem®) are indicated in heavy exuding wounds.
- Dressings containing silver (Mepilex® AG; Urgotul®silver/SSD; PolyMem®silver, Aquacel®Ag) may reduce the risk of skin infections. However, silver plasma level should be checked in case of large surface and/or prolonged treatment, because of the risk of silver absorption and its toxicity. Indeed in children, the use of those dressings should be very limited in time and treated surface.

Hyperkeratotic and Crusted Lesions

These lesions are itchy and may mask an underlying squamous cell carcinoma; thus they require an accurate treatment and follow-up. Emollient creams and bathing are indicated.

Exuberant Granulation Tissue

Very potent topical steroid ointments and silver dressings are effective.

Infected Wounds

- Wounds should be cleaned with mild antiseptics, such as chlorhexidine 0.1 %
- In case of lesions at risk of infection, the use of topical hydrogen peroxide (Crystacide®) is indicated. An aqueous solution of eosin (2 %) reduces the exudate.
- Topical antibiotics, which do not have a systemic formulation (e.g., fusidic acid, mupirocin), should be used for treatment of infected wounds and used for short periods.
- Treatment with systemic antibiotics is always indicated when the infected lesions are multiple and widespread. In malnourished and/or noncompliant patients and in infants, systemic therapy should be started at the first signs of infection.

Dressing Frequency

It depends on the type of material used and the type of the lesion:

- Paraffin-impregnated gauzes (e.g., Jelonet®) or medicated gauzes (e.g., Fitostimoline®) or hyaluronic acid (e.g., Connectivine®) dressing should be changed on a daily basis, increasing

wound manipulation, pain, and indirectly also the risk of infection. Furthermore, they adhere to the wound bottom.
- Advanced dressings could be kept in place for 2–4 days.
- Infected lesions should be dressed every day.

Acquired Epidermolysis Bullosa (EBA)

EBA is a rare chronic autoimmune bullous disease of the skin and mucosa due to the formation of IgG autoantibodies directed against collagen VII, the main constituent of anchoring fibrils. It generally affects adults but may occur in all ages. Clinically, it is characterized by skin fragility and subsequent formation of subepidermal blisters, predominantly in locations subjected to trauma, that heal with scar formation and milia, in a similar way to dystrophic epidermolysis. Nail loss may also occur. There are some variations, like inflammatory bullous pemphigoid or Brunsting-Perry pemphigoid-like and also IgA linear dermatosis. A genetic predisposition has emerged in some cases. The clinical diagnosis can be confirmed by ELISA, from IFD of salt-split skin and immunoelectron microscopy. Therapy is often frustrating because patients often do not respond to treatment with systemic steroids and immunosuppressive drugs, and there are no therapeutic guidelines. Medications that have been used with some success are colchicine, dapsone, immunosuppressants (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), steroids, intravenous IgG and plasmapheresis, and rituximab

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Erysipelas

25

Maria Balabanova

Key Points

- Erysipelas is a distinctive type of superficial cellulitis of the skin with prominent lymphatic involvement.
- Its hallmark is a well-defined, raised edge reflecting the more superficial (dermal) involvement.
- Seventy to 80 % of the lesions are on the lower extremities and 5–20 % are on the face.
- Erysipelas is almost always due to beta-haemolytic streptococci group A (uncommonly *S. dysgalactiae* group G or *S. dysgalactiae* group C).
- Mild early cases of erysipelas in adult can be treated with intramuscular procaine penicillin (600,000 units once or twice daily), oral penicillin V (250–500 mg every 6 h) and erythromycin (250–500 mg every 6 h).
- More extensive erysipelas is treated with hospitalization and parenteral aqueous penicillin G (600,000–2,000,000 units every 6 h for 5–10 days); clindamycin should be added in case of septic shock.
- Extensive cellulitis or necrotizing fasciitis requires surgical debridement of the necrotic tissue and intensive care for the shock syndrome.
- Alternative treatment includes the other macrolides (roxithromycin, clarithromycin, azithromycin); they appear to be as effective as parenteral penicillin G. Cephalosporins also may be used as a second-line treatment. Quinolones are not indicated in the treatment of erysipelas.
- Prophylactic treatment includes benzylpenicillin benzathine (Tardocillin) 2.4 million units every 3 weeks for 1 or 2 years and erythromycin 250 or 500 mg twice a day. Of importance for prophylaxis is the rigorous disinfection of minor injuries that may provide a portal for bacteria.

Definition and Epidemiology

Erysipelas is a distinctive type of superficial cellulitis of the skin with prominent lymphatic involvement. It is more common in infants, young children and older adults. Its incidence has declined since the middle of the twentieth century, probably due to the greater use of antibiotics

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_25, © Springer-Verlag Berlin Heidelberg 2015

and improved sanitation. Formerly the face was most commonly involved. Now the distribution of erysipelas has changed: 70–80 % of the lesions are on the lower extremities and 5–20 % are on the face. This is most probably because of the ageing population and risk factor such as lymphoedema.

Basic Concepts of Pathogenesis

Erysipelas is almost always due to beta-haemolytic streptococci group A (uncommonly *S. dysgalactiae* group G or *S.dysgalactiae* group C). Group B streptococci have produced erysipelas in newborns and may be the cause of abdominal or perineal erysipelas in post-partum women. *S. aureus*, *Pneumococcus* species, *Klebsiella pneumoniae*, *Yersinia enterocolitica* and *Haemophilus influenzae* type B have also been known to cause an erysipelas-like infection.

The portal of entry commonly includes skin ulcers, local trauma or abrasions, psoriatic or eczematous lesions or fungal infections; in the neonate, erysipelas may develop from an infection of the umbilical stump.

Predisposing factors include venous stasis, paraparesis, diabetes mellitus and alcohol abuse, lymphoedema and obesity. Other predisposing factors and ports of entry are surgical wounds, fissures of the nares, under the lobes of the ears, on the anus or penis, between or under the toes and athlete's foot.

Location and hepatic and renal disease are the most important risk factors, while diabetes is probably of less significance than previously suggested. Patients with the nephrotic syndrome are particularly susceptible. Erysipelas tends to occur in areas of pre-existing lymphatic obstruction or oedema (e.g. after a radical mastectomy). Also, because erysipelas itself produces lymphatic obstruction, it tends to recur in an area of an earlier infection. Over a 3-year period, the recurrence rate is about 30 %, predominantly in individuals with venous insufficiency or lymphoedema. An antecedent streptococcal respiratory tract infection preceded cutaneous involvement in about one-third of patients even though streptococci might not be found on culture at the time that the skin lesions become evident.

Clinical Presentation

Erysipelas has an abrupt onset of fever, chills, malaise and nausea. A few hours to a day later, these general symptoms are followed by a painful lesion with a bright red oedematous, indurated ('peau d'orange') appearance and an advancing, raised border that is sharply demarcated from the adjacent normal skin. The affected area is hot, tender and painful to palpation and may burn. A common form of erysipelas involves the bridge of the nose and the cheeks. Local clinical signs, without fever and inflammation, characterize the recurrent forms. Uncomplicated erysipelas remains confined primarily to the lymphatics and the dermis. Occasionally, the infection extends more deeply and produces cellulitis, subcutaneous abscess and necrotizing fasciitis. Other complications may include streptococcal bacteraemia which occurs in about 5 % of patients with erysipelas; when the infection resolves, desquamation and postinflammatory pigmentary changes may occur.

Diagnosis

The diagnosis is based on the:

- General symptoms.
- Local symptoms.
- Biopsy reveals diffuse oedema of the dermis and a dermal neutrophilic infiltrate. There is commonly dilation of lymph vessels, dermal foci of suppurative necrosis and a dermal–epidermal separation. There is no primary necrotizing vasculitis, thrombosis or leukocytoclasis.
- Gram or Giemsa stain, direct immunofluorescence, throat swabs, culture technique, swabs from the local portal of entry and serological tests.

Differential Diagnosis

- Early herpes zoster involving the second division of the fifth cranial nerve
- Contact dermatitis
- Giant urticaria
- Deep venous thrombosis
- Diffuse inflammatory carcinoma of the breast
- Erythema chronicum migrans
- An erysipelas-like skin lesion in patients with hypogammaglobulinaemia
- *Campylobacter jejuni* bacteraemia
- Lupus (butterfly pattern on the face)

General Principles of Treatment

Oral or parenteral penicillin is the treatment of choice. Elevation of the affected leg, bed rest and saline wet dresses are recommended.

Mild early cases of erysipelas in adult can be treated with:

- Intramuscular procaine penicillin (600,000 units once or twice daily)
- Oral penicillin V (250–500 mg every 6 h)
- Erythromycin (250–500 mg every 6 h)

More extensive erysipelas is treated as follows:

- Hospitalization and parenteral aqueous penicillin G (600,000–2,000,000 units every 6 h for 5–10 days).
- Clindamycin should be added in case of septic shock.
- Extensive cellulitis or necrotizing fasciitis requires surgical debridement of the necrotic tissue and intensive care for the shock syndrome.

Alternative Treatment

The other macrolides – roxithromycin, clarithromycin and azithromycin – appear to be as effective as parenteral penicillin G. Cephalosporins also may be used as a second-line treatment. Quinolones are not indicated in the treatment of erysipelas.

Although typical erysipelas can be readily distinguished from cellulitis (which can be of staphylococcal as well as streptococcal aetiology), differentiation may not be clear-cut in occasional circumstances. Under such conditions, particularly in an acutely ill patient, intravenous administration of penicillinase-resistant penicillin (nafcillin or oxacillin) or a first-generation cephalosporin is warranted.

Prophylactic Treatment

- Benzylpenicillin benzathine (Tardocillin) 2.4 million units every 3 weeks for 1 or 2 years
- Erythromycin 250 or 500 mg twice a day

Of importance for prophylaxis is the rigorous disinfection of minor injuries that may provide a portal for bacteria usually streptococci and the physical oedema therapy described by comprising manual lymph drainage and compression.

- Opinions differ about the duration of antibiotic prophylaxis. It has been established that recurrences are reduced, but the effect is not dramatic. Continuous antibiotic prophylaxis is indicated only in patients with high recurrence rate. Prophylactic antibiotic therapy should be considered as a long-term, even lifetime, treatment especially for certain predisposed subject (i.e. postphlebitic syndrome, lymphoedema, diabetes and immunocompromised hosts).
- Treatment of the local point of entry does not guarantee that there will be no recurrences. Recurrent episodes of erysipelas/cellulitis have also been associated with post-cellulitic oedema, which is a risk factor for recurrent disease. Reduction of the oedema would seem beneficial as well as a vigorous treatment of local factors.

Treatment Algorithm

First-Line Treatment

- Intramuscular procaine penicillin (600,000 units once or twice daily).
- Oral penicillin V (250–500 mg every 6 h); erythromycin (250–500 mg every 6 h).

- Hospitalization and parenteral aqueous penicillin G (600,000–2,000,000 units every 6 h for 5–10 days).
- Surgical debridement of the necrotic tissue and intensive care for the shock syndrome.
- In case of septic shock, clindamycin should be added.

Second-Line Treatment

- Macrolides – roxithromycin, clarithromycin and azithromycin.
- Cephalosporins also may be used as a second-line treatment.

Prophylactic Treatment

- Benzylpenicillin benzathine (Tardocillin) 2.4 million units every 3 weeks for 1 or 2 years
- Erythromycin 250 or 500 mg twice a day
- Rigorous disinfection of minor injuries

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Erythema Multiforme

26

Kristina Semkova and Jana Kazandjieva

Abbreviations

CMV	Cytomegalovirus
DIF	Immunofluorescence
DNA (*pol*)	DNA polymerase
EBV	Epstein-Barr virus
EM	Erythema multiforme
GVHD	Graft-versus-host disease
HSV	Human herpesvirus
IBD	Inflammatory bowel disease
IFN-γ	Interferon-γ
PMLE	Polymorphous light eruption
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
TEN	Toxic epidermal necrolysis
VZV	Varicella-zoster virus

Key Points

- Erythema multiforme (EM) is an acute, immune-mediated dermatological condition affecting the skin and mucous membranes. The most commonly identified triggering factor for EM is infection with human herpesvirus (HSV).
- A consensus clinical classification currently divides EM into EM minor and EM major. According to the frequency pattern, EM is classified into isolated cases, recurrent EM, and persistent EM.
- The characteristic clinical presentation is with typical target lesions with mainly acral, symmetrical distribution with or without mucosal erosions.
- Symptomatic therapy should be the mainstay in every patient with EM. Mild cutaneous involvement usually resolves without treatment within several weeks, but symptomatic improvement for occasional burning or pruritus may be achieved by using oral antihistamines or topical corticosteroids.
- Severe cases of EM major require special care for the mucous membranes to prevent complications.
- Early ophthalmologic consultation is important in the evaluation and management of eye involvement with daily examinations for signs of complications.
- Recurrent and persistent EM requires systemic therapeutic interventions. In HSV-associated or idiopathic EM, the first-line management is long-term prophylaxis with antiviral medications.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_26,

Definition

Erythema multiforme (EM) is an acute, immune-mediated dermatological condition affecting the skin and mucous membranes. It develops as a type IV hypersensitivity reaction to infections, medications, or other stimuli. The clinical presentation with target lesions and/or mucosal erosions with a history of exposure to a known trigger is usually sufficient for the diagnosis. Albeit self-limited in most cases, severe or recurrent forms of EM require systemic therapy.

EM was first described by Hebra in 1866 in his atlas of skin diseases (*Erythema Exudativum Multiforme typus benignus Hebra*). For many years, it was considered a variant from a continuous spectrum comprising EM, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Studying an extensive number of cases allowed for a more precise understanding of these diseases and their evidence-based distinction as separate entities (Table 26.1). A consensus clinical classification currently divides EM into EM minor and EM major (Bastuji-Garin et al. 1993). EM minor is characterized by typical targets or raised, edematous papules with predominantly acral distribution, while EM major presents with typical targets or raised, edematous papules distributed acrally with involvement of one or more mucous membranes. Epidermal detachment in EM major should involve less than 10 % of the total body surface area.

Table 26.1 Consensus classification of EM, SJS, and toxic epidermal necrolysis and types of targetoid lesions (by Bastuji-Garin et al. 1993)

Consensus clinical classification	Types of targetoid lesions
EM – detachment of <10 % of BSA, localized typical or raised atypical targets	1. Typical targets
SJS – detachment of <10 % of BSA, widespread erythematous or purpuric macules or flat atypical targets	2. Raised atypical targets
SJS/TEN overlap – detachment of between 10 % and 30 % of BSA, widespread purpuric macules or flat atypical targets	3. Flat atypical targets
TEN with spots – detachment of >30 % of BSA, widespread purpuric macules or flat atypical targets	4. Macules with or without blisters
TEN without spots – detachment of >10 % of BSA, large epidermal sheets and no purpuric macules	

Epidemiology

The exact incidence of EM is not known but is estimated to be between 0.01 and 1 %. Young adults are most commonly affected with a slight male predominance. EM before the age of 3 and after the age of 50 is exceedingly rare.

Higher risk of EM was suggested in patients with HIV infection, corticosteroid treatment, bone marrow transplant, systemic lupus erythematosus (SLE), graft-versus-host disease (GVHD), and inflammatory bowel disease (IBD), as well as in patients on chemotherapy or radiotherapy.

Basic Concepts of Pathogenesis

The most commonly identified triggering factor for EM is infection with human herpesvirus (HSV). Other infectious agents and medications have been implicated as well. Nevertheless, about 50 % of cases remain idiopathic with no identifiable etiologic factor.

Infections

Infectious stimuli are linked to the majority of all cases of EM with known etiology.

HSV, primarily type 1, is the most common, especially in patients experiencing recurrent episodes of EM minor and in young adults. A study with PCR detection and genotyping of HSV in EM patients revealed that 66.7 % of the patients had HSV1, 27.8 % had HSV2, and 5.6 % had HSV1 and HSV2 co-infection (Sun et al. 2003). Some of the idiopathic cases are also believed to be induced by a subclinical or silent HSV infection. In a PCR study of skin

samples from 16 patients with idiopathic EM, HSV DNA was found in 25 % of single-episode idiopathic EM and in 50 % of recurrent idiopathic EM (Ng et al. 2003).

Other viruses that may induce EM include cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza, adenovirus, coxsackievirus B5, echoviruses, enterovirus, hepatitis A/B/C viruses (HAV/HBV/HCV), measles, mumps, paravaccinia, parvovirus B19, poliomyelitis, and varicella-zoster virus (VZV).

Many bacterial infections have been reported to precipitate EM, including *Mycoplasma pneumoniae*, borreliosis, cat-scratch disease, diphtheria, hemolytic streptococci, legionellosis, leprosy, *Neisseria meningitidis*, *Mycobacterium avium* complex, pneumococci, tuberculosis, *Proteus*/*Pseudomonas*/*Salmonella*/*Staphylococcus*/*Yersinia* species, *Treponema pallidum*, tularemia, *Vibrio parahaemolyticus*, and rickettsial and chlamydial infections.

Mycoplasma pneumoniae is of particular importance for the development of EM as it is the most common known trigger in the pediatric population.

Drugs

Drug-related EM comprises less than 10 % of all cases. Multiple drugs and substances can precipitate EM, the most common being nonsteroidal anti-inflammatory agents, sulfonamides, antiepileptics, and antibiotics.

Newer agents, such as biologics and human papillomavirus vaccines, as well as over-the-counter preparations, such as weight loss pills and herbal medicines, can also trigger EM.

Other Triggers

Multiple other factors have been linked to EM development: menstruation; high intake of food preservatives, especially benzoic acid and cinnamon; hair dye exposure; tattoo dermatitis; and physical or mechanical factors, such as radiotherapy, tattooing, cold, and sunlight. However, a recent study challenged the role of radiation, as EM was observed predominantly in patients with concomitant prescribed medications and only rarely in patients who were irradiated only.

Albeit rarely, EM has been described in association with malignancy, mainly leukemias and lymphomas. Solid organ tumors, such as gastric adenocarcinoma, renal cell carcinoma, and extrahepatic cholangiocarcinoma, have been reported in patients with persistent and treatment-recalcitrant EM. Thorough screening and physical examination may be thus warranted in these cases.

The pathogenesis of EM is not yet clearly understood. An autoimmune nature of the disease was recently refuted by an identified lack of specific humoral autoreactivity in sera from patients with EM major. Its occurrence in a small proportion of the whole population exposed to the known triggers suggests a genetic predisposition. Specific HLA associations reported in the literature include HLA-DQB1*0301, HLA-DQB1*0302, HLA-B35, HLA-B62, and HLA-DR53. Different genetic background accounts for the difference in presentation and severity, and HLA-DQB1*0302 is particularly linked to severe mucous membrane involvement.

Although HSV-induced and drug-induced EM are delayed type hypersensitivity reactions, they evolve via different pathways. In HSV-associated EM, the main reaction targets are the keratinocytes which express HSV DNA fragments. These fragments are transported to the skin by blood CD34+ Langerhans cells progenitors after phagocytosis of the active virus. Skin homing receptors and upregulation of E-cadherin expression enhance the binding of these cells to keratinocytes. Expression of HSV DNA polymerase (*pol*) and other genes on the surface of basal layer keratinocytes recruits CD4+T-helper cells, which produce cytokines and initiate an inflammatory cascade. The main effector cytokine in HSV-related EM is interferon-γ (IFN-γ). By contrast, the primary effector cytokine in drug-induced EM is TNF-α.

Clinical Presentation

According to the frequency pattern, EM is classified into isolated cases, recurrent EM and persistent EM. Recurrent EM is defined as multiple episodes of EM over a period of years with an average of six episodes per year and a mean duration of 6–10 years. The most common association of recurrent EM is with HSV infection and complex aphthosis, but literature reports incriminate other factors as well, including menstruation, vulvovaginal candidiasis, hepatitis C, *M. pneumoniae* infection, and acetaminophen and benzoic acid ingestion. About 70 % of patients have oral involvement and about 20 % report genital lesions.

Persistent EM is a rare variant characterized by continuous appearance of target and targetoid lesions without remissions. Its rarity impedes proper etiological identification, but association with HSV, Epstein-Barr virus, hepatitis C, influenza, cytomegalovirus, inflammatory bowel disease, and various neoplasms has been reported in the literature.

The clinical presentation of EM may be variable from one patient to another and even in the same patient. A detailed history is important to identify the potential trigger and any possible morphological changes in the clinical manifestation of the rash before the initial presentation to the clinician. The hallmark of EM is the target lesion, but early or atypical target lesions may not have the characteristic appearance.

Prodromal Symptoms

In EM minor prodromes are rarely observed and are usually mild, consisting of nonspecific upper respiratory tract infection-like symptoms within about 3 days before the onset of the rash.

In EM major prodromes are common, and about half of the patients experience influenza-like symptoms, including malaise, fever, cough, sore throat, vomiting, chest pain, and diarrhea. These symptoms usually present 1–2 weeks prior to the cutaneous eruption, but in many cases it is not known whether they represent a genuine prodromal period or are part of the infectious process that incites EM development.

Skin Lesions

Early EM presents with oval to round erythematous-edematous macules or papules that expand gradually over a period of 24–48 h. During the first few days, the initial lesions develop a raised, pale, and edematous peripheral ring, surrounded by a second cyanotic or violaceous ring, thus forming the typical concentric, "target" lesion (Fig. 26.1). The central area of the target lesion represents necrosis and may appear clinically as a dusty red area or blister (Fig. 26.2). During the course of the disease, the lesions may evolve to form polycyclic, geographic, or annular configurations. Post-inflammatory hyperpigmentation or hypopigmentation may follow the clearance of the eruption.

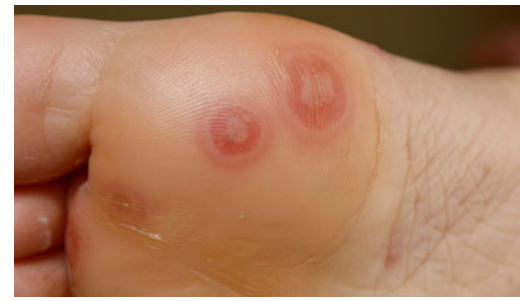

Fig. 26.1 Typical target lesions on the feet of a 32-year-old woman after an upper lip HSV infection

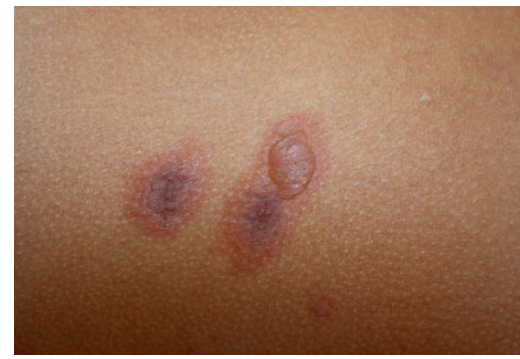

Fig. 26.2 Target lesions with bullous and hemorrhagic center

Atypical target lesions can also be observed, albeit uncommonly. They usually present as raised, edematous plaques that have only two concentric rings or poorly defined borders. In contrast, atypical target lesions in Stevens-Johnson syndrome are flat and not edematous.

The lesions are usually in a symmetrical distribution, affecting the acral extensor surfaces of the extremities. The eruption may spread to the trunk in a centripetal fashion. Palms, soles, and face are frequently involved (Fig. 26.1). Less commonly, other presentations, such as nail fold edema and grouping of lesions around the elbows and knees, may be observed.

The lesions may appear on areas of previous physical trauma or sunburn, suggesting a Koebner (isomorphic) phenomenon. Photo-sensitive variants of EM and distribution along the lines of Blaschko have also been reported.

Mucosal Lesions

Mucosal lesions are reported in as many as 60–70 % of EM patients. They usually appear simultaneously with skin lesions but can also precede or follow the cutaneous eruption within a time frame of several days. Isolated mucosal involvement is rare.

The most commonly affected mucous membrane sites are the oropharynx (lips, palate, and gingiva) (Fig. 26.3), conjunctivae, and the anogenital area, but potentially all mucosal sites may be involved. Initial presentation of mucosal EM is with erythema and edema, sometimes flaccid bullae, which rapidly progress to superficial erosions. Occasionally, the erosive areas may be extensive. When the lips are involved, they are covered by hemorrhagic crusts. Interestingly, a study in patients with recurrent EM with oral lesions showed that recurrent attacks have different site distribution from initial attacks, with a greater proportion having genital as well as skin and oral mucosal involvement.

The genital areas are affected in about 25 % of cases. The typical EM lesions at this site comprise painful, hemorrhagic bullae, and erosions.

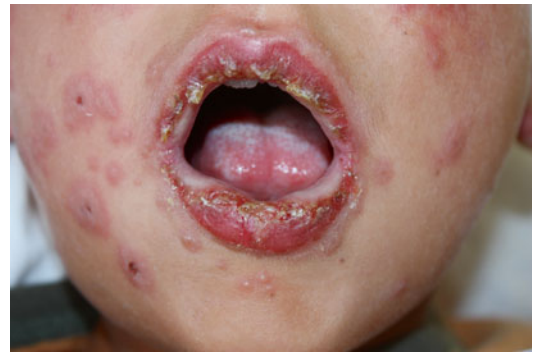

Fig. 26.3 EM major in a child after *M. pneumoniae* infection

Eye involvement (9–17 %) is usually mild and may present as injection of the conjunctivae, chemosis, and lacrimation.

Clinical Course and Prognosis

Mild cases of EM are usually self-limited. In EM minor, the lesions develop over a period of 3–5 days and subside within 2–3 weeks without sequelae. The whole duration of the process is usually less than 4 weeks. Post-inflammatory discoloration may persist for several months after disease resolution. Scarring is not a feature, except after secondary infection. Despite the benign course, over one third of patients have repeating episodes over years (recurrent EM) or, rarely, a prolonged continuous disease without remissions (persistent EM).

EM major usually has a protracted course, and resolution may take up to 6 weeks. It is associated with higher morbidity, primarily due to the pain and functional impairment with poor oral and fluid intake. Dehydration may result from the impeded fluid intake, diarrhea from bowel mucosal involvement, increased sweating due to elevated body temperature, and evaporation through denuded areas of skin. Rare serious complications include conjunctival scarring and permanent visual loss in ocular involvement, genital synechiae, esophageal strictures, and upper airway erosions leading to pneumonia.

The mortality rate in EM major is less than 5 % and correlates with the affected total body surface area with sepsis being the principle cause of death. Advanced age, visceral involvement, increased serum urea nitrogen level, and previous bone marrow transplantation are poor prognostic factors.

Diagnosis

EM is primarily a clinical diagnosis with clue findings in the history and clinical presentation. The important points in the clinical history include acute presentation with episodic and self-limiting course, temporal association with infections, and use of new medications. The typical clinical presentation includes target lesions in mainly acral distribution with or without mucosal involvement.

There are no laboratory tests that confirm or refute the diagnosis. In severe cases an array of nonspecific findings, such as elevated ESR, leukocytosis, thrombocytopenia, and mild anemia, is expected. Electrolyte disturbance can also develop due to the dehydration.

Histopathologic examination of a biopsy specimen is useful to confirm the diagnosis of erythema multiforme (EM) and discriminate it from other clinically similar diseases in the differential diagnosis. Histologically, EM is characterized by basal cell hydropic degeneration with apoptosis of the keratinocytes and lymphohistiocytic infiltrate along the dermoepidermal junction and around the superficial vascular plexuses. Apoptotic keratinocytes may be focal in the basal layer or affect the whole epidermis. Pronounced basal cell hydropic degeneration may result in subepidermal clefting and vesiculation.

Histological presentation depends on the evolutionary stage of the lesion and the site of biopsy. In early lesions and from the periphery, the changes may be predominantly dermal with edema of the papillary dermis with chronic inflammatory cell infiltrate and red blood cell extravasation. Epidermal changes are more prominent in evolving lesions and from the central portions of the target lesions.

Blistering lesions with nonspecific histological features might require direct immunofluorescence (DIF) to exclude immunobullous disorders. In EM the DIF findings are usually nonspecific and include granular deposition of C3 and immunoglobulin M (IgM) at the dermoepidermal junction and around the superficial blood vessels. Homogeneous C3 and IgM can be observed in regions of epidermal necrosis.

Differential Diagnosis

In typical EM, the clinical presentation and history are usually sufficient for a straightforward diagnosis. Nevertheless, it is very important to exclude other possible diseases that can resemble EM but have a more serious prognosis. Mimickers of EM include SJS, fixed drug eruption, vasculitis, bullous pemphigoid, paraneoplastic pemphigus, Behcet's disease, Rowell's syndrome, polymorphous light eruption, and Sweet's syndrome.

SJS is a distinct entity with similar mucosal lesions but a different pattern of cutaneous involvement. In SJS the eruption is usually widespread and comprises erythematous or purpuric macules or flat atypical targetoid lesions. Acral predominance is not a feature. Medications are the main culprit for SJS. Timely diagnosis of SJS is essential as it may have function-threatening and life-threatening complications and may progress to toxic epidermal necrolysis.

Immunobullous disorders usually have insidious onset and protracted, chronic course. DIF is positive with a characteristic histological presentation. The Nikolsky sign is negative in EM and positive in the immunobullous disorders.

Fixed drug eruption may look like EM clinically and histologically, but usually there is one single or just a few lesions and the infiltrate extends deeper and contains sparse neutrophils with prominent melanin incontinence. History of starting new medication within the previous 2 months is usually present.

Rowell's syndrome is a rare clinical entity with lupus erythematosus and EM lesions. It is now believed to be a form of subcutaneous lupus

erythematosus presenting with EM-like lesions. In Rowells' syndrome, DIF shows continuous granular immunoglobulin and complement deposits, a speckled ANA pattern, and sometimes positive rheumatoid factor, anti-Ro, and anti-La antibodies. Chilblains are usually a part of the clinical presentation.

Polymorphous light eruption (PMLE) may present with EM-like lesions, and clinical and histological distinction is challenging. In PMLE the vacuolar interface reaction and epidermal necrosis are rarely seen. Photo-distribution, seasonal recurrence, and lack of prior HSV infection may be clue to the diagnosis, but it should be borne in mind that cases of photo-incited or photo-aggravated EM have also been reported in the literature.

General Principles of Treatment

The treatment strategy for a patient with EM would depend on the type, severity, site of involvement, and triggering factors, with special consideration for underlying conditions or age. The cause for EM development should be identified when possible. If a medication is suspected to be the inciting stimulus, it should be discontinued as soon as possible. This includes all drugs and herbal supplements introduced within 2 months of presentation. Suspected or known preceding infections should be treated accordingly after confirmatory cultures and/or serologic tests.

Symptomatic therapy should be the mainstay in every patient with EM. This includes oral antihistamines, analgesics, local skin care, and soothing mouthwashes. Mild EM is usually self-limited, and specific treatment is not required, unless recurrent or persistent. In severe cases of EM major, though, appropriate therapeutic and prophylactic measures are indispensable. Local supportive care for anogenital, upper respiratory tract, and ocular involvement is very important to prevent serious complications (Table 26.2).

Table 26.2 Treatment options for isolated, recurrent, and persistent EM

Type of EM	Treatment options (suggested dosage and treatment duration)
Isolated episode	Topical antiseptics
	Oral antihistamines
	Topical corticosteroids
	Systemic antibiotics (when bacterial infection present) (treatment dosage and duration should be according to the type of infection)
	Oral corticosteroids in severe mucous membrane involvement (40–60 mg/daily in tapering doses)
Recurrent and persistent EM	Antivirals (acyclovir 400 mg/2× daily, valacyclovir 500 mg/day, famciclovir 250 mg/2× daily) (treatment should continue for at least 6 months up to 2 years)
	Oral corticosteroids (1–2 mg/kg/day in slowly tapering doses)
	Dapsone (100–150 mg/daily)
	Azathioprine (100–150 mg/daily)
	Mycophenolate mofetil (≤2 g/daily)
	Cyclosporine
	Thalidomide (100 mg/daily for suppression of a recurrent episode or 50 mg/daily to maintain remission)
	Immunoglobulins

Isolated Episode of EM Minor

Isolated occurrence of EM is most commonly associated with HSV infection, but antiviral drugs do not change the course of an already developed post-herpetic EM. Mild cutaneous involvement usually resolves within several weeks, but symptomatic improvement for occasional burning or pruritus may be achieved by using oral antihistamines or topical corticosteroids. For erosions developing from bullous EM lesions, topical antiseptics and wound care are sufficient to prevent secondary infection, and analgesics are useful to manage the pain. In cases of extensive involvement, the use of liquid antiseptics, such as 0.05 % chlorhexidine, during bathing may also decrease the risk of superinfection.

Isolated Episode of EM Major

The treatment for cutaneous lesions should be the same as in EM minor. The approach to mucosal lesions should depend on site and severity. Minimal involvement, presenting as several painful erosions, can be managed with oral antiseptic washes, oral anesthetic solutions, and high potency corticosteroids in gel or spray form.

For extensive mucosal involvement, some authors recommend the use of systemic steroids (such as prednisone 40–60 mg with tapering over 2–4 weeks). However, this approach remains controversial, and others believe that systemic steroids protract the course of the disease. There are no controlled studies in the literature, and all data for application of systemic steroids in EM is based on personal observations. A study of 25 patients, randomized into two groups, one on supportive treatment plus systemic steroids and one on supportive treatment only, found no outcome difference in the two groups. To achieve maximum benefit and to avoid possible side effects, advocates of systemic steroids, however, emphasize on the early administration of a high dose for a short period of time.

Early ophthalmologic consultation is important in the evaluation and management of eye involvement with daily examinations for signs of complications. Local supportive care includes topical lubricants for dry eyes, sweeping of conjunctival fornices, and disruption of fresh synechiae with the help of lubricating or antibiotic eye drops. Administration of eye preparations should be at the discretion of the ophthalmologist, and all procedures should be carried out by the appropriate specialist.

Hospitalization is usually not required for EM patients, except in the rare cases of life-threatening complications such as dehydration, severe electrolyte imbalance, or secondary infection.

Recurrent and Persistent EM

Treatment of recurrent EM is a challenge for the dermatologist. In HSV-associated or idiopathic EM, the first-line management is long-term prophylaxis with antiviral medications. The treatment target for long-term acyclovir is the reduction of HSV recurrences and, consequently, of EM episodes. Several ways of administration have been used, including continuous oral therapy, intermittent oral therapy, and topical therapy, but continuous oral antivirals for at least 6 months remain the most effective approach. Topical application failed to reduce the frequency or severity of EM episodes.

Acyclovir at a dose of 400 mg twice daily is usually the preferred agent, but in acyclovir-resistant cases, other agents, such as valacyclovir at a dose of 500 mg once daily or famciclovir, can be a worth-to-try alternative. The treatment should continue for at least 6 months, and any extension should be according to the clinical response. Doses of antiviral drugs may be doubled in recalcitrant cases.

Once achieved, remission is usually difficult to maintain after treatment discontinuation. In case of relapse of EM, patients who responded well to treatment should restart the antiviral agent at the lowest effective dose and continue the therapy for 6–12 months.

Multiple therapeutic agents have been tried for recurrent EM resistant to prophylactic antiviral treatments. These include dapsone, azathioprine, mycophenolate mofetil, thalidomide, cyclosporine, hydroxychloroquine, and cimetidine. Unfortunately, the scarcity of literature data and the limited experience with these agents impede guidance on the most optimum period of treatment.

Dapsone is a drug with antibacterial, anti-inflammatory, and immunomodulatory effects. In a series of nine patients with treatment-resistant recurrent EM, eight had complete or partial remission with dapsone at a dose of 100–150 mg/day (Schofield et al. 1993). Another study identified ten patients at dapsone therapy (dose <200 mg/day) with three complete and two partial remissions (Wetter and Davis 2010). Isolated case reports claim dapsone is also effective in persistent EM. Dapsone treatment should be initiated after testing for glucose-6-phosphate dehydrogenase deficiency and requires close

monitoring for adverse events, including hemolytic anemia, methemoglobinemia, and agranulocytosis. Interestingly, dapsone was reported to induce EM with neutropenia in a patient with IgA linear dermatosis.

Azathioprine has been used with variable success in patients who are not responsive to antiviral therapy. Most of the patients reported in one study of recurrent EM had a dose-dependent remission (at doses 100–150 mg/day) but relapsed after treatment discontinuation.

Mycophenolate mofetil has also shown efficacy in the treatment of EM. Complete or partial remission was reported in about 75 % of patients treated with ≤2 g/day.

The clinical experience with *cyclosporine* for treatment of EM is limited. An intermittent short therapeutic course with initiation of treatment within 1–2 days of the onset of a new episode has been proposed as an effective and safe alternative to long-term treatment.

Thalidomide is effective to suppress a recurrent episode of EM at a dose of 100 mg/day or to maintain remission at a lower dose. It could be used as an intermittent therapy for new episodes of recurrent EM or as a continuous course in persistent EM.

Other treatments, such as antimalarials, immunoglobulin, and cimetidine, represented an effective treatment for isolated cases of patients with EM, but the controversial results and limited number of reports preclude correct analysis of the results and treatment recommendations.

Topical tacrolimus 0.1 % cream was used in one patient to achieve faster resolution of cutaneous lesions and induce remission.

Treatment of EM in Children

Treatment principles in children should follow the guidance for adults with age-dependent modifications in drug therapy and dosage. Supportive care is first-line in the management plan, and in almost all reported cases, it suffices on its own. Systemic steroids could be used in severe cases when the potential benefits outweigh the possible risks. Recurrent and/or persistent cases have not been reported in children, and immunosuppressive agents are not used to treat EM in this population group.

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Erythema Nodosum

27

Eva Remenyik

Key Points

- Erythema nodosum is an inflammation of the subcutaneous tissue (panniculitis), usually appears in acute fashion. It may recur but is rarely chronic.
- Histopathologically the mixed inflammatory cells involve the septa of the panniculus without vasculitis.
- Erythema nodosum is a secondary hypersensitivity reaction to a known or unknown antigen.
- Underlining causes always have to be vigorously investigated.
- The diagnosis is mostly based on case history and the clinical picture. Deep biopsy is rarely needed to differentiate from other nodular inflammatory lesions mainly from vasculitides and other panniculitides.
- The first step of treatment is to eliminate the antigen (or aggravating factor) and treat the underlying disease.
- Symptomatic treatment is also indicated:
  - Physical: bed rest, elevation of the limbs, cold compresses, elastic bandage
  - Topical: anti-inflammatory (aluminum salt, NSAID)
  - Systemic: NSAID, antihistamines, corticosteroids, antibiotics, potassium iodine, colchicine, dapsone, hydroxychloroquine, thalidomide

Definition and Epidemiology

Erythema nodosum (EN) is typically characterized by suddenly symmetrically appearing deep painful red nodules on the pretibial area. It rarely recurs, but in some cases it becomes chronic. Histopathologically EN is a septal panniculitis without vasculitis. It is presumed a hypersensitivity reaction. The most common underlying causes are infections, inflammatory bowel diseases, sarcoidosis, drugs, and it can also be idiopathic. It is self-limited but reacts well and rapidly to anti-inflammatory therapy, healing without any remaining sign.

Basic Concepts of Pathogenesis

EN is probably a hypersensitivity reaction to a known or unknown antigen. Antigens from the underlying primary disease initiate the inflammatory process most likely via delayed-type hypersensitivity reaction, but the role of immune complexes is also suspected especially in inflammatory bowel disease-associated EN.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_27, © Springer-Verlag Berlin Heidelberg 2015

Table 27.1 Possible etiologic factors of erythema nodosum

			Incidence (%)
Unknown	Idiopathic		50–55
Physiological conditions	Gravidity		2–5
Drugs	Antibiotics	Sulfonamide, amoxicillin	3–4
	Oral contraceptive		
Diseases	Infective		
	Bacterial	Streptococcal infection (tonsillitis)	20–40
		Bacterial gastroenteritis: *Yersinia*, *Campylobacter*, *Salmonella*; other bacterial: *Mycobacteria*, *Rickettsia*, *Brucella*, *Bartonella*, *Treponema*	
	Viral	Mostly upper respiratory, but hepatitis B	
	Fungal	Coccidioidomycosis, blastomycosis	
	Parasitic	Giardiasis	
	Chronic inflammatory	Sarcoidosis	10–20
		Inflammatory bowel diseases mostly Crohn	1–4
		Neutrophilic dermatoses (Behcet's disease, Sweet syndrome)	
	Malignancy	Acute myelogenous leukemia	
		Hodgkin disease	

Histopathologically there is a mixed inflammatory infiltrate in the septa of the panniculus and the overlying dermis without evidence of vasculitis. Neutrophils may predominate during early septal edematous change but eosinophils may also be present. A characteristic feature is Miescher's granuloma (a group of histiocytes surrounded by neutrophils); giant cells are also frequently seen. Latter perivascular lymphocytic infiltration predominates with fibrosis.

A physician diagnosing EN always has to consider it as a secondary disease, and underlying causes must be sought. Possible initiating causes are shown in Table 27.1. Among them, streptococcal infection is the most common in children and adults besides sarcoidosis and inflammatory bowel disease.

Clinical Presentation

Suddenly appearing painful 2–5 cm-diameter red tender nodules develop symmetrically on the anterior shins (see Fig. 27.1). Pain can be

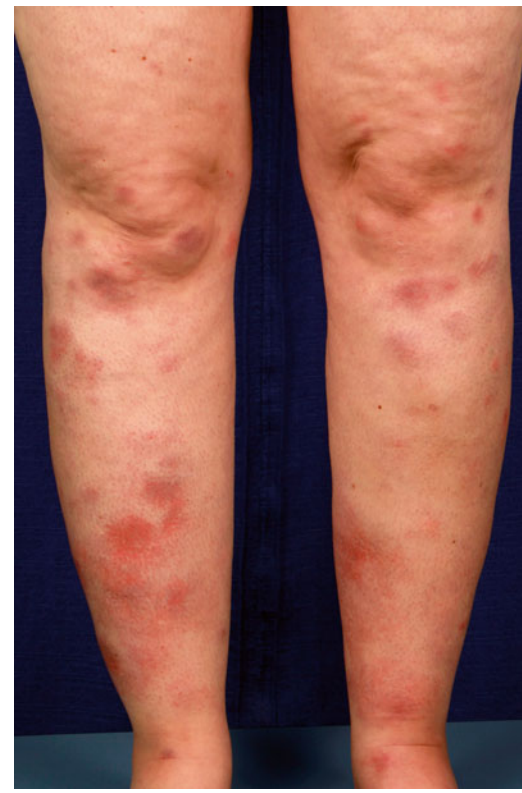

Fig. 27.1 Red painful nodules symmetrically on the shins

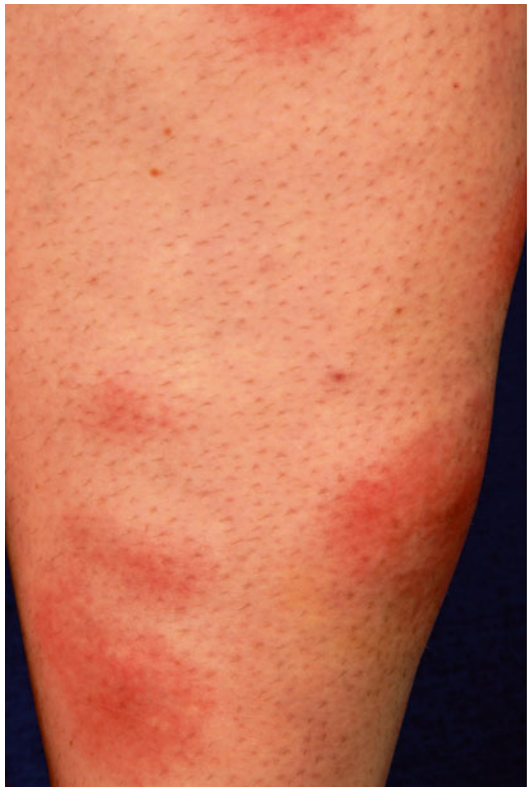

Fig. 27.2 Closer view of nodules

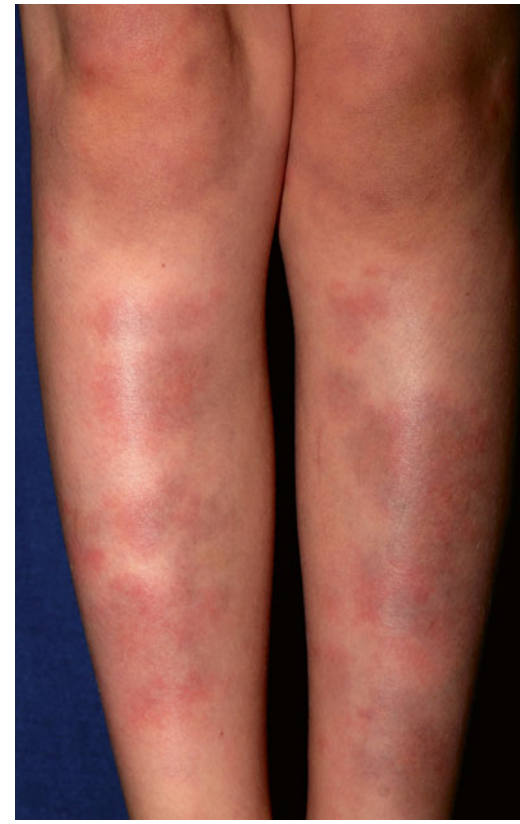

Fig. 27.3 Erythema nodosum, nodules in resolution stage: bluish color

disabilitating. The skin is usually elevated at the center of the nodule with poorly defined borders and more intensive bright red color in the middle during the acute eruptive phase (see Fig. 27.2). The color of the nodules may at times also be violaceous especially during the resolution phase turning to yellow, resembling a bruise (see Fig. 27.3). Suppuration and ulceration never develop. Sometimes only one nodule appears, but more often simultaneously and consecutively multiple lesions appear. Although extensor surface of the lower extremities is the typical site of the lesions, it is not rare for the nodules to present on thighs and arms or other body areas. Regional lymph node enlargement does not accompany the deep inflammation. Half of the patients experience joint pain mainly at the early development of the skin symptoms or preceding them. Signs of systemic inflammation like fever, flu-like syndromes can precede and/or accompany the development of skin symptoms. Nodules can spontaneously resolve, but frequently patients seek medical care. Skin symptoms heal without scar formation. The nodules recur in a third of the patients (mainly in idiopathic cases), and rarely they may also remain chronic. The later the discoloration of the affected area takes place, usually the more brownish the nodule becomes and the less elevated the central portion of the nodule will be. These lesions also show a tendency for centrifugal spread.

Regardless of the initiating cause, the skin symptoms of EN are the same, but systemic complaints sometimes are modified by the symptoms of the underlying conditions.

Differential Diagnosis

In typical cases, the clinical picture is characteristic, and the diagnosis can be established without the need for biopsy and histopathology. If biopsy is needed it has to be deep enough to reach the subcutaneous fat and provide optimal amount of tissue sample from the inflammatory site. Usually incisional biopsy is preferred, but a double punch, with a larger-diameter superficial punch biopsy followed by a deeper smaller punch of the subcutis, may prove sufficient.

In everyday clinical settings on the first examination, erysipelas/cellulitis, thrombophlebitis, insect bite, or sometimes urticaria are the most common differential diagnoses. After ruling out these diseases, other panniculitides and vasculitides have to be considered (see Fig. 27.4). EN leprosum is a separate disease characterized histopathologically with small vessel vasculitis.

General Principles of Treatment

EN is usually self-limited, and its outcome is not independent of the course of the underlying disease. Therefore the therapy is often only symptomatic besides eliminating or treating aggravating causes. These latter interventions include discontinuation of possible aggravating drugs and initiation of adequate antimicrobial treatment if infection is suspected and intensification of regimen for underlying chronic uncontrolled diseases.

Physical pain relief methods (bed rest and cooling the inflamed skin) are the bases of symptomatic care. EN quickly responds to systemic steroid, but in most cases its use is neither recommended nor necessary. Therapeutic options consist mainly of nonsteroidal anti-inflammatory drugs (NSAID) but are also influenced by the underlying conditions.

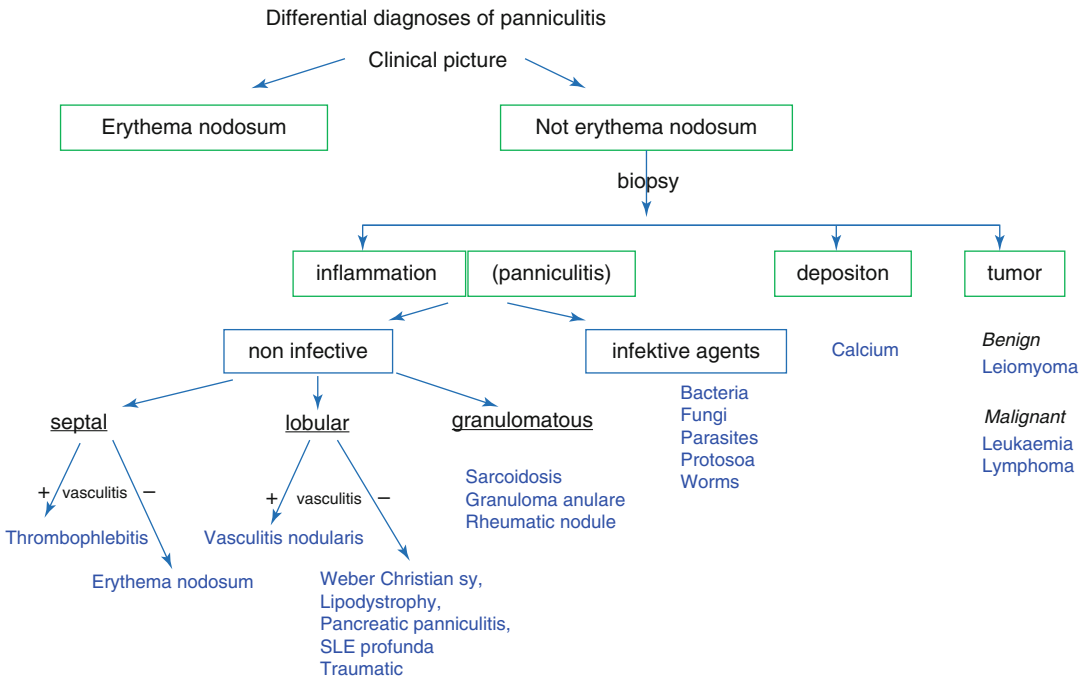

Fig. 27.4 Differential diagnosis of erythema nodosum after emergency

Topical Treatments

Given the experienced pain, patients usually intuitively find relief in bed rest. Nevertheless physicians have to counsel patients to avoid physical activity and potential trauma. Moreover physical cooling of the inflamed area with cold compresses or ice packs helps also reduce subjective complaints. Elastic bandages or low pressure compression stockings are also recommended. Solutions with aluminum salt in cold compress and also in barrier creams further increase anti-inflammatory effects of topical therapy. Topical NSAIDs may also be used but their higher sensitizing potential has to be considered. Potent topical corticosteroids can also be applied. Some reviews mention intralesional injection of corticosteroids, but only based on anecdotal evidence. In resolving phase Ichthyol can enhance the healing process, but its effect is also based on only personal clinical experiences.

Topical Treatments at a Glance

- Bed rest
- Cold compress
- Elastic bandage

Systemic Treatments

It is crucial to *treat the underlying disease*. However, in most EN cases systematic therapy is needed to reduce pain and speed up recovery even before the initiating factor is identified.

Salicylates and other *NSAID*s are the most commonly recommended drugs. Their main effect is inhibition of cyclooxygenase enzyme producing pro-inflammatory mediators like prostaglandins. NSAIDs modify cytokine production of T cells. They are recommended in the regular anti-inflammatory dose. Pain and subjective symptoms react quicker than inflammation. Continuous treatment is necessary for a few weeks, sometimes for an even longer period. The most frequently observed side effects are gastrointestinal, including hyperacidity, impairment of renal function, and also allergic reactions.

Important warning! NSAIDs have to be avoided in inflammatory bowel disease-associated EN, because they may trigger exacerbation of bowel symptoms or compromise maintenance therapy.

Systemic Corticosteroids As potent anti-inflammatory drug with immunosuppressive effects, corticosteroids effectively control EN. Clinical symptoms react very well and rapidly to systemic administration of corticosteroids. The severity of the symptoms of EN and the underlying diseases determine their indication. It is recommended if NSAIDs fail to reduce pain and inflammation. Concomitant infection should be ruled out or treated with suitable anti-infective agent (antibiotics, antimycotics, antimycobacterials). Usually 0.5 mg/kg body weight prednisone-equivalent dose substantially alleviates the symptoms within 24 h. The dose should be gradually tapered according to the clinical symptoms and also to the underlying disease. Meanwhile other causative agent-dependent treatment can also be recommended. Well-known side effects of systemic steroid therapy have to be considered and preventive management has to be initiated.

The use of *potassium iodine* solution is another systemic therapeutic option in EN. Daily dosage is 300–1,500 mg orally for adults. For better palatability dissolving the recommended amount in fruit juice or water is recommended. Its exact effect is not well established. It is thought to help in EN by suppression of neutrophil ROS release and chemotaxis and by inhibition of cell-mediated immunity via induction of heparin release from mast cells. For the onset of therapeutic benefit, usually at least 2 weeks is needed. Thyroid gland function before and during the application has to be checked. Acute side effects are nausea,

bitter taste, excessive salivation, and allergic reactions (urticaria, cutaneous small vessel vasculitis). Occasionally chronic side effects also can be seen. These include enlargement of salivary and lacrimal glands, acneiform eruptions, and hypothyroidism or rarely hyperthyroidism.

Colchicine is an antimitotic agent and arrests cell division by interfering with microtubule and mitotic spindle formation, and it also has direct anti-inflammatory effect by reducing neutrophil chemotaxis and adhesion to endothelial cells by decreasing expression of adhesion molecules. It is widely used in acute gout. There is empirical evidence that Behcet's disease-associated EN reacts well to colchicine and recurrences are also decreased by this medication. It can also be effective in EN associated with other conditions. Close monitoring is required during the therapy because colchicine has relatively low therapeutic index. Kidney failure contraindicates its usage. Hematological side effects are relatively common (anemia, neutropenia) and peripheral neuropathy can occur.

Dapsone (diaminodiphenyl sulfone) is an antibacterial drug commonly used in the treatment of leprosy in combination with other agents. It inhibits bacterial synthesis of dihydrofolic acid via direct structural competition for dihydropteroate synthetase. It also has anti-inflammatory and immunomodulatory effects most likely by inhibiting myeloperoxidase in neutrophils. Dapsone is mainly used in EN leprosum, but it can be considered in classical EN refractory to conventional therapy, especially EN in Behcet's disease. Hematologic side effects are the most pronounced including methemoglobinemia, aplastic anemia, leukopenia, agranulocytosis, eosinophilia, and macrocytic anemia. Hemolytic anemia is more likely with doses greater than 200 mg/day or in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before initiation of the drug, G6PD activity should be determined; if it is not available, closer monitoring of the red blood cell count, methemoglobin level, and evidence of hemolysis should be performed besides monitoring for clinical symptoms of peripheral neuropathy. Dizziness, vertigo, blurred vision, and headache have also been reported as side effects of dapsone.

Hydroxychloroquine is an antimalarial agent also used in rheumatoid arthritis, lupus erythematosus, and some other photosensitive and inflammatory skin conditions. Its anti-inflammatory mechanisms are broad, involve immunocomplex production and T cell-mediated immune response, inhibit lysosomal enzymes, reduce ROS and nucleic acid synthesis, and also reduce antigen presentation by macrophages. It is mainly used and indicated in EN associated with Behcet's disease and EN leprosum. Hydroxychloroquine is usually well tolerated. Leukocytopenia and gastrointestinal and eye side effects rarely appear. During a long-term use, minimum yearly ophthalmologic examination has been previously advised, although recent evidence questions the cost-effectivity of this practice, and after good triage of patients for risk, less frequent follow-up is acceptable.

Thalidomide Launched as a hypnosedative drug in the 1950s, thalidomide later turned out to induce birth defect and was withdrawn from the market due to its teratogenicity. After the discovery of its excellent effect in EN leprosum, it was relicensed in some countries and since has proven its therapeutic efficacy in several autoimmune and inflammatory diseases. Thalidomide has FDA approval only for treating EN leprosum and multiple myeloma. Thalidomide can directly inhibit angiogenesis induced by bFGF or VEGF, also inhibit IL-6 and TNF alpha secretion, activate apoptosis, and increase NK-dependent T cell cytotoxicity. It has immunomodulating effects on the innate and adaptive immune system, as well as on tumorigenesis and angiogenesis. A wide variety of diseases, several dermatological conditions among them (Kaposi sarcoma, lupus erythematosus, prurigo nodularis, erythema nodosum, Behcet's syndrome, Langerhans cell histiocytosis, graft-versus-host disease, cutaneous sarcoidosis, erythema multiforme, Jessner-Kanof lymphocytic infiltration of the skin, lichen planus, melanoma, pyoderma gangrenosum, and uremic pruritus), have been successfully treated

with thalidomide. Due to its teratogenicity, proper contraception (two different methods) is inevitable during its use. In everyday practice, neuropathy is the most limiting side effect, but prescribing physicians need to also be aware of the relative frequency of anemia, leukopenia, constipation, and susceptibility to deep vein thrombosis. With close monitoring and good counseling, several patients may benefit from thalidomide therapy.

TNF-a Inhibitors TNF alpha is a key cytokine in granulomatous inflammation. Its inhibitors reduce chronic inflammation in rheumatoid arthritis and psoriasis. Moreover, it has been published to be effective in EN refractory to conventional therapy. Receptor antagonist etanercept in sarcoidosis-associated EN and chimeric immunoglobulin G1 monoclonal antibody (infliximab) in inflammatory bowel disease-associated EN had therapeutic benefit according to some reports.

Other immunosuppressants and chemotherapeutic agents (azathioprine and methotrexate, cyclosporine) have also been shown to have benefit in some forms of EN.

From the treatment choices, physicians should choose the best according to the possible or proven underlying/aggravating agent (*see in* Table 27.1) *and also consider that most of the drugs recommended based on case reports and personal experiences are off-label.*

Systemic Treatments at a Glance

Treat underlying infection or disease

- NSAID
- Corticosteroids
- Potassium iodine
- Colchicine
- Dapsone
- Hydroxychloroquine
- Thalidomide
- TNF alpha inhibitors

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Erythrasma

28

Alexander Yu. Turkevych

Key Points

- Erythrasma is a chronic superficial infection of the intertriginous areas of the skin that causes brown, scaly skin patches. It occurs most often between the third and fourth toes, but it can also frequently be found in the groin, armpits, and under the breasts.
- Erythrasma is caused by the Gram-positive bacterium *Corynebacterium minutissimum*, which usually is present as a normal human skin inhabitant.
- The diagnosis can be made on the clinical picture alone.
- Erythrasma can be treated with topical fusidic acid or topical erythromycin gel or clindamycin solution twice a day for 2 weeks. Extensive infection may benefit from the treatment with systemic macrolides.

Definition and Epidemiology

Erythrasma is a chronic superficial infection of the intertriginous areas of the skin that causes brown, scaly skin patches. It presents as a slowly enlarging area of pink or brown dry skin. It occurs most often between the third and fourth toes, but it can also frequently be found in the groin, armpits, and under the breasts. Because of the color and location, it is often confused with a fungal infection like jock itch.

It is usually reported in the literature that the incidence could be over 20 % in general population. Erythrasma is caused by the Gram-positive bacterium *Corynebacterium minutissimum*, which usually is present as a normal human skin inhabitant. This may coexist with the dermatophyte fungi or with *Candida albicans*. It is prevalent among diabetics and the obese and also in warm climates. Wearing occlusive clothing can worsen erythrasma.

Clinical Presentation

The patches of erythrasma are initially pink but progress quickly to become brown and scaly (as skin starts to shed), which are classically sharply demarcated. Erythrasmic patches are typically found in intertriginous areas (skinfold areas – e.g., armpit, groin, under breast). The slightly webbed spaces between toes (or other body region skinfolds) can be involved, making it

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_28, © Springer-Verlag Berlin Heidelberg 2015

difficult to distinguish from various tineas. The patient is commonly otherwise asymptomatic. Occasionally, itching, or burning sensation, may start because of sweating. Without treatment, lesions can persist for months, with exacerbations during the summer.

Diagnosis

The diagnosis can be made on the clinical picture alone. However, to tell the difference between erythrasma and a fungal infection is to do a Wood's lamp examination on the rash. Under the UV light of a Wood's lamp, erythrasma turns a bright coral red, but fungal infections do not. Some other tests that may help include Gram stain (Gram stain of erythrasma shows delicate Gram-positive rods and filaments in the cornified layer), hematoxylin-eosin stains (there is orthokeratosis within which blue-staining organisms in the form of delicate rods and filaments can be found), and KOH test (test used to identify fungal elements and might be done to confirm that there is no fungus present). Also skin biopsy can be done, if necessary. In the case of erythrasma, the bacteria can be seen in the upper layer of the specimen.

Erythrasma can easily be missed on routine histopathologic sections as the inflammatory response is typically minimal; well-established lesions will reveal a sparse superficial perivascular infiltrate of lymphocytes.

Differential Diagnosis

The main differential diagnoses are with the diseases involving intertrigo, tinea cruris or pedis, and candidal intertrigo.

Pityriasis versicolor – *Malassezia* (formerly known as *Pityrosporum*) yeasts colonize the stratum corneum and also fail to elicit much of an epidermal response. The yeast forms are larger than *Corynebacteria* and fail to stain with Gram stain.

Pitted keratolysis – this may be indistinguishable from erythrasma without clinical correlation.

Also erythrasma may be confused with impetigo, contact dermatitis, inverse psoriasis, and seborrheic dermatitis.

General Principles of Treatment

General Recommendations

Regular washing with antiseptic is helpful during the treatment and may prevent relapses.

Given the fact that there is a pronounced tendency to recurrence, the intertriginous areas should be kept dry, with the use of suitable powders, while clothes and/or shoes should be appropriate.

Topical Treatments

Erythrasma is treated with topical fusidic acid or topical erythromycin gel or clindamycin solution twice a day for 2 weeks.

Systemic Treatments

Extensive infection can be treated with systemic macrolides:

- Erythromycin 250 mg four times a day for 7–10 days
- Clarithromycin 1 g once
- Azithromycin 1 g once

There is no sure way of knowing which of the above treatments should be preferred. It seems that systemic treatment is more effective. The disappearance of the red-coral fluorescence confirms the efficacy of the treatment. A brownish hyperpigmentation can persist for a while.

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Erythroderma

29

Annalisa Patrizi and Michela Venturi

Key Points

- Erythroderma (E), also named exfoliative dermatitis, is a rare severe skin disease and represents an extreme state of skin irritation involving the whole or most (more than 90 %) of the skin surface. The resulting failure of the skin functions can coexist with other organ failures, so E is potentially life-threatening.
- E may arise from or be caused by a preexisting dermatosis, a drug-induced reaction, a malignancy, an infection, a miscellaneous of rare diseases or may represent an idiopathic disorder. In this last case, the term "red man" may be used when no primary cause can be found, despite serial examinations and tests.
- Idiopathic E begins as a patch(es) of erythema accompanied by pruritus. The patch(es) enlarges and coalesces to form extensive areas of erythema which eventually spread to cover the whole or most of the skin surface. E is also associated with profuse scaling, which has its onset 2–6 days after the erythema with individual variations. In the acute form of E, the formation of large scales is typical, while the chronic form is frequently characterized by small scales. The skin is notably dry, hot, and indurated. Mild to severe pruritus is usually present. Malaise and fever may occur.
- Since E is mainly a secondary process, it is mandatory to establish its etiopathogenesis in order to facilitate its correct management. The diagnosis is mainly based on histology; immunocytochemistry (ICC) and molecular biology techniques can be helpful.
- E is a serious disease; in fact the mortality rate is around 18–64 % on the basis of its different etiology. The management frequently requires hospitalization, as well as general and local treatment.
- *The treatment of E* varies according to the underlying condition and includes systemic treatment as systemic corticosteroids, antihistamines, and systemic antimicrobials. Moreover, according to the underlying condition, systemic specific treatment is added.

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Definition

Erythroderma (E), first described by Hebra in 1868, is a reaction pattern, characterized by diffuse and confluent erythema with desquamation

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_29, © Springer-Verlag Berlin Heidelberg 2015

affecting most of or the entire body surface. E is usually accompanied by systemic manifestations including several metabolic changes. E may be the morphologic presentation of a variety of cutaneous and systemic diseases or, ultimately, the culmination of different skin disorders.

Its phenotype varies from mild skin symptoms to lethal forms.

E and exfoliative dermatitis are quite synonyms; however, E is the term currently preferred. Nonetheless, it is imperative to define both conditions. E is characterized by extensive and pronounced erythema with diffuse slight scaling, whereas exfoliative dermatitis presents a more conspicuous and marked scaling. The prerequisite to make the clinical diagnosis of E is a ≥90 % involvement of the skin surface.

Epidemiology

The overall precise incidence of E is difficult to define as most reports are retrospective.

E is surely a rare condition and its estimated annual incidence can vary from 1–2 per 100,000 general patients per year to 35 per 100,000 dermatologic outpatients, depending on the series. E accounts for about 1 % of all hospital admissions with dermatologic conditions. In adults a male predominance has been reported, with a male/female ratio from 2:1 to 4:1 with no racial predilection. The most frequent reported age range is from 40 to 60 years, in the published series excluding children, but any age group may be affected; however, the affected patients are usually over 45 years of age (excluding hereditary disorders/atopic dermatitis), with an average onset age of 55 years. On the Indian subcontinent, the onset age is slightly lower.

Even though E usually represents an adult disease, it shows another incidence's peak in the pediatric age. Pediatric E has a mean onset age of 3.3 years, with a male/female ratio of 0.89:1.

Basic Concepts of Pathogenesis

Adults

E may be idiopathic when the personal and family history, the physical examination, and the laboratory data are inconclusive, or E may be due to different preexisting dermatoses, drug adverse reactions, malignancies, and systemic disorders. E is considered idiopathic in 9–47 % of cases, while it may be linked to an exacerbation of a preexisting dermatosis in more than 50 % of cases; therefore, patients should be carefully evaluated for an underlying skin disease.

The subtle/sudden generalization of a preexisting dermatosis to E is an intriguing dilemma and may reflect individual variations. A detailed outline of the patient's history is important to understand the possible triggering events as infections, drugs, sun/ultraviolet light exposure, vitamin deficiency, and other factors.

In adults, the most common causes of protracted E are preexisting dermatoses, drug intake, pre-lymphomatous conditions, and occult malignancies. The underlying diseases that more frequently can cause E are eczema (40 % of cases), psoriasis (25 %), lymphomas and leukemias (15 %), drug intake, vitamin deficiency (10 %), and, more rarely, other dermatoses or skin infections and infestations (2 %) (Tables 29.1 and 29.2).

When considering a patient affected with E, the list of drugs assumed should always be asked, as E's pathogenesis may involve many drugs (Table 29.2).

Topical and systemic drugs are notorious for triggering E. The agents that mainly and most frequently induce E are calcium channel blockers, carbamazepine, phenytoin, and phenobarbital. Other medications include antibiotics, corticosteroids, diaminodiphenyl sulfone, NSAIDs, phenothiazines, antihypertensive drugs, cimetidine, lithium and gold, synthetic antimalarials, sulfonamides, peptic ulcer drugs, sulfasalazine, allopurinol, thalidomide, cytokines, trimethoprim, sodium clodronate, zidovudine, and codeine.

Table 29.1 Dermatoses and diseases associated with erythroderma

Eczema group	Atopic dermatitis
	Contact dermatitis
	Nummular eczema
	Photosensitive eczema
	Seborrhoeic dermatitis
	Stasis with autoeczematization
Infections and infestations	Candidiasis
	AIDS
	Viral hepatitis
	Staphylococcal scalded skin syndrome
	Toxic shock syndrome
	Dermatophytosis
	Scabies and Norwegian scabies
Malignancies	Leukemias, lymphomas, histiocytosis, malignant neoplasms
Inflammatory and immunological diseases	Psoriasis
	Lichen planus
	Pemphigus
	Pemphigoid
	Cutaneous graft-versus-host disease
	Dermatomyositis
	Pityriasis rubra pilaris
	Prurigo
	Subacute cutaneous lupus erythematosus
	Systemic lupus erythematosus
	Lymphomatoid granulomatosis
	Angioimmunoblastic lymphadenopathy with dysproteinemia
Rare and/or genetic diseases or idiopathic disorders	Darier's disease
	Hailey-Hailey's disease
	Ichthyosis
	Mastocytosis
	Ofuji papuloerythroderma
	Sarcoidosis
Irradiation	Actinic reticuloid syndrome (chronic actinic dermatitis)

The same drug exanthems that commonly appear as morbilliform, lichenoid, or urticarial may progress to extensive erythema and exfoliation. E onset due to drugs is typically sudden and rapid and its resolution should be faster than

Table 29.2 Drugs associated with E

Class of drugs	Drugs
Antibiotics, antimycotics, antimalarials	Actinomycin D, aminoglycosides, aztreonam
	Cephalosporins
	Clofazimine
	Chloroquine
	Clotrimazole
	Dapsone
	Hydroxychloroquine
	Isoniazid
	Mefloquine
	Minocycline
	Neomycin
	Nitrofurantoin
	Para-amino salicylic acid
	Penicillins
	Quinacrine
	Rifampin
	Streptomycin
	Sulfadiazine
	Sulfonamides
	Tetracyclines
	Trimethoprim
	Vancomycin
Anticonvulsants	Carbamazepine
	Hydantoins
	Mephenytoin
	Phenytoin
Antipsychotic	Chlorpromazine
	Lithium
	Phenothiazines
Hypoglycemics	Tolbutamide
	Chlorpropamide
	Sulfonylureas
Diuretics	Chlorothiazide
	Thiazide
Antihistamines	Cimetidine
	Ethylenediamine
Laxative	Phenolphthalein
Antidotes	Dimercaprol
Immunomodulators	Interleukin-2
	Interferon alpha
	Interferon beta
Antiarrhythmics	Amiodarone
	Mexiletene
	Quinidine
	Ranitidine

(continued)

Table 29.2 (continued)

Class of drugs	Drugs
Chemotherapeutic agents	Mitomycin-C
	Cisplatin
	Thalidomide
β2-Adrenergic receptor agonist	Terbutaline
Tetrachloroethylene	
Arsenic	
Chinese herbs	
Codeine	
Cyclobenzaprine	
Iodine	
Gold	
Mercury and mercurials	

in E induced by other causes. A different situation is E accompanied by systemic drug hypersensitivity reactions (DRESS, Drug Rash with Eosinophilia and Systemic Symptoms) due to antibiotics, anticonvulsants, and allopurinol. DRESS develops within 2–5 weeks after the start of treatment and may persist for weeks despite stopping the medication. Edema, fever, leukocytosis with marked eosinophilia, lymphadenopathy, organomegaly, and liver and renal dysfunction are characteristic of DRESS. Drug-induced E due to dapsone/antileprosy drug hypersensitivity may appear quite similar to a cutaneous T-cell lymphoma in the clinical features and histopathology. Anyway, it disappears after the withdrawal of the drug and the administration of a supportive therapy.

Lymphomas and leukemias may cause E, for instance, Hodgkin's and non-Hodgkin's lymphomas, myeloid and lymphoid leukemias, and myelodysplasia. Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome) are one of the most common malignancies associated with E. E may derive from a previous cutaneous T-cell lymphoma as a marker of progression and may appear simultaneously, or its onset may be antecedent to the cutaneous T-cell lymphoma lesions. When E precedes cutaneous T-cell lymphoma lesions, the interval between E's appearance and cutaneous T-cell lymphoma's manifestations ranges from months to years.

Acute and chronic leukemia could cause E. The relative risk of leukemia inducing E is not well definite, varying from 11 to 50 %.

Reticular cell sarcoma and malignant histiocytoses are a few other implicated conditions.

E may ultimately be one of the clinical expressions of reticuloendothelial neoplasms and internal malignancies. Malignant E invariably affects older individuals, and in the elderly age E is considered to be a cutaneous marker of an internal malignancy. Its incidence is around 1 % and about 1 % of all cases of E are due to visceral malignancies.

The suspicion of an underlying malignancy may arise when the development of E is insidious, the patient becomes progressively debilitated, no previous skin diseases are recognized, and the lesions resist to standard therapies.

In the literature, eosinophilic E is suggested to be a paraneoplastic syndrome.

Children and Neonates

In children, E due to atopic dermatitis is the most frequently observed.

Other causes of children's E are ichthyosis, Netherton syndrome, primary immunodeficiency syndromes (PIDS), and metabolic diseases in neonates (aged less than 1 month of life). Psoriasis, Omenn syndrome, seborrheic dermatitis, and atopic dermatitis usually appear after the first month of life.

The pathogenesis of E is not clarified. A complex interaction of cytokines and cellular adhesion molecules, such as interleukins 1, 2, and 8, intercellular adhesion molecule-1 (ICAM-1), and tumor necrosis factor (TNF), is considered to be responsible for E, causing a strong increase in the epidermal turnover rate. In patients with this disorder, the mitotic rate and the absolute number of germinative skin cells are higher than normal. Moreover, the time required by the cells to differentiate and travel through the epidermis is shorter. This compressed maturation process results in an overall greater loss of corneocytes, which clinically appears as scaling and shedding. Normal epidermis undergoes some exfoliation

every day, but the lost scales contain little, if any, important viable material, such as nucleic acids, soluble proteins, and amino acids. In patients with E, several pathological alterations appear, in particular regarding thermoregulation, metabolism, and water balance; in addition some laboratory parameters show abnormal values.

E causes a severe aberration of the body's metabolism. The increased skin blood flow leads to higher skin temperature and heat loss. This elicits a cold sensation that induces a higher compensatory basal metabolic activity. The patient's dehydration derives from the elevated transepidermal water loss (TEWL) and skin evaporation. Otherwise, hypoproteinemia is due to protein loss (because of the desquamation) and to the significant exudation. Hence, changes in laboratory parameters include hypoalbuminemia (brought by increased protein loss in the skin, decreased synthesis, and increased catabolism of proteins), anemia, electrolyte disturbances (hypernatremia), serum urea increase, and all alterations due to dehydration; lymphocytosis, possible eosinophilia, elevated inflammatory markers, and polyclonal gammaglobulinemia may be also observed. In specific forms of E, increased IgE serum levels or Sezary cells may be found.

Clinical Presentation

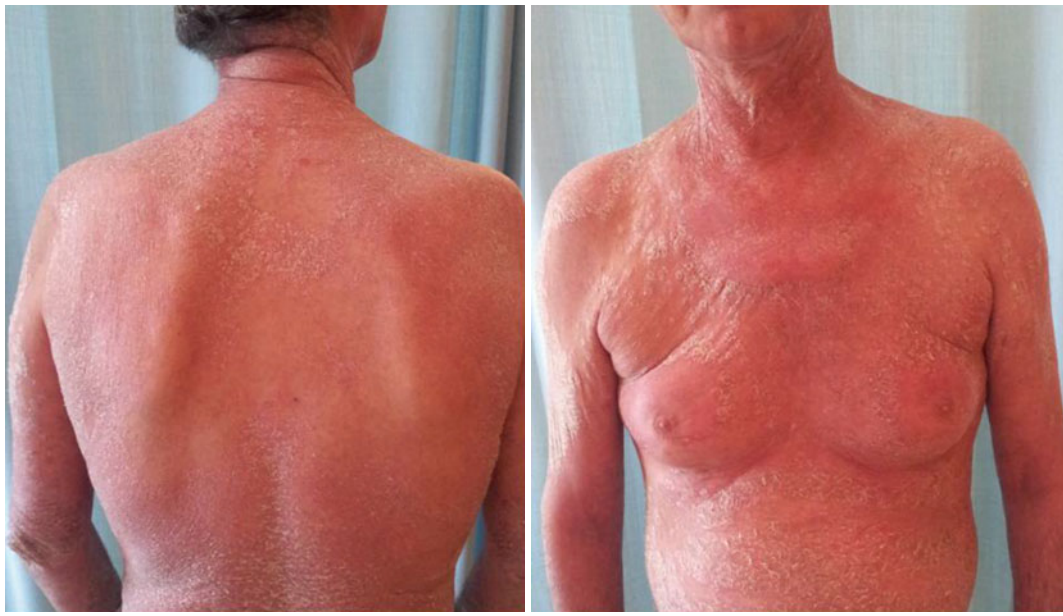
Adults

E's phenotype varies from less severe skin symptoms to lethal forms. E can erupt simply with erythrodermic features or can be the aggravation of a preexisting dermatosis. The underlying disease is hidden by the erythrodermic nonspecific inflammatory manifestations, although it could emerge again during regression. Nonetheless, E's clinical profile varies consequently to the nature of the underlying disease.

A clinical classification distinguishes three different types of E:

1. Dry with large scales E (Wilson–Brocq) (Figs. 29.1 and 29.2)
2. Dry with small scales E (Hebra)
3. Vesiculo-edematous E (Fig. 29.3)

From the clinical point of view, erythema is the first stage of primary E. It often erupts as single or multiple pruritic patches, localized most



Figs. 29.1 and 29.2 Erythroderma with large scales and skin dryness (Wilson–Brocq)

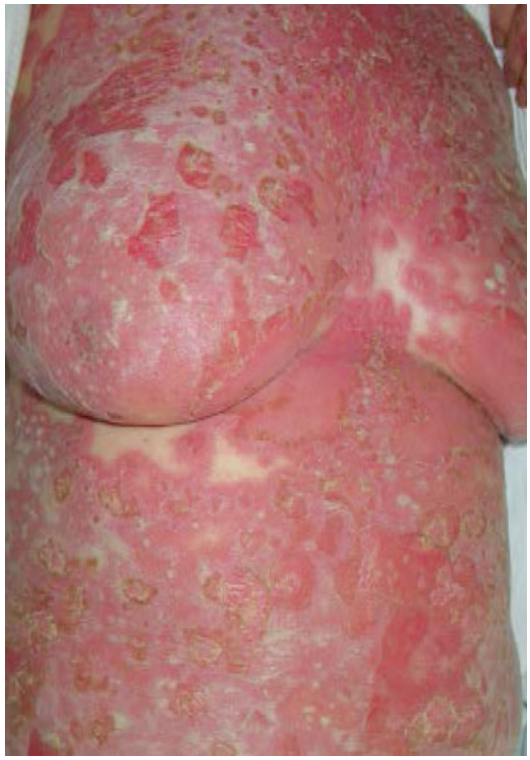


Fig. 29.3 Vesiculo-edematous E

frequently in the head, trunk, and genitalia. In a few days or weeks, they tend to spread, and an erythematous, pruritic eruption comes to cover a great part of the skin. The palms, the soles, and the mucous membranes are usually not involved. The nose and the paranasal area are sometimes not affected. This is generally referred to as the "nose sign." Two to six days after the appearance of erythema, scaling begins.

The erythema has a variable intensity and scales are dandruff-like or lamellar, large in acute forms or small in chronic cases of E. Skin failure, that is, the inability to maintain homeostatic functions, may occur. Edema is due to extravasation of proteins into the tissues because of the vasodilation. In E, the edema can be generalized or localized only on the lower limbs. In some cases, and exudation may occur.

In long-standing E, clinical presentation encompasses injuries due to scratching, dyschromia as hyperpigmentation or hypopigmentation, and palmar-plantar fissurated keratoderma when palms and soles are involved. The patient's face can present a leonine appearance and/or ectropion. Changes in skin appendages may also be observed. Alopecia and eyebrow and eyelash thinning are frequently part of the clinical profile. Nails can appear thickened, corrugated, yellowish, and friable with transverse grooves. Some alterations may involve mucous membranes: cheilitis, conjunctivitis, and stomatitis could develop. Even lymph nodes may be moderately enlarged, hard-elastic, and painless (dermopathic lymphadenopathy).

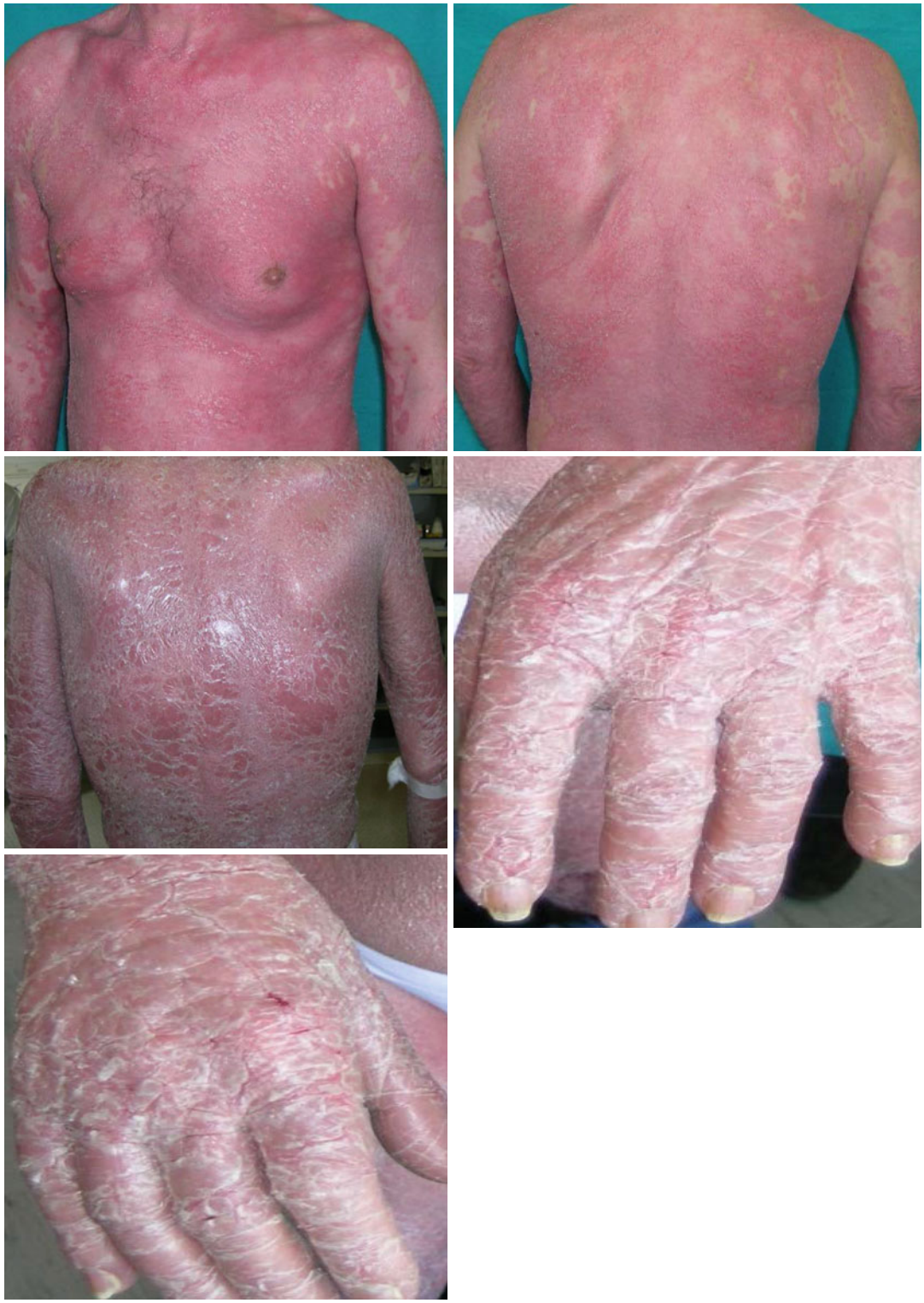
Itching, skin tension sensation (feeling tightness on the skin), and cold feeling are the subjective most frequently referred symptoms.

E may be complicated by some general signs and symptoms, such as fever, chills, asthenia, fatigue, myalgia, shortness of breath, weight loss, insomnia, gynecomastia, splenomegaly, hepatomegaly, and pedal edema.

Psoriasis is a frequent cause of E. Chronic plaque psoriasis precedes psoriatic E in more than 80 % of patients. An identifiable/unidentifiable triggering factor drives to the transition from chronic plaque psoriasis to a more extensive involvement, characterized by the onset of an inflammatory phase; here, there are predominant erythema and limited scaling, as well as pruritus and burning. Triggers include sudden stopping of methotrexate, topical or systemic corticosteroids, the use of topical irritants as tars, systemic medications (antimalarials, lithium, terbinafine, gold, antimalarials, etc.), systemic illness, phototherapy burns, local and systemic infections (as HIV), pregnancy, and emotional stress.

This unstable psoriasis could become a whole-body disease. Pustular and erythrodermic psoriasis (Figs. 29.4, 29.5, 29.6, 29.7, and 29.8) are the most severe clinical variants of the disease spectrum.

In the erythrodermic psoriasis, generalized erythema, superficial scales, and loss of psoriatic clinical features are observed. Hence, psoriatic E is very similar to E due to other causes. Sometimes scales do not look like those of chronic plaque psoriasis that are thick and adherent. Erythema involves the whole skin surface and derives from vasodilation, inducing a high heat loss. E can regress to extensive



Figs. 29.4, 29.5, 29.6, 29.7, and 29.8 Erythrodermic psoriasis

plaque psoriasis but erythrodermic psoriasis recurs in 15 % of patients after an initial clearing.

In some patients, generalized pustular psoriasis may lead to erythrodermic psoriasis when there is no more pustular formation.

E can follow pityriasis rubra pilaris. It often appears as a seborrheic dermatitis-like eruption of the scalp and, in a short time, evolves into a widespread erythema with islands of sparing. An early prominent feature is keratoderma. Pink papules may affect the hair follicles in the dorsal fingers, wrists, and elbows.

Blisters and erosions are helpful for the diagnosis of E secondary to immunobullous diseases. Ruptured blisters may be highlighted by impetigo-like erosions or collarettes, leading to the recognition of superficial pemphigus, and tense blisters are usually indicative of an erythrodermic bullous pemphigoid.

E associated with dermatomyositis is rare, and in half the cases it is associated with digestive neoplasia (stomach and liver). Moreover, erythrodermic dermatomyositis may present Gottron's papules, heliotrope rash, poikiloderma, periungual telangiectasias, and muscle weakness.

E associated with mycosis fungoides (Fig. 29.9) is preceded by patches, plaques, or nodules, or there can be an E ab initio. An immunophenotypic study using advanced antibody panels may be required to distinguish it.

Sezary syndrome, the leukemic variant of mycosis fungoides, is characterized by itching, infiltration of the skin, enlarged lymph nodes, hepatosplenomegaly, and circulating Sezary cells.

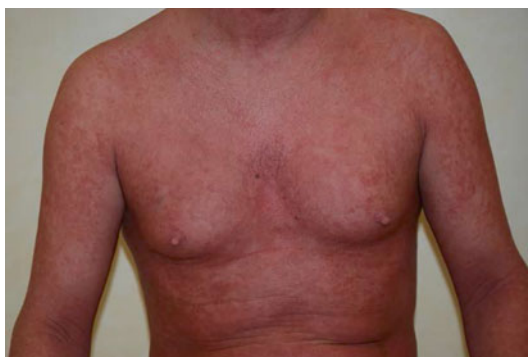


Fig. 29.9 E associated with mycosis fungoides

A rapidly progressive E can be associated with lymphomatoid granulomatosis, a rare EBV-associated lymphoproliferative disorder. It affects mainly males in an immunodeficiency state. Clinical superficial lymph node swelling, subcutaneous nodules, and lung involvement are characteristic. The central nervous system is frequently involved. The diagnosis is based on histology.

Children and Neonates

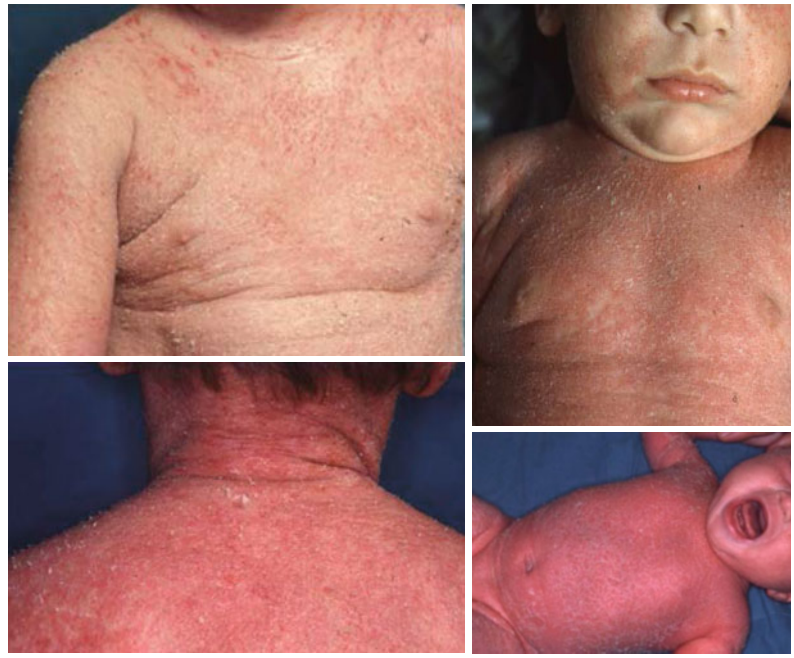
Atopic dermatitis may occur with E at birth but, more frequently, it develops in infants or small children. Atopic dermatitis presenting as E is usually observed after the first months of life. Skin lesions consist of vesicles or exudative areas mainly on the face and flexures. They can overlap those of infantile seborrheic dermatitis in smaller children. After the age of 1 year, the disease is often complicated by itch sensation and excoriations or overinfections (Figs. 29.10, 29.11, 29.12, and 29.13).

E due to psoriasis is rare in children. It usually starts on the napkin area, but sometimes it may be yet observed at birth. Erythrodermic psoriasis should be differentiated by pityriasis rubra pilaris when it starts with erythematous scaly plaques.

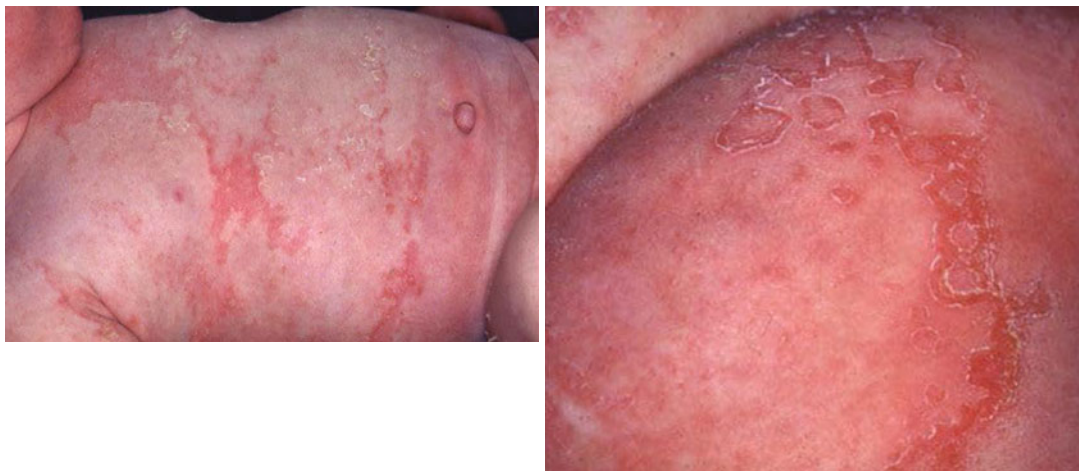
In neonates with E, a delay in reaching the correct diagnosis can be fatal. Clinical evaluation, knowledge of familial anamnesis, and laboratory tests are key points in the differential diagnosis of E. A skin biopsy is essential.

In particular, microscopy, histology, and immunohistochemistry could be useful tools for the distinction of severe diseases, such as PIDS and Netherton syndrome.

Several varieties of ichthyoses can manifest as E in neonates or infants (see Chap. 44). Netherton syndrome is a rare skin disease classified within ichthyoses (Figs. 29.14 and 29.15). It has a recessive inheritance pattern. In small children with Netherton disease, scaly E is associated with fragile hair with trichorrhexis invaginata (named "bamboo hair"), immunological abnormalities of varying severity, IgE-mediated allergic reactions, infections, and defective temperature regulation.



Figs. 29.10, 29.11, 29.12, and 29.13 E in atopic dermatitis



Figs. 29.14 and 29.15 E in Netherton syndrome: with picture of ichthyosis linearis circumflexa. Notice the characteristic serpiginous erythematous plaque with double-edged scale at the margin

E of Netherton syndrome can be noted at birth or during the first weeks of life; it often induces retarded growth and development of the newborn.

Neonatal E can be the early manifestation of PIDS such as Omenn syndrome.

Omenn syndrome is a rare, autosomal recessive disease. Severe combined immunodeficiency, infections, E, alopecia, hypereosinophilia, hepatosplenomegaly, lymphadenopathy, hypogammaglobulinemia and elevated IgE serum levels, chronic diarrhea, and failure to thrive are characteristic of this condition.

Diagnosis

The diagnosis of E is usually easy, but finding the underlying disease of E is a hard work. Unfortunately, the clinical profile of E is not contributive and certain clues such as scaling or

pruritus cannot be related to a specific cause. So, the clinical picture does not always contribute to the underlying skin disease's diagnosis. Patients with dermatologic disorders resistant to the therapy may develop E during a flare-up. In such cases, the etiologic diagnosis of E is easy; otherwise, its origin remains a diagnostic challenge. Long-duration E may cause hair loss and/or nail dystrophy regardless of its origin, so these changes are sometimes nonspecific. In erythrodermic patients, clinic-pathologic correlation is usually insufficient, because the specific skin changes due to dermatoses or drug reactions are masked by the nonspecific changes induced by the inflammatory erythrodermic process.

The diagnosis of E is mainly based on histology; immunocytochemistry (ICC) and molecular biology techniques can be helpful. Conclusive clinic-pathologic correlation may require multiple and repeated skin biopsies. The histopathology of E varies, according to the underlying pathology. Therefore, in a skin bioptic sample, it is important to perform a careful examination of all the skin layers. Anyway, specific diagnostic features are not found in biopsies in about one third of erythrodermic cases. Furthermore, only a half of histopathologic examinations are indicative of the underlying disease. Histopathology shows a context of nonspecific subacute or chronic dermatitis, even if there has been a previously well-known dermatosis, whose specific features are no more evident. The main histologic findings found in E are parakeratotic hyperkeratosis, acanthosis, spongiosis tending to vesiculation, exocytosis, dermal edema, and perivascular infiltrates mainly composed by lymphocytes with or without eosinophils (Fig. 29.16).

The stage of the disease can make changes in the histopathologic features; the acute stage is mainly characterized by spongiosis and parakeratosis, while the chronic stage presents acanthosis and elongated rete ridges.

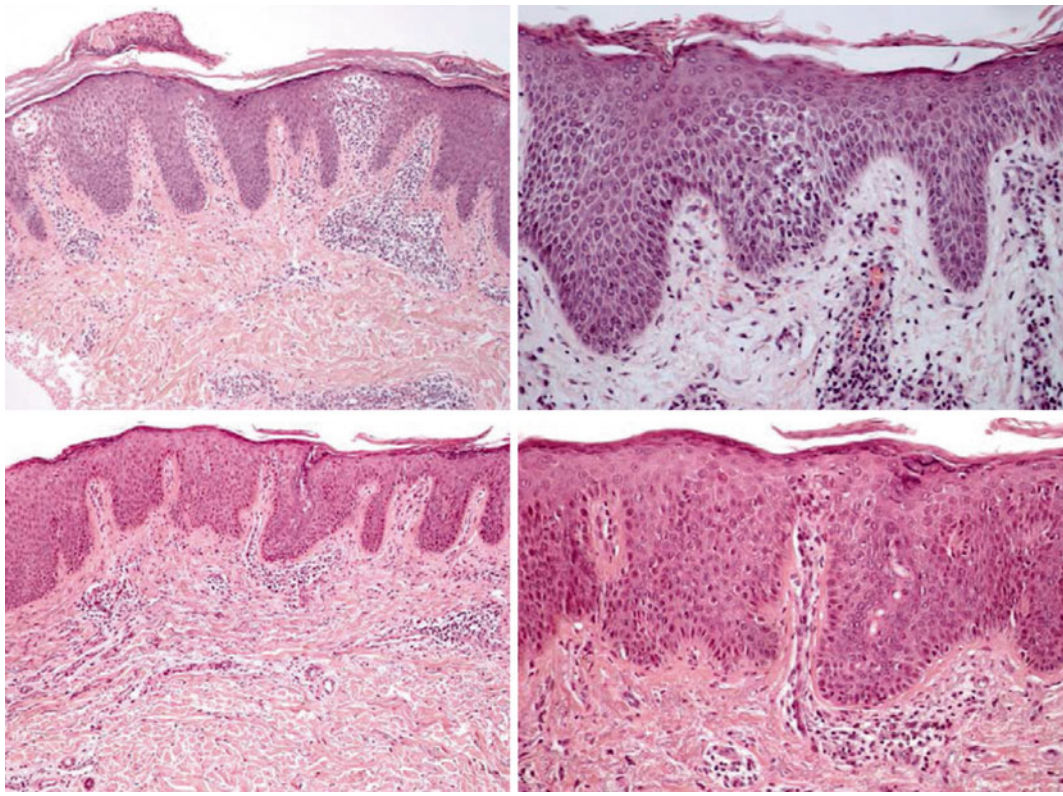


Fig. 29.16 Histopathology of E. Parakeratotic hyperkeratosis, acanthosis, spongiosis tending to vesiculation, exocytosis, dermal edema, and perivascular infiltrates mainly composed by lymphocytes

Drug-induced E may often show a lichenoid interfacial dermatosis at the histopathologic evaluation.

In E due to lymphoma, the infiltrate may progressively come to be polymorphic until it reveals its diagnostic aspects. A lymph node biopsy shows a histiocytic infiltrate in the place of the previous perifollicular lymphatic (dermopathic lymphadenopathy). In E due to epidermotropic T-cell lymphoma, histopathology presents a band-like lymphoid infiltrate in the superficial dermis, intraepidermal exocytosis, cerebriform cells, and Pautrier microabscesses. Sometimes, in this kind of E, some aspects of chronic dermatitis coexist, and in the case of benign E, there are aspects of lymphoma. Thus, the ICC is not always decisive, nor it is even the molecular biology.

Taking care of E, basic investigations include monitoring vital parameters as temperature, weight, pulse, and respiratory rate charting. Laboratory tests should explore a complete blood cell count and morphology, total and differential leukocyte counts, absolute platelet count, erythrocyte sedimentation rate, liver and kidney function tests, total and fractionated protidemia, serum electrolytes, fluid intake/output charting, and scheduled urine macro- and microscopy. Moreover, electrocardiogram and chest radiograph should be performed. Furthermore, disease-specific investigations are required:

- Scabies/skin mycosis: skin scrapings/KOH
- Allergic contact dermatitis, photoallergic contact dermatitis, and airborne contact dermatitis: patch test
- Atopic dermatitis: serum immunoglobulin E testing, RAST, and prick tests
- Multiple myeloma: serum and urine protein electrophoresis
- Sarcoidosis: angiotensin-converting enzyme levels and serum calcium level
- Bacterial overgrowth or herpes simplex virus: microbiologic cultures
- Acquired immunodeficiency syndrome: screening for human immunodeficiency virus 1 and 2
- Immunological disorders: antinuclear antibodies, anti-DNA antibodies, and rheumatoid factor
- Lymphoma/leukemia: lymph nodes examination, CD4/CD8 ratio, fine-needle aspiration cytology, bone marrow examination, immunophenotyping, flow cytometry, and B-cell and T-cell gene rearrangement analysis
- Pemphigus, pemphigoid, lichen planus, lupus erythematosus, and graft-versus-host disease: cutaneous direct and indirect immunofluorescence
- Occult malignancy: stool search for occult blood, prostate examination, cervical smear ultrasonography of the abdomen, chest radiograph, computed tomography scan, mammography, and sigmoidoscopy

About 10–25 % of patients with E do not receive a specific etiologic diagnosis. In these cases, E is defined as primary or idiopathic. In patients with primary, idiopathic E, laboratory abnormalities frequently comprise leukocytosis, anemia, raised erythrocyte sedimentation rate, lymphocytosis, eosinophilia, and hypergammaglobulinemia with elevated IgE serum levels. Other findings are increased creatinine level, hyperuricemia, and hypoalbuminemia. Eosinophilia is not diagnostic for the E's etiology. In Sezary syndrome, more than 20 % of circulating Sezary cells is a diagnostic point, whereas less than 10 % is a nonspecific finding. This lower count of Sezary cells can in fact be found in different benign dermatoses.

A diagnostic algorithm for an erythrodermic patient is presented in Fig. 29.17.

Complications and Prognosis

In E, some complications may occur such as pressure ulcers, pneumonia, venous thrombosis, heart or renal failure, depressive syndrome, and side effects of systemic corticosteroids and immunosuppressors. Loss of fluid and electrolytes develops from leaky capillaries. E increases protein loss by 25–30 % in psoriatic E and by 10–15 % in non-psoriatic E. This protein loss causes hypoalbuminemia, with fatigue, edema, and muscle wasting.

Systemic complications include alteration of fluid and electrolyte imbalances, thermoregulatory disturbance, high-output cardiac failure, and acute

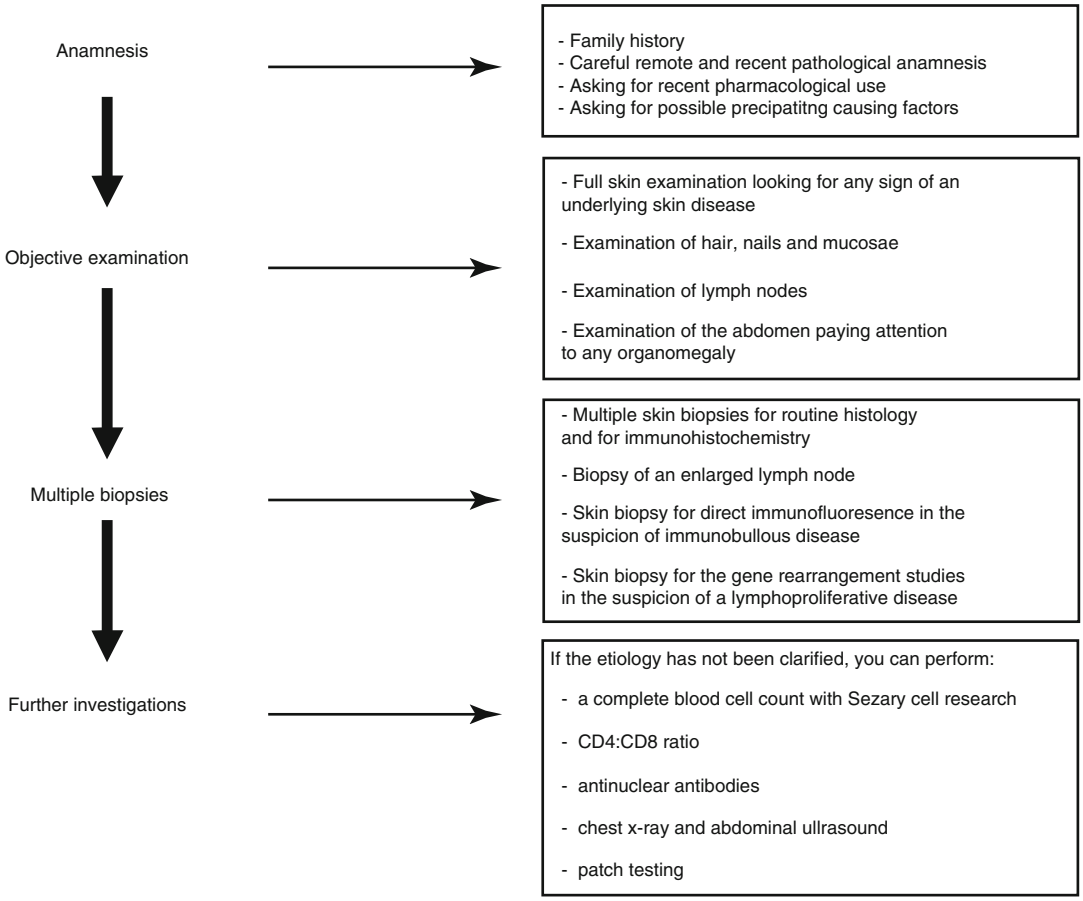


Fig. 29.17 Diagnostic algorithm for an erythrodermic patient

respiratory distress syndrome. The inflamed, fissured, and excoriated skin is susceptible to impetiginization, and sepsis may occur. Staphylococcal sepsis is especially a risk for patients with cutaneous T-cell lymphoma and/or HIV positive.

The clinical course of E is variable, but many patients have a bad prognosis; in fact E is a severe disease, the mortality rate ranges from 18 to 64 % of cases on the basis of the underlying disease. Pneumonia, septicemia, and heart failure represent the most common causes of death. In patients who develop complications (e.g., infection, fluid and electrolyte abnormalities, cardiac failure), the mortality rate increases. Death from sepsis, cardiac failure, adult respiratory distress syndrome, and capillary leak syndrome continues to be present. The prognosis has improved with the advent of the innovative dermatologic therapies (e.g., cyclosporine and synthetic retinoids, biologic therapies) and the advances in the management of systemic manifestations.

A high index of suspicion for complications must be maintained to facilitate an early medical intervention. The long-term prognosis is better in patients with drug-induced disease, whereas the course tends to remit and relapse in idiopathic E, although in some of these cases spontaneous resolution occurs. The prognosis of cases associated with malignancies depends on the outcome of the underlying cancer.

Post-inflammatory hypopigmentation or hyperpigmentation may occur. Generalized vitiligo or pyogenic granulomas have also been reported after drug-induced acute E. Alopecia, nail dystrophy, nevi, and keloid formation rarely follow E.

General Principles of Treatment

Treatment approach should include discontinuation of any potentially causative medications and a search for any underlying malignancy. The initial management of E of any etiology includes paying attention to nutrition, fluid and electrolyte replacement, and the institution of gentle local skin care measures. All cases should be considered as a dermatologic emergency and patients should preferably be hospitalized for treatment. Hospitalization is usually necessary for initial evaluation and for the administration of the general therapy.

When dealing with a patient with E, local and systemic treatments are necessary (Table 29.3). First of all, bed rest and sedation of patient

Table 29.3 Treatment of E

	Treatment	Remarks (dose and period of treatment)
General	Hospitalization	
	Fluid intake monitoring	
	Electrolyte balance check	
	Temperature measuring	
	Hyper-proteic diet	
	Nutritional implementation	
	Stop of any unuseful drug	
Specific (topical)	Lukewarm bath every day	
	Wet dressing with topical steroids and emollients (triamcinolone acetonide cream, 0.025–1.0 %)	Every 2–3 h and slowly decrease frequency
Specific (systemic)	Sedative antihistamine	Hydroxyzine hydrochloride, 25–50 mg per os every 4–6 h
	Systemic antimicrobials	First- or second-generation cephalosporins or semisynthetic penicillins for 7–10 days, or macrolides, or clindamycin
		Because of the subsequent infection by *S. aureus*
		Prudence due to the worsening of a drug-induced erythroderma
	Systemic steroids	Prednisone 1 mg/kg/24 h, then gradually decreased
	Acitretin	0.3–0.75 mg/kg
	Cyclosporin	Initial mean dose 4 mg/kg/day slowly reduced after remission by 0.5 mg/kg every 2 weeks
Specific disease		
Psoriasis	Systemic corticosteroid	It is better to avoid
	Methotrexate	Initial dose 10–25 mg/week, maintenance
		Dose 7.5–15 mg/week
	Cyclosporin	Initial mean dose 4 mg/kg/day slowly reduced after remission by 0.5 mg/kg every 2 weeks
	Acitretin	0.3–0.75 mg/kg
	Phototherapy	UVB, UVA, PUVA
	Etanercept	50 mg subcutaneous injection twice a week, reduced 50 mg/week after 3 months
	Infliximab	5 mg/kg i.v. at week 0, 2, 6, and later every 8 weeks
		Can be combined with methotrexate or acitretin
	Ustekinumab	45/90 mg (according to the weight) at week 0.4 and later every 12 weeks
	Adalimumab	80 mg at week 0, 40 mg at week 1, later 40 mg every 2 weeks

(continued)

Table 29.3 (continued)

	Treatment	Remarks (dose and period of treatment)
Atopic dermatitis	Systemic steroids	Prednisone 1 mg/kg/24 h, then gradually decreased
	Antimicrobials	First- or second-generation cephalosporins or semisynthetic penicillins for 7–10 days, or macrolides, or clindamycin, etc.
	Cyclosporin	Initial mean dose 5 mg/kg/day, slowly reduced after remission by 0.5 mg/kg every 2 weeks
	Phototherapy	Broadband UVB (280–320 nm)
		Narrowband UVB (311–313 nm)
		UVA (320–400 nm), UVA1 (340–400 nm), PUVA
		Balneo PUVA
		Possibility of combination of phototherapy (UVA/UVB) with corticosteroids
	Azathioprine	100–200 mg/day slowly reduced after remission
	Methotrexate	10–25 mg/week slowly reduced after remission
	Mycophenolate mofetil	1–2 g/day slowly reduced after remission
	Intravenous immunoglobulins	2 g/kg/month for 3–6 months
	Other	Interferon (50 g/m^2/day for 12 week)
		Rituximab
		Alefacept
Pityriasis rubra pilaris	Acitretin	0.3–0.75 mg/kg/day slowly reduced after remission
	Methotrexate	10–25 mg/week slowly reduced after remission
	Systemic steroids	Prednisone 1 mg/kg/24 h, then gradually decreased
Toxic epidermal necrolysis	Intravenous immunoglobulins	High dose (1 g/kg/day for 3 days)
	Systemic steroids	Prednisone 1 mg/kg/24 h, then gradually decreased
Lymphoma	Extracorporeal phototherapy, PUVA, alkylating agents	
Scabies	Topical permethrin, 5 %	Once a day for 5 consecutive days
	Oral ivermectin	200 μg/kg/day

should be suggested with monitoring of temperature, fluid intake, and electrolyte balance. A nutritional support should be added.

A local therapy with daily tepid baths, emollient creams, and soothing, in addition to low-power corticosteroids, is indicated. The maintenance of the skin hydration and avoiding of scratching and precipitating factors are mandatory as well as the treatment of the underlying cause of E (e.g., scabies) and of its complications (overinfections). As antipruritic agents, mild topical steroids/emollients can be used as well as wet wrap dressing.

Systemic therapy is usually necessary to achieve a good improvement of E. Oral, i.m., or i.v. sedative antihistamines are frequently added. In severe cases, systemic corticosteroids are the first-choice drug. They reduce itching and improve the general status, but they have many side and rebound effects. To increase the skin improvement, further treatments can be used depending on the E's etiology. Antimicrobials can be used to control secondary infections. Any hemodynamic or metabolic abnormalities must be correctly treated.

The outcome is unpredictable in idiopathic E and the course is marked by multiple exacerbations, so prolonged steroid therapy is often needed.

Erythrodermic psoriasis and eczematous E are usually severe; thus patients should be treated

with systemic drugs. Acitretin, cyclosporine, methotrexate, and biologic drugs (e.g., tumor necrosis factor-alpha blockers) are the treatment options in E due to psoriasis (see Chap. 81). E due to eczema usually improves within several weeks to several months, although chronic cases of atopic or contact eczematous E are not uncommon.

E secondary to cutaneous T-cell lymphomas or to other malignancies is often long-standing and refractory to treatment.

Complete remission occurs in one third of patients with idiopathic E, while 50 % of these patients demonstrate only partial remission. Patients where idiopathic E shows a chronic course are at high risk to evolve to cutaneous T-cell lymphomas.

Therapy for lymphomatous E includes PUVA, re-PUVA, total body electron beam irradiation, topical nitrogen mustard, chemotherapy, and extracorporeal photopheresis.

Treatment of Erythroderma in Childhood

Also in childhood, and in particular in neonatal and infantile period, E could be a severe condition. The connection between the pediatrician and the dermatologist is essential in this situation, and a prompt diagnosis of the underlying disease is fundamental to avoid any circumstance that could lead even to the death of the young patient. In the literature, the infantile mortality is quite high (16 %), due to primary dermatosis or to the complications. As a matter of fact, different life-threatening complications of E can occur; in particular, neonates with E have a higher risk of severe systemic infections, hypernatremic dehydration, hypoalbuminemia, hyperpyrexia, or hypothermia. These complications are more evident in collodion baby, severe lamellar ichthyosis, harlequin ichthyosis, Netherton syndrome, and Omenn syndrome. The skin fragility, fissures, cracks, erosions, or immunodeficiency of these conditions can lead to severe septicemic infections, resulting in high morbidity and mortality.

Hence, a child with E requires a proper supportive management, because it is necessary to correct the metabolic, hematologic, and biochemical imbalance. It is important to monitor the vital signs, check electrolyte balance, and provide an adequate fluid, caloric, and protein intake (per os or parenteral), according to the hypermetabolic state and requirements of normal growth. To obtain a normal weight gain of 15 g/kg/day, an estimated energy intake of 120–130 kcal/kg/day is necessary. In stressful situations, the energy intake can be increased by 10–30 %. The physician should pay attention also to the prevention of infections. The results of skin culture, hemoculture, and antibiogram should allow the choice of the correct antibiotics. In neonates, parenteral antibiotics are preferred.

In general, topical emollients such as petrolatum or white soft paraffin and antifungals or topical steroids are recommended, with wet dressing, to maintain the barrier function of the stratum corneum. When the diagnosis of the underlying disease is established, the specific therapy must be started.

The prognosis for an erythrodermic patient would vary because it depends on the primary etiology of the E. With an adequate treatment, children affected by E due to staphylococcal scalded skin syndrome, infantile seborrheic dermatitis, or nutritional deficiencies can be completely cured. A short administration of systemic steroids (1 mg/kg/day) could be necessary in case of atopic dermatitis and drug-induced E, while systemic methotrexate or acitretin (0.5 mg/kg/day) could be helpful in psoriatic E. Some more difficulties could be found in ichthyotic E, because a long-lasting therapy with retinoids may be required.

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Erythroplasia of Queyrat

30

Konstantinos Krasagakis

Key Points

- Erythroplasia of Queyrat is a carcinoma in situ involving the mucosal surface of the penis.
- Treatment includes surgical procedures and either local or systemic medical treatment.
- Treatment of choice is surgical excision with microscopically controlled surgical margins. Defects depending on the size are managed by primary closure or reconstructive plastic surgery.
- Alternative surgical treatment includes laser vaporization by neodymium:YAG or carbon dioxide.
- Topical drug treatment in cases where surgery is not selected can be performed with 5-fluorouracil or imiquimod.
- Photodynamic treatment gives moderate results with efficacy ranging to 50 %.
- Close control is required when treatments other than excision with controlled or safety margins are chosen due to the risk of recurrence.

Definition and Epidemiology

Erythroplasia of Queyrat (EQ) is a carcinoma in situ of the mucosal surface of the penis. It is clinically distinctive from other forms of carcinoma in situ of the penis as Bowen's disease and bowenoid papulosis. The terminology regarding these entities is sometimes confusing and discrimination is not always done. Erythroplasia of Queyrat is a lesion with sharply defined borders and a red, smooth surface, involving the glans and the inner surface of the prepucial skin of the penis. Bowen's disease of the penis should be used to describe red, sometimes slightly pigmented, scaly patches and plaques of the keratinized penis, whereas bowenoid papulosis is described as multiple warty lesions, often pigmented in keratinized sites, and more numerous and more inflamed at mucosal sites (Bunker and Neil 2010). The histological features of erythroplasia of Queyrat and Bowen's disease are almost identical.

Basic Concepts of Pathogenesis

The etiology of erythroplasia of Queyrat remains unknown. Since it affects the mucosal surfaces of uncircumcised men, local factors such as poor hygiene and local irritation from retained

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_30, © Springer-Verlag Berlin Heidelberg 2015

smegma or trauma have been all postulated as potential risk factors. More solid appears the presence of a coinfection of HPV type 8 with high-risk HPV-16. Wieland et al. (2000) reported that the presence of HPV-8 may discriminate EQ from Bowen's disease.

Clinical Presentation

The disease preferentially affects non-circumcised men older than 50 years. The typical presentation of erythroplasia of Queyrat is a well-demarcated, velvety red plaque of variable size, having a smooth surface, which involves the glans penis or the inner surface of the prepucial skin (Fig. 30.1). The lesion is flat or with slight infiltration, and multiple lesions are possible as well. Some authors use the term to describe squamous intraepithelial neoplasia in other mucosal localizations such as the conjuctiva, the oral mucosa, and the vulva. The disease progresses slowly, but if the lesion becomes increasingly indurated or ulcerated, this might be a sign for progression to an invasive SCC. The rate of progression to SCC is between 10 and 33 % (Graham and Helwig 1973). Rarely, cases of metastatic disease to the lymph nodes in the absence of an invasive component have been reported (Kim et al. 2007).

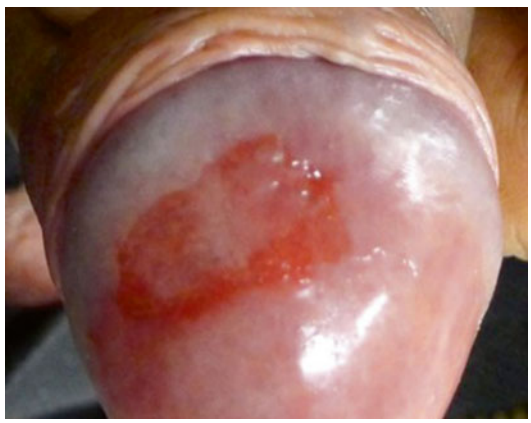

Fig. 30.1 Erythroplasia of Queyrat involving the glans penis

Diagnosis

Histology is necessary to discriminate EQ from other benign conditions mentioned above and to establish the diagnosis. Histologically, the lesion shows a hyperkeratotic epidermis with acanthosis and focal parakeratosis. Keratinocyte polarity and maturation have been lost. The cell nuclei are hyperchromatic and bizarre; multinucleated cells and atypical mitoses are seen. The basement membrane is not affected. In the upper dermis a dense infiltrate is found with mononucleated cells often having many plasma cells.

Differential Diagnosis

A variety of dermatological diseases may be considered in the differential diagnosis of EQ. These include conditions like psoriasis or lichen planus that may rarely manifest at the penis only, or even coexist with EQ. In such a case proper diagnosis may be delayed. Typically, Zoon's balanitis plasmacellularis, lichen sclerosus et atrophicus, and candida balanitis are more common conditions in this specific region. Rarely, sexually transmitted diseases such as syphilis or granuloma inguinale may be confused with EQ.

General Principles of Treatment

Large, well-designed studies on the treatment of EQ are missing, and much information is derived from studies on therapy for carcinoma in situ of the penis. Treatment of choice for EQ is surgical excision of the lesion. Concerns exist regarding remaining functionality from such an excision or even from a partial amputation of the penis, depending on the size of the lesion. Such considerations may pose limitations to the extent and radicality of surgery. Safety margins of 5 mm are generally acceptable for excision, which however result on most occasions in large defects. Therefore, Mohs micrographic surgery is suggested as an effort to spare unaffected tissue.

Neodymium:YAG or carbon dioxide laser therapy or the application of 5-fluorouracil cream

or imiquimod cream is also possible as an alternative to surgery in order to preserve function and not to affect sexual activity.

Local Excision

Local excision (with or without circumcision) remains the gold standard. Recurrence rates for carcinoma in situ of the penis may vary from 13 to 33 % (Cripsen and Mydlo 2010). The surgical excision of the lesion often has to be completed with coverage of the defect with skin from the body of the penis or with free skin transplantation. This is necessary when a safety margin of 0.5–1.0 cm is taken. Reports for cure rates are very sparse for these margins, even though it is a generally accepted safety limit. Also when these margins have been kept, the risk of recurrence is not negligible, and follow-up is recommended (Angerer-Shpilenya et al. 2010). Mohs micrographic surgery, when feasible, combines the benefit of excising the lesion with a sparing of uninvolved tissue, which is important for preventing disfigurement of the glans penis.

Some authors advocate total glans resurfacing as a surgical alternative for managing intractable EQ after failure to control disease with topical 5-FU cream or imiquimod (Hadway et al. 2006). According to this technique, the glans and subcoronal epithelial and subepithelial tissues are completely excised and replaced with healthy skin from an extragenital site. The penis is also circumcised. The graft, usually from the lateral thigh, is secured with several absorbable sutures to delineate the coronal sulcus, the external meatus, and the shaft skin ends. This technique, as reported in a study of ten patients, had not affected their sensation and had improved the quality of their sexual life in most of them giving a high overall patient satisfaction.

Laser Treatment

An alternative to surgical excision is the treatment of EQ with a laser source. Laser vaporization allows the adequate destruction of the lesion and limits the depth of penetration and the unnecessary destruction of healthy tissue. The preferred type of laser is the neodymium:YAG compared to other laser sources such as the carbon dioxide laser, but selection may depend upon the availability of the device and the experience of the user. Carbon dioxide laser has been suggested for treatment of penile carcinoma, alone or in conjunction with neodymium:YAG, as a penis-preserving surgery with reported cosmetically and functionally excellent results (Malek 1992; Conejo-Mir et al. 2005). Laser therapy also carries the risk of recurrences, and relapse rates of 0–33 % for carcinoma in situ have been reported (Malloy et al. 1988; Tietjen and Malek 1998; Schlenker et al. 2010). Invasive squamous cell carcinomas or even lymph node metastases have been observed after laser surgery (Frimberger et al. 2002; Meijer et al. 2007). Disadvantages are prolonged time for healing and the absence of histological control for clearance from the tumoral tissue.

Other Ablative Methods

Curettage and cautery is another treatment modality, widely used for therapy of basal cell cancer and Bowen's disease, which can also be applied for treatment of erythroplasia of Queyrat (Bunker and Neill 2010). A disadvantage compared to laser ablation is the risk of disfigurement.

Cryosurgery is included among the ablative treatments for erythroplasia of Queyrat. It is considered as a minimally invasive treatment able to offer good results as reported in two cases (Sonnex et al. 1982), but the selection of this type of treatment should be individually considered, and a close follow-up has to be ensued. Other authors do not recommend cryosurgery because of the lack of consistent depth of treatment (Crispen and Mydlo 2010).

In Bowen's disease of the skin, a comparison of curettage and cautery with liquid nitrogen cryotherapy showed a superiority of the curettage procedure (Ahmed et al. 2000).

Photodynamic Therapy

Photodynamic treatment (PDT) gives moderate results with overall efficacy ranging to 50 %. In a study with methyl aminolevulinate PDT for carcinoma in situ of the penis, excellent cosmetic results have been reported, but three out of ten patients had histopathologically residual disease (Axcrona et al. 2007). Also, Paoli et al. (2006) found initially a response to photodynamic therapy in seven out of ten patients treated with delta-5-aminolevulinic acid or methyl aminolevulinate PDT. Four of these patients presented no recurrences during a mean follow-up of 35 months and were completely cleared after two to eight treatments (mean 4.5 treatments). Three patients presented recurrences after treatment. Typically methyl aminolevulinate can be applied for 3 h under occlusion with a condom, and illumination is performed under regional anesthesia with 1 % Xylocaine. Side effects include mild swelling, redness, and pain (Lee and Ryman 2005). PDT may be useful in erythroplasia of Queyrat of the penis where tissue sparing is important, but several cases refractory to this modality have been reported with development of squamous cell carcinoma (Stables et al. 1999; Varma et al. 2000).

Topical Treatment

Topical treatments may be as well used for EQ. The 5-FU cream has been used since several decades as alternative to surgical therapy with success. The protocol includes the twice daily application of 5 % 5-FU cream to the lesion and the immediately adjacent area under occlusion with the foreskin or a condom. If the irritative reaction with pain, erythema, and edema, which usually appears after few days, is too strong, frequency of application can be reduced or treatment can be subsided for a few days before reinstituted again. In most cases a treatment period of 4–5 weeks is necessary to achieve clearance (Goette and Carson 1976). The inflammatory reaction often poses limitations to this type of treatment. Other protocols describe initially the application of lower concentrations of 5-FU cream (i.e., 2–3 %), and if the reaction is not strong enough, then the higher concentration of 5 % can be used. After treatment, close follow-up is necessary, with biopsies in case of any suspicion of inadequate response to the primary therapy or relapse.

Imiquimod is an immune-response-modifying agent with both antiviral and antitumor properties indicated for topical treatment of actinic keratosis, superficial basal cell carcinoma, and condylomata acuminata. Few anecdotal reports and a small open-label case series suggest a role for treatment in EQ, considering that besides its antineoplastic activity, imiquimod possesses efficacy against benign HPV conditions. Some authors consider 5-FU as the first-line and imiquimod as the second-line topical chemotherapy agent in penile carcinoma in situ (Alnajjar et al. 2012).

Other Treatments

The advent of radiation therapy is debatably discussed, since some authors prefer to avoid its use. A study of 11 cases with carcinoma in situ treated with primary radiotherapy reported complete responses without recurrences (McLean et al. 1993). Nevertheless, radiotherapy is used for therapy of more advanced cancerous lesions when surgery is not selected. In the case of erythroplasia of Queyrat, 8–10 fractions of single doses of 4 Gy may be used.

Follow-Up

There are presently no evidence-based recommendations on the frequency or the duration of the follow-up examinations. Recommendations are largely based on the knowledge that despite adequate therapy, erythroplasia of Queyrat still carries a risk for relapse depending on the type of treatment, as mentioned above. Close control is required when treatments other than excision with controlled or safety margins are chosen, due to the risk of recurrence. In the case of

complete local resection with histologically controlled excision margins and eventually circumcision, the risk of local relapses is rather small, but when other methods are selected, the risk can become higher. A tight clinical follow-up is recommended, i.e., a first visit after 3 months to evaluate for signs of persistent or recurrent disease. The National Comprehensive Cancer Network® panel suggests for penile cancer clinical exams every 3 months for the first 2 years, thereafter every 6 months until the fifth year, and then once per year for the next 5 years.

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Factitial Dermatitis

31

Razvigor Darlenski and Nikolay Tsankov

Abbreviations

FD	Factitial dermatitis
SISL	Self-inflicted skin lesions
SSRIs	Selective serotonin reuptake inhibitors

Key Points

- Factitial dermatitis (FD) has been classified as part of the so-called self-inflicted dermatoses.
- A factitious skin disorder refers to artificial or faked, self-provoked or alleged skin diseases, without clear external incentives. In these cases the behavior responsible for the somatic damage is denied or kept "secret" by the patient.
- Lesions are most often found at skin sites accessible by the patient, with sharp demarcation borders and geometrical figures.
- A multidisciplinary psychocutaneous team is required in FD treatment.
- Dermatological care for FD includes topical bland therapy, antiseptics, and epithelizing agents.
- Nondrug psychological approaches include psychosomatic primary care (complaint diary), psychoeducation (no confrontation), relaxation techniques, and deep psychological therapy with the inclusion of behavior therapy concepts (aversion therapy, systemic desensitization, operant conditioning).
- As factitial dermatitis is often accompanied by psychiatric comorbidity, psychoactive drugs such as antidepressants, neuroleptics, and anxiolytics are used as adjunctive therapy.

Definition and Epidemiology

Factitial dermatitis (FD), also named dermatitis artefacta, artifact dermatitis, and factitious dermatitis, is an interdisciplinary problem that often involves dermatologists, general practitioners, and psychiatrists/psychologists (Dourmishev and Kazandjieva 1999). Historically there has been confusion with regard to terminology and classification of this pathologic condition. Recently a position paper (Gieler 2013). classified FD as a part of the so-called self-inflicted

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_31, © Springer-Verlag Berlin Heidelberg 2015

dermatoses. Many terms have been used overlapping clinical correlations and disregarding some nuances between conditions such as neurotic excoriations, psychogenic excoriations, skin pickling syndromes, pathomimicry, and malingering. The panel suggests that instead of "FD," the term "factitious disorders in dermatology" should more appropriately be used, as this clinical entity is not always concurrent with "dermatitis."

Self-inflicted skin lesions (SISL) are defined as skin lesions actively and directly produced by the patient on his/her skin or mucosa that are not better explained as a consequence of another physical or mental disorder. In the narrower sense, a factitious skin disorder refers to artificial or faked, self-provoked or alleged skin diseases, without clear external incentives. In these cases the behavior responsible for the somatic damage is denied or kept "secret" by the patient. Dermatitis para artefacta can be regarded as disorder of impulse control, often as manipulation of an existing specific dermatosis (often semiconscious, admitted self-injury) (Ehsani 2009).

The prevalence of SISL ranges from 0.03 to 9.4 % (reviewed in Gieler et al.). Many cases of FD are underreported; that is why the real incidence cannot be critically estimated. It is clear that females are more commonly affected with male-to-female ratio of 1:3–20, and no race predominance could be established. The most common age of onset is in adolescence and early adulthood.

Clinical Presentation

Classically when there is no dermatological diagnosis that could explain the lesions upon physical examination, this could lead to the diagnosis of FD. Lesions are most often found at skin sites accessible by the patient (Figs. 31.1, 31.2, and 31.3). The morphology is in a way bizarre with sharp demarcation borders, geometrical figures, linear tracks, superficial erosions, deep ulcers, excoriations, crusts, papules, hyperpigmentations, and purpuric lesions.

Triggers such as emotional stress can precipitate the course of FD, but the lack of one cannot rule out internal, unconscious determinants (Nielsen 2005). Child physical, sexual, or psychological abuse or neglect is quite frequent in the history of these patients.

Self-mutilations are often observed in a spectrum of primarily psychiatric diagnoses, e.g., anxiety, depression, personality disorder, dissociative disorder, body dysmorphic disorder, post-traumatic stress disorder, autism, schizophrenia, delusion of parasitosis, Munchausen's syndrome (and by proxy), and mental retardation (Baranska-Rybak 2011).

Differential Diagnosis

FD is primarily a psychological disorder, but the clinical picture could mimic many different dermatoses: neurotic excoriations, pruritic lesions in underlying systemic disease, friction blisters, insect bites, impetigo, and impetiginized atopic or contact dermatitis, erythema multiforme, basal cell carcinoma, cutaneous lymphoma, and pyoderma gangrenosum.

General Principles of Treatment

The disease management is complex, and establishing a confident doctor-patient relationship is important. Often the induction behavior is kept secret until an appropriate relationship with the physician is established. In accordance with this, early referral to a psychiatrist may result in loss of confidence of the patient (Mohandas 2013). At this point, open-ended questions are more suitable instead of the direct: "Did you make these skin lesions by yourself?" The main motivation is assumed to be a method for coping with a severe psychological background and a preference for the sick role. In everyday setting FD can be regarded as "cry for help" with regard to the psychological comorbidity.

In the best way, a multidisciplinary psychocutaneous team is required in FD treatment, particularly as the patient is likely to require psychological intervention (to facilitate the resolution of the precipitant) in addition to dermatological (diagnosis setup and to exclude organic

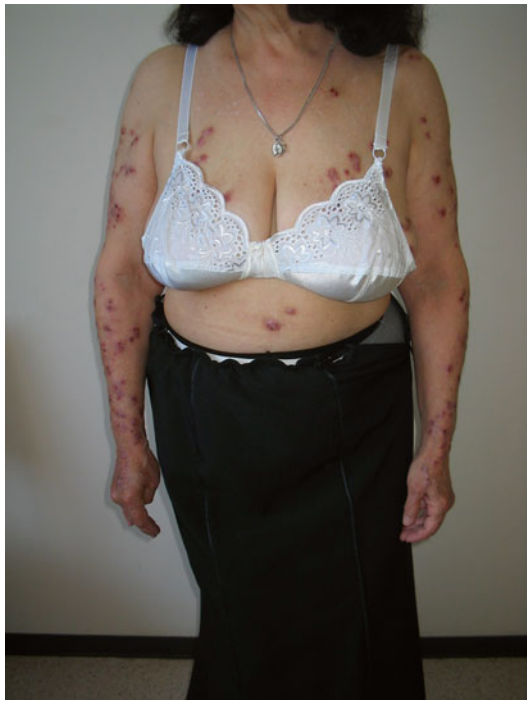

Fig. 31.1 Erosions, excoriations, and ulcerations on the patient's body and upper extremities

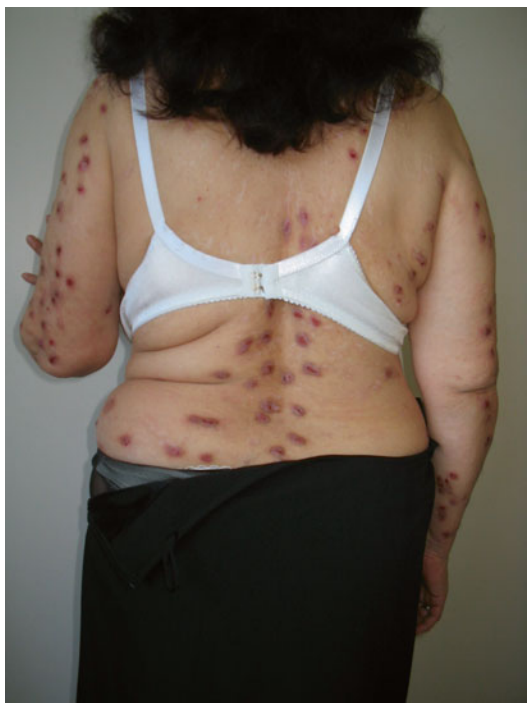

Fig. 31.2 Lesions distributed on accessible sites of the patient's back

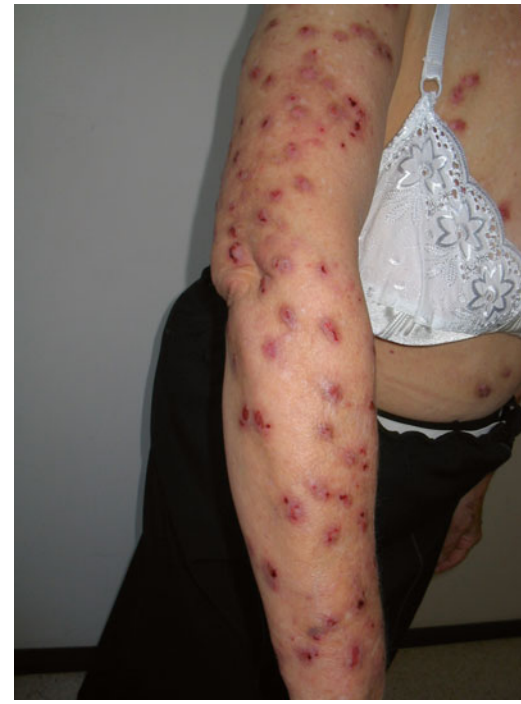

Fig. 31.3 Closer view of the skin lesions on the upper limb

disease) and psychiatric (to management of psychiatric comorbidity) help.

Dermatological care for FD includes topical bland therapy, antiseptics, and epithelizing agents. Occlusive dressing may be used to prevent from further self-infliction. When discussing the cutaneous lesions, it may be helpful to emphasize on stress or depression as a possible mediator in order to avoid counterproductive confrontation about the disease origin.

Nondrug psychological approaches include psychosomatic primary care (complaint diary), psychoeducation (no confrontation), relaxation techniques, and deep psychological therapy with the inclusion of behavior therapy concepts (aversion therapy, systemic desensitization, operant conditioning).

Pharmaceuticals are mainly used to treat psychiatric comorbidities (Tamakuwala 2005). Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, and fluvoxamine, in relatively high doses, are typically first-line treatment for self-injurious behavior (Koblenzer 2010). These can be combined with atypical antipsychotics (pimozide, olanzapine,

or risperidone), or the latter can be used alone. When anxiety is dominating, anxiolytics such as benzodiazepines and buspirone can be introduced.

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Furuncles and Carbuncles

32

Demetris Ioannides and Elizabeth Lazaridou

Definition

A furuncle (*boil*) is a deep, necrotizing form of folliculitis with involvement of the subcutaneous tissue. It occurs as the follicular infection progresses deeper and extends out of the follicle. Several furuncles may coalesce to form *a carbuncle* with several pustular openings. *Staphylococcus aureus* (*S. aureus*) is the causative agent.

Basic Concepts of Pathogenesis

The initial pathophysiological event involves *S. aureus* colonization of the skin surface and proliferation with spread within follicles. The organism may spread through follicular walls to the dermis or can be inoculated through cuts and scratches into the dermis leading to the formation of a furuncle. The attraction of polymorphonuclear leukocytes by the *S. aureus* chemotactic factors and the elaboration of several enzymes by the microorganism result in clinical inflammation. These enzymes include enterotoxins, proteases, hemolysins, and leukocidins.

Clinical Presentation

A furuncle is manifested by a tender, round subcutaneous *nodule*, which is usually capped with *a small pustule*. It is a firm or fluctuant mass of walled-off purulent material. The follicular abscess enlarges, becomes fluctuant, and then softens and ruptures spontaneously to discharge a core of necrotic tissue and pus and may result in scarring. Furuncles may occur anywhere on the body but have a predilection for hairy parts of areas exposed to friction and maceration, especially the *face*, *scalp*, *buttocks, and axillae*.

A carbuncle forms a deep, swollen, erythematous, and painful mass with multiple draining sites and is found commonly on the neck, back, and thighs.

Predisposing factors are obesity, diabetes, prolonged sitting, tight irritating pants, or immunodeficiencies.

Systemic symptoms, such as fever and malaise, are more frequently present with carbuncles. When infection occurs in the nasolabial area, extension via the vein draining into the cavernous

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_32, © Springer-Verlag Berlin Heidelberg 2015

sinus may lead to thrombosis. Perinephric abscess and osteomyelitis are other complications.

Recurrent furunculosis is the sequential occurrence of many furuncles over a period of months or even years in the same patient and sometimes develops in patients in whom there is no evidence of harboring specific staphylococcal strains or having any deficiency in their host defense mechanism. Panton-Valentine leukocidin (PVL) is the primary virulence factor of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and is associated with recurrent furunculosis. Such patients, who suffer from repeated infections, are usually nasal carriers of the infecting strain. It has been estimated that nasal carriage of *S. aureus* is the primary risk factor for recurrent furunculosis and accounts for 60 % of the cases. Therefore, nasal colonization with CA-MRSA interspersing the PVL toxin is a very strong risk factor for recurrent furunculosis. The anterior nares can serve as a reservoir for spread into the skin and subsequent reinfection. Less common reservoirs for the pathogenic staphylococci may be found in the axillae or perineum.

Differential Diagnosis

Furuncles must be differentiated from other bacterial infections, such as *anthrax* and *tularemia,* or from some other infections of the follicles, such as *conglobate acne* and *hidradenitis suppurativa*. In the last case, the location and the multiplicity of lesions usually lead to the correct diagnosis.

General Principles of Treatment

Furuncles or carbuncles associated with fever or located on the face are better to be treated with *a systemic antibiotic*. Isolated lesions on other areas of the body can be treated with only local care and, sometimes, *surgical drainage of pus*.

Eradication of recurrent lesions is often difficult. Prolonged antibiotic therapy, along with adjuvant measures, is often necessary. It is important to consider modifiable exogenous risk factors like hyperhidrosis, tight clothing, or obesity, which cause local moisture and occlusion, thus promoting local bacterial growth and injury to the hair follicle contributing to repeat infection. Endogenous risk factors like underlying acquired immune dysfunctions must also be taken into account. These include diabetes mellitus, human immunodeficiency virus, alcoholism, and malnutrition. If no skin colonization is detected, neutrophil dysfunctions should be investigated.

Recommended Therapies

(a) Systemic antibiotics
(b) Local treatment

Systemic Antibiotics

Antibiotics systemically are given in furuncles or carbuncles associated with surrounding cellulitis or those >5 cm diameter and/or associated with fever or located on the forehead, nose, cheeks, or upper lid. Patients with recurrent furunculosis and immunocompromised patients are also treated with systemic antibiotics.

Due to lack of clinical trials with many patients, treatment guidelines for furuncles and carbuncles are often based less on evidence and more on expert opinion. Knowledge of antibiotic sensitivity of the responsible organism is desirable for the selection of treatment. If this is hard to pursue, it is reasonable to begin with a semisynthetic penicillinase-resistant penicillin by mouth, such as cloxacillin at a dose of 250 mg every 4–6 h or dicloxacillin at a dose of 500 mg every 6 h for 10 days. For penicillin-sensitive patients, erythromycin (500 mg every 6 h for 10–15 days), clindamycin (300–600 mg every 6–8 h for 10–15 days), or fusidic acid (500 mg 8-hourly) is suggested. For CA-MRSA cases, empiric therapy with penicillins or cephalosporins may be inadequate. MRSA sensitivities vary according to geography, but co-trimoxazole, clindamycin, and doxycycline are the most likely oral agents to be effective empirically against MRSA and most non-MRSA too.

We prefer to start with azithromycin, one of the relatively newer macrolides, at a dose of 500 mg on day 1, followed by 250 mg on days 2–5. We believe that patient compliance is better with this dose schedule. If the organism is resistant to macrolides, we consider oral therapy with a cephalosporin such as cefaclor or one of the newer quinolones, such as ciprofloxacin.

In *recurrent furunculosis*, which represents a difficult therapeutic problem, the organism's antibiotic sensitivity should be assessed. The appropriate drug, most often a semisynthetic penicillin, is usually given for 1–3 months, but it can be administered for longer periods (6–12 months), if necessary. Rifampicin (300–600 mg 12-hourly) or rifabutin (300 mg daily), because of the potential for fewer than rifampicin drug interactions and greater tissue penetration, can be given for 7–10 days, along with a semisynthetic penicillin. In especially stubborn cases, their administration for longer periods, alone or in combination with other antibiotics, can be considered. A proposed treatment regimen for recurrent disease is the so-called CMC regimen that consists of skin disinfection with chlorhexidine for 21 days, nasal mupirocin ointment for 5 days, and oral clindamycin 1,800–2,400 mg for 21 days.

Local Treatment

Topical therapy consists of the application of warm normal saline compresses (1 teaspoon of table salt in 2 cups of tap water) followed by the application of an antibiotic ointment. A daily bath with antimicrobial soap is advisable. Incision and drainage, needed in 80 % of cases, are particularly helpful to relieve the pressure and pain associated with furunculosis and usually suffice if lesions are <5 cm diameter.

Local anesthetics are usually not required before small furuncles are incised. Spray anesthesia is in most cases adequate to provide enough local analgesia. The use of a number 11 blade with its sharp-tapered end is preferable, and, initially, a small (2–4 mm) rather than lengthy incision is better to prevent unsightly scarring. If the furuncle has been present for a long time or is large, a longer incision may be required. Care should be taken to not incise deeper than the pseudo capsule that has been built at the site of infection. Pressure is then applied to the abscess, but with caution, because sudden rupture of intrafollicular loculi may shoot purulent material from the wound. Sometimes, it is necessary to probe into the abscessed cavity with a curved mosquito forceps or curette to break these loculi, but only after injecting a small amount of 2 % lidocaine into the skin overlying the abscess.

In *recurrent furunculosis*, topical antibiotic ointment should be applied to the potential reservoir areas, e.g., the nostrils, axillae, and perineum. However, decolonization regimens are not always used due to fears of encouraging mupirocin and other resistance. Special measures for maintaining topical hygiene have been also proposed in repeated infections. It is not clear whether these measures add anything of benefit to the care of such patients. According to these instructions, patient and family should bathe and shampoo one to two times daily, nails should be clipped short to avoid scratching, precautions should be taken during shaving to soak the beard with hot water and discard or boil the blade, and clothing, including underwear, should be changed daily and laundered thoroughly.

Alternative and Experimental Treatments

Interferon gamma, iron supplements, zinc sulfate, levamisole, pentoxifylline, and vitamin C have been used in the treatment of furunculosis in clinical and experimental settings.

Long-standing improvement of recurrent furunculosis was noted in patients with HIV, following the administration of interferon-γ. It was given at a dose of 50 μg on days 1, 2, and 3 of the first week, with a new cycle every 4 weeks.

Human immunoglobulin has been administered intramuscularly, at monthly intervals, in patients with recurrent, nonresponding to conventional treatments furunculosis with promising results. Once a period without new lesions was achieved, treatment was discontinued, and if new lesions developed, treatment was reinitiated.

Treatment with iron supplements for a period of 4 weeks was very beneficial in patients with

furunculosis and hypoferremia without anemia. Recurrences of furunculosis were prevented after treatment with oral zinc sulfate, in cases with low serum zinc levels.

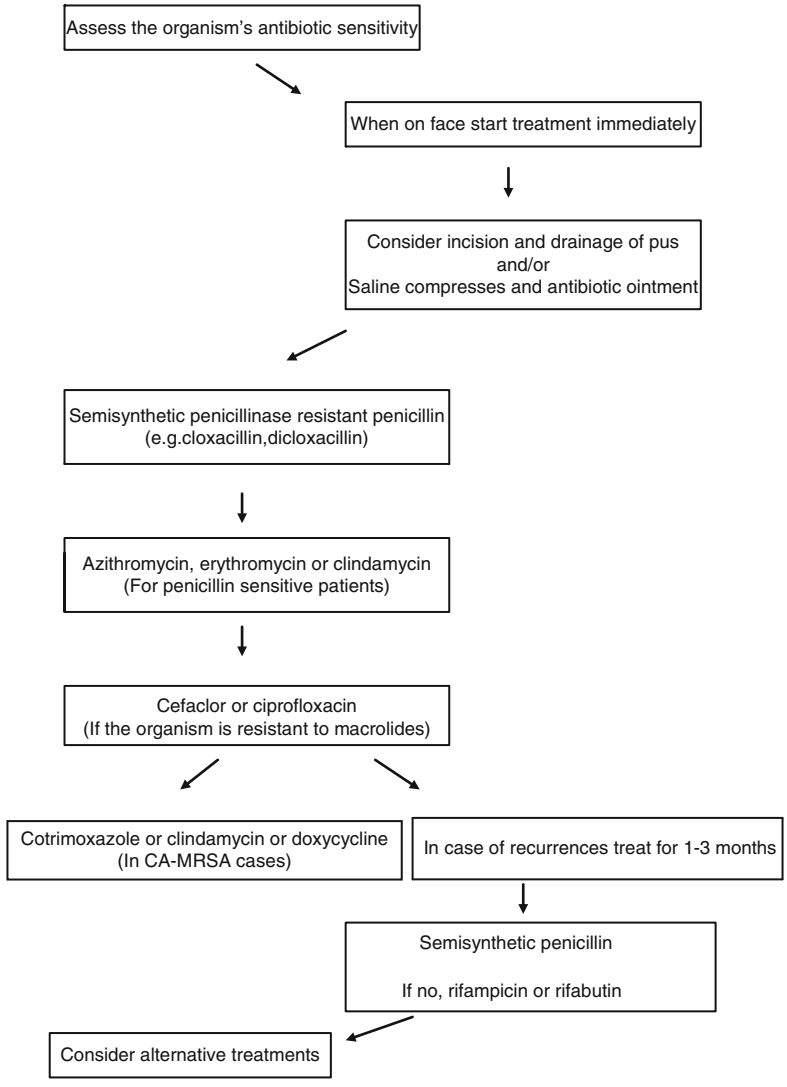
Pentoxifylline 400 mg t.i.d. for 2 months was successful in reducing recurrences in patients with chronic furunculosis.

Vitamin C has been found to be effective in the treatment of recurrent furunculosis in patients with impaired neutrophil function. It was administered alone at a dose of 500–1,000 mg per day for at least 30 days, or in combination with levamisole at a dose of 2.5 mg/kg for 3 days per week.

The excision of carbuncles with primary split-thickness skin grafting has been published in the recent literature as a new treatment modality aiming to the shortening of the recovery time and alleviation of pain.

Clinical data on the potential usage of new antimicrobials such ceftobiprole, ceftaroline, and oritavancin are expected.

Treatment Algorithm



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Granuloma Annulare

33

Rolland Gyulai and Ágnes Kinyó

Key Points

- Granuloma annulare (GA) is a benign, usually self-limited granulomatous dermatosis.
- While localized forms can usually be managed with topical treatments, disseminated variants generally require systemic therapy.
- Topical high-potency glucocorticosteroids (both as ointments or intralesional injections) and macrolide immunomodulators (such as tacrolimus and pimecrolimus) are most commonly recommended for localized GA.
- Isotretinoin, anti-tumor necrosis factor (TNF) biologic agents, and fumaric acid esters are the most frequently recommended systemic treatments for generalized GA.
- Cryotherapy and light-based treatment modalities (such as PUVA, lasers, and photodynamic therapy) may be used with success in both localized and generalized clinical forms.
- Combination treatments are often proposed to enhance effectiveness and tolerability.

Definition

Granuloma annulare is a benign, usually self-limited granulomatous dermatosis affecting predominantly children and young adults. Clinically, GA typically occurs as localized or disseminated annular, skin-colored or erythematous plaques or individual papules. Lesions are most common on the extremities (especially on the dorsa of the hands and feet); however, in generalized forms, the trunk is frequently affected. Subcutaneous and perforating forms are rare GA variants. Although GA is usually self-limited and asymptomatic, patients often need treatment for cosmetic reasons.

Basic Concepts of Pathogenesis

Although GA has been reported to be triggered by several factors (such as insect bites, sun exposure, viral infections, etc.), the etiology of the disease remains largely unknown. It is generally accepted that a delayed-type hypersensitivity reaction leads to matrix degeneration and elastic tissue damage in the skin and, ultimately, to granuloma formation. GA has been associated with several systemic diseases, including diabetes mellitus, malignancy, thyroid disease, viral infections (such as HIV, hepatitis B and C), and rheumatoid arthritis.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_33, © Springer-Verlag Berlin Heidelberg 2015

Clinical Presentation

GA can be classified based on the extent of the disease and the morphology of the individual lesions. Localized GA occurs primarily in children and young adults and is characterized by less than ten skin lesions, typically localized to the distal extremities (Fig. 33.1). Disseminated GA forms (Fig. 33.2), developing in about 15 % of patients, are often chronic and difficult to treat. Apart from the typical erythematous-violaceous annularly arranged papules and plaques, GA may present as rare clinical variants as well. Subcutaneous GA is characterized by large, skin-colored, deep-dermal or subcutaneous nodules, whereas in perforating GA lesions develop central umbilication, crusting, or ulceration.

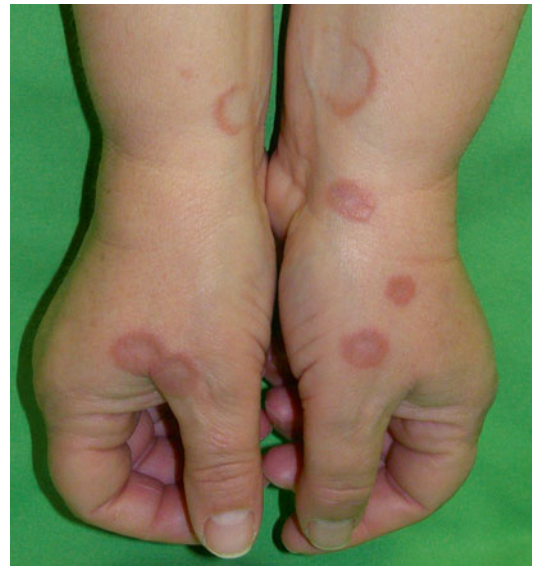

Fig. 33.1 Solitary granuloma annulare lesions on the hands

Differential Diagnosis

The differential diagnosis of GA is determined by the type and number of skin lesions. Biopsy is often required to establish a firm diagnosis when GA is suspected.

Localized forms should be distinguished from:

- Tinea: epidermal surface change; cultures for fungi are positive.
- Erythema migrans: history of tick bite, spontaneous resolution within weeks, "migration."
- Nummular eczema: epidermal involvement, severe itch, ill-defined borders.
- Discoid lupus erythematosus: epidermal surface change, involvement of skin appendages.

Generalized forms should be distinguished from:

- Sarcoidosis: usually less erythematous; biopsy is required.
- Necrobiosis lipoidica: typical (pretibial) localization, association with DM; biopsy is required.
- Disseminated lichen planus: epidermal involvement, mucous membrane lesions.

Subcutaneous forms should be distinguished from:

- Rheumatoid nodules: presence of joint symptoms; biopsy is required.

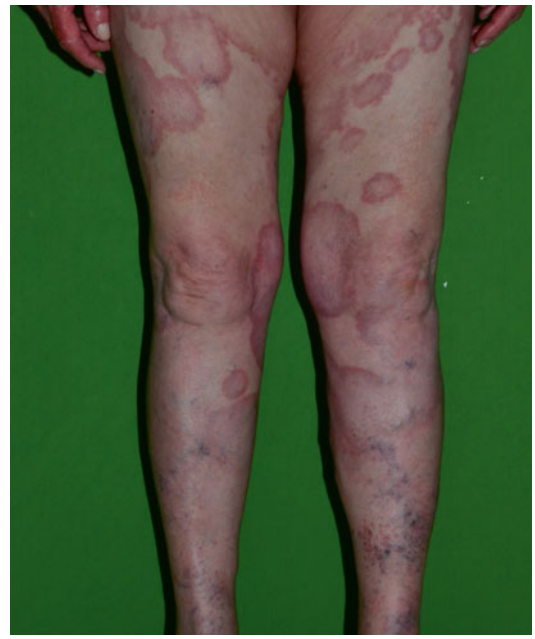

Fig. 33.2 Disseminated form of granuloma annulare on the lower extremities

General Principles of Treatment

Patients should be advised about the potentially self-limited nature of localized GA, as well as about the often chronic and treatment-resistant

course of disseminated disease. Therefore, treatment is not always necessary in localized variants; however, most patients request therapy for cosmetic reasons or symptomatic lesions. Disseminated GA presents significant therapeutic challenge, as evidence-based treatments and well-established recommendations are lacking. In most disseminated cases, systemic drug administration is recommended; however, risk of adverse drug reactions must be weighed against the benefit of treatment. The presence of comorbidities (both as potential trigger factors and treatment contraindication), prior therapies, gender, age, as well as the adherence to treatment must be taken into account when designing the therapeutic plan. Camouflage should also be considered in cases of recalcitrant, cosmetically disturbing lesions. Although the development of GA has been historically linked to type 2 diabetes mellitus, convincing evidence is still missing to establish this association. Therefore, GA patients will most likely not benefit from antidiabetic diet.

Topical Treatments

Topical Corticosteroids

Medium- to high-potency topical glucocorticosteroid (e.g., clobetasol propionate, betamethasone dipropionate, mometasone furoate, fluticasone propionate) preparations are the most commonly used treatments in localized GA. Although their efficacy and safety in GA have not been assessed by randomized clinical trials, there is ample clinical experience to justify their use as first-line treatment. Topical corticosteroids are relatively safe; however, patients should be advised about potential side effects, such as hypo/hyperpigmentation, atrophy, and development of striae distensae. Therefore, once- or twice-daily continuous application of topical corticosteroids should be continued only for a maximum of few weeks, and special attention should be paid to sensitive skin areas, such as the face or genitals. Intermittent application (such as once every 2–3 days, once a week, etc.) is recommended if long-term treatment is necessary to maintain results.

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (tacrolimus 0.1 % ointment and pimecrolimus 1 % cream) have been reported to be effective in localized GA. The mode of action of these macrolide immunosuppressants is through a nonsteroidal pathway; therefore, the use of these medications is associated with significantly less side effects than corticosteroids. Tacrolimus and pimecrolimus should be applied twice daily, and usually 4–8 weeks of treatment is required to achieve clinically meaningful improvement. Topical calcineurin inhibitors may also be used sequentially in order to maintain long-term control after other therapeutic interventions (e.g., corticosteroids or cryotherapy).

Topical Imiquimod

Imiquimod, a Toll-like receptor agonist, is licensed for the treatment of external genital warts and cutaneous neoplasia. The efficacy of imiquimod in GA has been reported in one case report and a case series of four patients (Kuwahara and Skinner 2002; Badavanis et al. 2005). Imiquimod 5 % cream was used once daily for 6–12 weeks, and the medication was left on the lesional skin for 10–12 h without occlusion and was then removed by washing. Complete remission and no recurrence for 10–18 months were reported in all patients. Based on these results, imiquimod may be used as a second-line therapy in localized GA.

Intralesional Corticosteroid Injection

Triamcinolone, in a dose of 5 mg/ml, is commonly used for localized GA, especially in treatment-resistant, more infiltrated, or deeply localized forms. As treatment is often associated with relatively intense pain, it is generally

recommended to combine the corticosteroid with 1–2 % lidocaine in the same syringe. Attention should be paid to corticosteroid side effects, especially skin atrophy. Frequent administration, therefore, should be avoided. Combination with lidocaine also helps to distribute the medication to a wider area, which, in turn, may further decrease the risk of local skin atrophy.

Intralesional Interferon Gamma

Intralesional injection of low-dose recombinant interferon gamma has been reported to be effective in localized granuloma annulare in a case series. Also, a few more recent case reports describe the disappearance of granuloma annulare upon interferon treatment of concomitant hepatitis B or C infection. On the other hand, interferon treatment reportedly can also lead to the development of generalized GA. It is, therefore, possible that interferon treatment is only effective in cases associated with hepatitis infection.

Topical Therapies at a Glance

- Localized GA is potentially self-limited, and treatment is not always necessary.
- Medium- to high-potency topical glucocorticosteroid preparations are the mainstay of the treatment in localized GA.
- Topical calcineurin inhibitors (tacrolimus 0.1 % ointment and pimecrolimus 1 % cream) are almost similarly effective and are associated with fewer side effects.
- Imiquimod cream, intralesional corticosteroid, and interferon gamma injections could also be tried with success if other therapies fail.

Cryosurgery

Cryosurgery is one of the most commonly used treatments in localized GA, although there has been only one prospective study proving its efficacy (Blume-Peytavi et al. 1994). In this report lesions resolved after a single freeze-thaw cycle in 25 of 31 patients (80.6 %). Relapse occurred in only 1 of 11 patients who were followed up for more than 2 years. The optimal dosing, duration, and frequency of freezing cycles have not been defined and generally depend on the experience of the treating physician.

Psoralen Plus UVA (PUVA) and Narrowband (NB) UVB Phototherapy

Cream PUVA treatment for localized GA was reported in a case series of five patients (Grundmann-Kollmann et al. 2001). Treatments were repeated four times a week; the mean number of treatments was 26, and the mean cumulative UVA dose was 55.9 J/cm^2. Complete clearance of the localized GA lesions was achieved in four patients and significant clinical improvement in one patient.

The efficacy of systemic PUVA therapy in GA was recently assessed by a retrospective analysis (Browne et al. 2011). This report analyzes the data of 33 patients treated with PUVA for generalized GA. Sixty-six percent of courses resulted in clearance of disease or in good improvement, 25 % had moderate benefit, and 9 % had a poor outcome. Of the patients that cleared, 79 % remained in remission at 6 months but only 32 % were still clear 12 months following treatment. PUVA treatment is usually administered three to four times per week, and on average 20–30 treatment sessions are required. Side effects, especially the long-term risk of skin cancer development, should be considered and weighed against the benefit of treatment.

Despite its frequent use in clinical practice, there is only very limited published evidence supporting the use of NB-UVB in the treatment of localized or disseminated GA. One case report describes the complete resolution of generalized symptoms after once weekly NB-UVB administration for 24 weeks. Therefore, frequency, dose,

and duration of sessions should be individually assessed by the provider for each patient.

Photodynamic Therapy

The use of photodynamic therapy (PDT) has been reported in both localized and generalized GA. Both 5-aminolevulinic acid and methyl aminolevulinate PDT resulted in complete or significant resolution of symptoms in the majority of the participating GA patients. The number and frequency of PDT sessions differed considerably in these trials; however, it seems that even in disseminated GA few treatment sessions may lead to significant clinical improvement.

Lasers

Different types of lasers (CO_2, 585 nm pulsed dye, 308 nm excimer, Nd:YAG) were reported in individual case reports as effective treatment modalities in GA. Session numbers differed according to laser types, and remission was complete or near complete and lasted for several months after the therapy.

Systemic Treatments

The use of systemic therapy is indicated for generalized GA. Although several different therapeutic approaches have been proposed, none is effective in more than 50 % of patients, and some of these treatments may have severe side effects (Table 33.1). Current treatment modalities are based on case series and consensus, as randomized controlled studies are missing.

Fumaric Acid Esters

Fumaric acid esters (FAEs) have been used with success in several inflammatory skin disorders, including GA. FAEs have been shown to suppress tumor necrosis factor (TNF)-α and other Th1 cytokine production via NF-κB-dependent mechanisms. As TNF-α and Th1 cytokines are required for granuloma formation, the therapeutic effect of FAEs in GA may be due to this phenomenon.

FAEs are administered in tablets using two formulations differing in strength. The tablets contain a mixture of dimethyl fumarate (DMF) and three salts of monoethylfumarate (MEF) in different doses. In the standard therapy regimen, FAE therapy is started with one low-dose tablet, and dosage is increased weekly by one tablet per day up to three tablets per day. Dose escalation is done weekly with a final maximum dosage of six high-dose tablets. FAEs significantly improved disseminated GA in approximately two thirds of the patients. Clinically meaningful response may be seen as early as 4–6 weeks after initiating treatment; however, some patients may need a longer therapy (Weber et al. 2009).

Adverse events are generally mild, transient, and dose dependent. Nausea, diarrhea, flushing, leukopenia, lymphopenia, eosinophilia, and transient elevation of transaminases are the most common findings. Laboratory monitoring (blood count, differential blood count, transaminases, gamma-glutamyl transferase, serum creatinine, and urine analysis) before initiation of and during FAE therapy is recommended. FAEs are not available in all the European countries.

Retinoids

Etretinate, an aromatic retinoid, has been reported as a successful treatment modality in GA. It has been used at a dosage of 0.8–0.9 mg/kg/day in monotherapy and in combination with PUVA therapy. In one case report, short-term administration of etretinate was enough to achieve complete remission in monotherapy (Asano et al. 2006).

Isotretinoin may improve GA symptoms via its antiproliferative effect and inhibition of collagen synthesis. Several case reports describe the successful use of isotretinoin (in doses of 0.5–1 mg/kg/day, 30–50 mg once daily, or 30–40 mg twice

Table 33.1 Dosage and adverse events of systemic treatments in GA

Treatment type		Dosage	Side effects	Level of evidence	References
FAE		Variable	Nausea, diarrhea, flushing, leukopenia, lymphopenia, eosinophilia, and transient elevation of serum transaminases	C	Meissner et al. (2012), Eberlein-König et al. (2005), Weber et al. (2009)
Isotretinoin		0.5–1 mg/kg/day	Elevation of serum transaminase levels, elevation of cholesterol and triglyceride levels, blood count abnormalities, teratogenicity	D	Schleicher et al. (1992)
Biologic agents	Adalimumab	80 mg followed by 40 mg every 2 weeks	Allergic reactions	D	Rosmarin et al. (2009), Werchau et al. (2010), Kozic and Webster (2011), Torres et al. (2011)
	Infliximab	5 mg/kg at 0, 2, and 6 weeks and bimonthly	Allergic reactions	D	Hertl et al. (2005)
Antibiotics	Dapsone	100 mg/day	Methemoglobinemia, hemolytic anemia	D	Martin-Saez et al. (2008), Duarte et al. (2009), Marcus et al. (2009)
	Doxycycline	100 mg/day	Gastrointestinal symptoms, photosensitivity	D	
	Rifampin+	600 mg/month	Epigastric burning, abdominal discomfort, nausea, vomiting	D	
	Ofloxacin + minocycline	400 mg/month			
		100 mg/month			
Corticosteroids		0.5–1 mg/kg/day	Weight gain, elevation of blood pressure, elevation of serum glucose level	D	
Antimalarials	Chloroquine	Variable	Retinopathy, aplastic anemia, liver toxicity	D	Cannistraci et al. (2005)
	Hydroxychloroquine				
Cyclosporine		4 mg/kg/day × 4 weeks, then tapered by 0.5 mg/kg/day every 2 weeks	Elevation of blood pressure, elevation of serum creatinine level	D	Fiallo (1998), Spadino et al. (2006)

daily for 8–16 weeks) in disseminated GA. Potential adverse effects are elevated serum transaminase levels, elevated cholesterol and triglyceride levels, blood count abnormalities, and teratogenicity. Laboratory controls are recommended frequently to control for potential side effects. Some patients require dosage reduction due to drug-related adverse reactions.

In summary, retinoid treatment is effective in disseminated GA; however, its use is limited by its unfavorable adverse event profile and the requirement for frequent monitoring.

Antitumor Necrosis Factor (TNF)-α Biologic Agents

Tumor necrosis factor (TNF)-α inhibitors are approved for the treatment of rheumatoid arthritis, psoriatic arthritis, moderate to severe plaque psoriasis, ankylosing spondylitis, Crohn's disease, and juvenile idiopathic arthritis. This group of drugs has sporadically been reported to be effective in granulomatous diseases. Interestingly, the occurrence of granulomatous skin symptoms has also been reported during anti-TNF therapy. The complete mechanism by which anti-TNF therapy works in granulomatous disease is uncertain. It is, however, well established that TNF-α plays essential role in granuloma formation. Thus, blocking TNF-α prevents the organization of newly forming granulomas and helps to dismantle existing lesions.

Infliximab, an antitumor necrosis factor-α monoclonal antibody, administered intravenously at a dosage of 5 mg/kg at weeks 0, 2, and 6 and thereafter at two monthly intervals resulted in initial improvement of GA lesions in 4–8 weeks and total resolution in a few months. The standard adalimumab treatment is 80 mg initially, followed by 40 mg every other week. A quick response was noted often within 1–3 weeks, and only postinflammatory hyperpigmented maculae remained after a few weeks. Histopathologic examination revealed significant reduction in the interstitial histiocytic infiltration and the precipitations of mucin. Etanercept has shown mixed results: only one patient showed improvement after a 12-week treatment, and a later series reported no improvement or worsening disease after treatment.

Methotrexate

Methotrexate (MTX) is an antimetabolite used in the treatment of many chronic inflammatory diseases. Several pharmacological mechanisms for MTX action have been proposed, both in respect to its immunomodulatory and anti-inflammatory effects. The dose of methotrexate can be adjusted between 10 and 20 mg/week. Side effects are gastrointestinal symptoms, liver toxicity, and blood count abnormalities.

Cyclosporine

Cyclosporine A (CsA) inhibits cell-mediated immunity by downregulating T-lymphocyte responses. A cycle of systemic cyclosporine therapy (started at a dose of 4 mg/kg/day for 4 weeks, subsequently reduced by 0.5 mg/kg/day in every 2 weeks) results in a good therapeutic response in GA in 3–6 weeks. The dosage of the drug and the period of treatment may be modified according to the therapeutic response and therapy-related side effects. Complete response can be achieved in disseminated GA with 3 mg/kg CsA daily for 12 weeks or 200 mg daily for 7 months. Close monitoring of blood pressure and laboratory control of renal function (serum creatinine) and blood counts are recommended with this drug.

Antimalarials

Antimalarial agents, including hydroxychloroquine and chloroquine, are used widely and successfully in the treatment of several connective tissue disorders and granulomatous diseases. They have been presumed effective because of their immunosuppressive and anti-inflammatory properties. Chloroquine is administered in a dosage of 250 or 500 mg daily; hydroxychloroquine is administered in a dosage of 200 mg/day for months. Possible side effects are retinopathy, aplastic anemia, and liver toxicity.

Corticosteroids

Oral steroids (prednisolone, methylprednisolone) are effective in the treatment of disseminated GA. Lesions cleared after a course of steroids (0.5–1 mg/kg/day), but the disease recurs quickly when the drug is discontinued.

Antibiotics

Dapsone is a sulfone antibiotic with many dermatologic indications, and it has been reported to be effective in disseminated GA (Martìn Saez et al. 2008). Its mechanism of action involves an anti-inflammatory effect, although the pathways by which it acts are not yet understood. The recommended dosage of the drug is 100 mg/day. Improvement may be seen between 4 and 12 weeks of treatment, and there is no recurrence after suspension of the drug. The main side effects are methemoglobinemia and hemolytic anemia. Blood dyscrasias, heart, liver and kidney abnormalities, pregnancy, and glucose-6-phosphate dehydrogenase or folic acid deficiency should be ruled out with laboratory tests before beginning treatment. During treatment, blood and urine tests should also be performed every week for the first month and every month thereafter.

Tetracyclines are broad-spectrum antibiotics that interfere with protein synthesis, inflammation, immunomodulation, cell proliferation, and angiogenesis. Doxycycline 100 mg administered twice daily for 12 weeks is effective in the treatment of GA. Adverse effects are gastrointestinal symptoms and photosensitivity.

The rationale for using rifampin + ofloxacin + minocycline (ROM) therapy for treating disseminated GA is based on the morphologic and histologic similarities between GA and tuberculoid leprosy. In addition to its antimicrobial effects, rifampin has also proved to influence antibody formation and cellular immune response, specifically delayed-type hypersensitivity. Minocycline has anti-inflammatory effects that are likely related to its antioxidant activity. It also interferes with lymphocyte (especially T cell) proliferation and reduces collagenase activity.

The standard regimen in paucibacillary leprosy for adults is as follows: rifampin (600 mg), ofloxacin (400 mg), and minocycline hydrochloride (100 mg). This regimen is administered for 3 months in disseminated GA (Marcus et al. 2009). Complete clearance of the plaques is achieved 3–5 months after the initiation of treatment. Some patients experience postinflammatory hyperpigmentation. Adverse effects most commonly include gastrointestinal tract symptoms: epigastric burning, abdominal discomfort, nausea, vomiting, and orange-red discoloration of urine.

Other Treatment Options

Pentoxifylline

The clinical efficacy of pentoxifylline is based on the hypothesis that an immune-mediated vasculitis may be involved in the pathogenesis of GA. Pentoxifylline is thought to reduce blood viscosity via effects on all major blood components. Although the standard pentoxifylline therapy (400 mg twice daily) offers a well-tolerated treatment option, the efficacy of the therapy is unclear.

Allopurinol

Allopurinol, a urate-lowering drug, has been successfully used in granulomatous diseases, such as sarcoidosis. A higher dose of the drug (300 mg twice daily) results in improvement of skin lesions in disseminated GA. The use of allopurinol significantly increases the incidence of serious drug hypersensitivity reactions, and in some patients allopurinol can also induce GA.

Niacinamide

The participation of delayed hypersensitivity reaction in the pathogenesis of GA suggests a possible efficacy of niacinamide. Niacinamide is a reasonably safe drug; even relatively high doses (1,500 mg/day) are associated with low incidence of side effects. Liver toxicity is an

important side effect; liver enzymes should be monitored during therapy.

Vitamin E and Zileuton

Oral vitamin E in monotherapy or vitamin E (400 IU) in combination with zileuton (2,400 mg) daily is a safe and probably effective treatment in patients with prolonged generalized GA.

Calcitriol

Oral calcitriol (0.25 γg/day) is also a safe and probably effective treatment in GA. Serum calcium levels should be monitored.

Defibrotide

Defibrotide is a deoxyribonucleic acid derivative derived from cow lung or porcine mucosa. It has been shown that defibrotide has protective effects on vascular endothelial cells, particularly those of small vessels. It has extensive beneficial pharmacological effects owing to its antithrombotic, anti-inflammatory, and anti-ischemic properties. Intramuscular use of defibrotide in a dosage of 400 mg/day results in improvement after 7-month administration. Frequent control of coagulation tests is recommended.

Combination Therapy

Fumaric Acid Esters (FAE) Plus PUVA

FAE should not be combined with other systemic drugs (methotrexate or cyclosporine A), but a better response was reported for FEA in combination with PUVA than in PUVA only.

PUVA Plus Prednisolone

PUVA therapy combined with 10 mg prednisolone every other day has also been effective in one case report.

Isotretinoin Plus Topical Pimecrolimus

Oral isotretinoin combined with topical pimecrolimus 1 % cream has been reported as a successful treatment.

Systemic Treatments at a Glance

- Isotretinoin is recommended as a first choice in disseminated or refractory GA alone or in combination with PUVA therapy.
- FAE is second-line treatment if previous treatments have failed or to enhance PUVA therapy. Adverse effects do not require discontinuation of the drug; dose reduction may be enough.
- Triple therapy with rifampin, ofloxacin, and minocycline has a positive outcome with a relatively few side effects.
- TNF-α inhibitors, mainly adalimumab, demonstrated a good clinical response in disseminated GA, but further well-designed clinical trials are needed to better direct treatment.

Future Perspectives

Treatment is often challenging for GA, especially because of the often recalcitrant nature of the disease and a lack of evidence-based therapy. Future investigations should focus on the evaluation of larger cohorts, not only to establish treatment recommendations in randomized, placebo-controlled trials but also to reach a greater understanding of disease pathogenesis and clinical-pathological presentation.

Guidelines for Treatment of GA

The treatment of choice should be individualized for the patient on the basis of dissemination of the symptoms, comorbidities, blood evaluations, drug interactions, compliance, adverse effect profiles, and reproductive status. In localized GA topical treatments are recommended as first-line therapy; in refractory cases phototherapy or

lasers could be applied. Systemic treatment in localized forms should be avoided of unnecessary side effects. In case of prolonged cosmetic disfigurement, systemic therapy can be attempted. Generalized forms of GA require systemic treatment in monotherapy or in combination with topical treatment. An algorithm of GA treatments is summarized in Fig. 33.3.

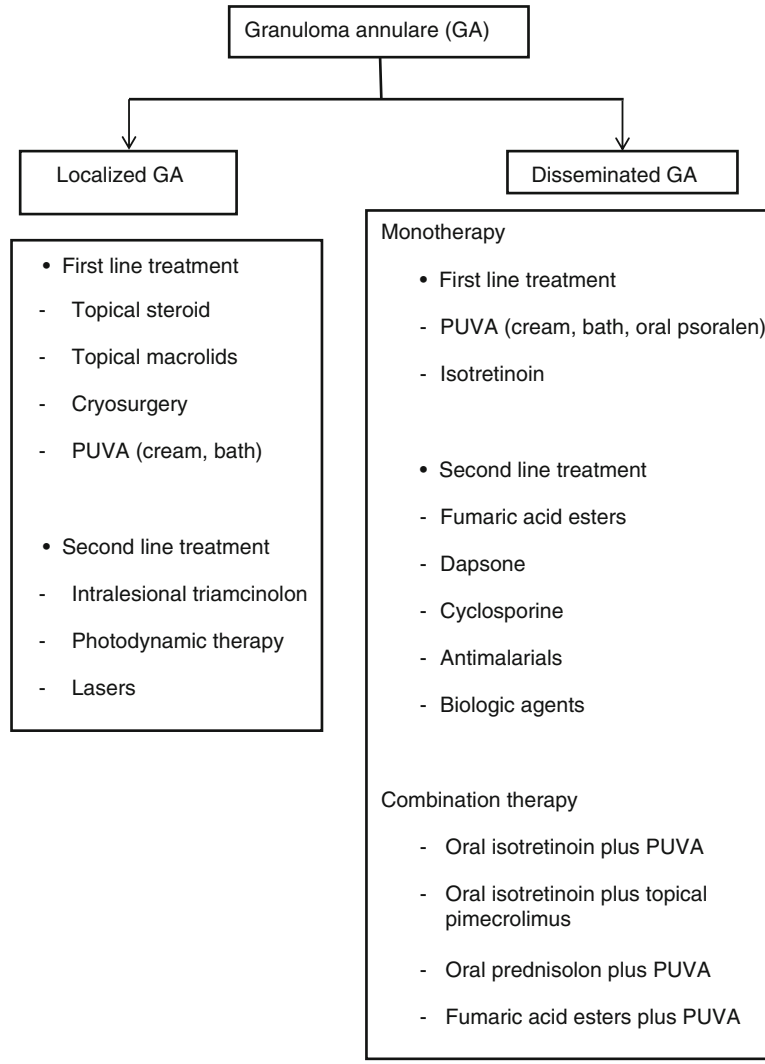

Fig. 33.3 Treatment algorithm for granuloma annulare

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Grover Disease

34

Bengu Gerceker Turk and Sibel Alper

Key Points

- Grover disease is an acquired pruritic papulovesicular disease which is characterized by acantholysis on histology.
- The pathogenesis of the disease is unclear.
- The first step is the avoidance of the exacerbating factors including heat, exercise, sweating, and ultraviolet (UV) radiation.
- Topical agents including corticosteroids, synthetic retinoids, and vitamin D analogues are recommended for localized disease.
- Antihistamines may obtain symptomatic relief.
- For recalcitrant and generalized disease, oral retinoids (isotretinoin, acitretin), systemic steroids, methotrexate, etanercept, Psoralen-UVA, or UVB phototherapy may be used.

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Definition

Grover disease (GD), namely, "transient acantholytic dermatosis," is an acquired disease which is characterized by pruritic papulovesicular rash on the trunk and extremities.

Basic Concepts of Pathogenesis

The main histologic feature is the acantholysis with dyskeratosis. The obstruction of damaged eccrine ducts, leakage of the sweat, or the small molecules seeping through the ductal epithelium have been proposed to induce the acantholysis in GD. Heat is also blamed directly to cause acantholysis. However, the pathogenesis remains largely unknown.

The acantholysis in GD shows six patterns including: pemphigus vulgaris like, pemphigus foliaceus like, Darier like, Hailey–Hailey like, spongiotic, and mixed. Additional patterns also have been observed. Recent electron microscopic evaluation showed poorly developed tonofibrils in the basal cells. The number of the desmosomes was observed as increased without any change in the structure. These poorly developed tonofibrils are suggested to cause the acantholysis in GD.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_34, © Springer-Verlag Berlin Heidelberg 2015

Clinical Features

GD usually affects older white men (male-to-female ratio: 3/1) with significant photo damage. Its frequency is estimated to be 0.1 %. Prolonged fever and the bed rest are predisposing factors. Thus the disease's frequency increases in bedridden and hospitalized patients to 0.8 %. Exacerbations are induced by heat, exercise, sweating, xerosis, and ultraviolet (UV) radiation. Some drugs including sulfadoxine-pyrimethamine, recombinant human interleukin-4, an aromatase inhibitor (namely, anastrozole), RAF inhibitors such as vemurafenib and dabrafenib, cetuximab, ribavirin, and penicillamine may trigger GD.

The disease is characterized by pruritic papulovesicles or keratotic papules that mainly affect the trunk. Lesions may disseminate to the neck, arms, or thighs. Scalp, mucosa, and palmoplantar areas are usually spared. Unusual presentations of GD include bullous, follicular papules and eczematous plaques. GD may appear along the Blaschko lines or in herpetiform and zosteriform distribution. The size of the lesions ranges between 1 and 3 mm in diameter. Lesions may arise on preexisting lentigines. Pruritus may be absent in approximately 40 % of the patients with GD and cancer. On the other hand, pruritus may be the only symptom of the disease which presents without a cutaneous eruption.

Although the disease is self-limited, recurrences and persistency may be observed. On follow-up, the disease resolves within weeks or months in 43 % of the patients, shows recurrences in 46 %, and persists in 11 % of the patients. Complete remission may be observed between the recurrent attacks. Patients usually have typical flares in summer or winter months.

GD is also reported to be associated with malignancies in 8 % of the patients. Chemotherapy for various malignancies and immunodeficiency conditions, including HIV infection, ionizing radiation, and transplantation, may also associate with the disease. Its incidence has been found as 6 % in acute myelogenous leukemia patients and 1.8 % in bone marrow transplants. Dermatoses such as asteatotic eczema, allergic contact dermatitis, atopic dermatitis, irritant contact dermatitis, and psoriasis may accompany GD in 11 %.

Differential Diagnosis

Grover disease should be differentiated from:

- Darier disease: Involvement of scalp and nails; onset in adolescence or early adult life.
- Hailey–Hailey disease: Onset in younger patients; the flexural involvement including the axilla, groin, perianal region, and lateral aspects of the necks together with the family history.
- Folliculitis: Reveals positive bacterial culture; follicular localization of pustules.
- Acne vulgaris: Earlier presentation with comedones and pustules.
- İmpetigo: Positive bacterial culture and typical crusting.
- Herpes zoster: Multinucleated giant cells on Tzanck smear.
- Scabies: Tunnels on the interdigital spaces; involvement of the glans and the nipples.
- Seborrheic keratoses: Typical dermoscopic features including milia-like cysts, comedo-like openings, brain-like appearance, and light brown fingerprint-like structures.
- Syphilis: Positive serologic tests.
- Pemphigus: Positive characteristic directs immunofluorescence deposition in a fishnet pattern.
- Galli–Galli disease: It is the acantholytic variant of Dowling–Degos disease. Focal reticulated pattern together with generalized involvement of the body including the hands. Skin biopsy lacks acantholytic patterns seen in Grover disease.

General Principles of Treatment

Since GD may regress spontaneously, there are no placebo-controlled trials and no guidelines for the treatment. Patients should be instructed to avoid exacerbating factors.

Soothing baths, emollient bath oils, colloidal oatmeal, regular use of emulsions, zinc oxide lotion, mentholated or calamine lotion, and pramoxine-containing preparations help to control the pruritus. Irritant products should not be used to avoid an isomorphic response. Antihistamines may obtain symptomatic relief. But they do not effect development of new lesions. Topical retinoids may be prescribed. Systemic therapy should be considered for recalcitrant, generalized cases. Treatment modalities are given in Table 34.1.

Table 34.1 Treatment modalities in GD

Topical
Corticosteroids
Calcipotriol
Tacalcitol
Tretinoin
Phototherapy
PUVA, narrowband UVB, UVA1
Systemic
Vitamin A
Corticosteroids
Retinoids
Methotrexate
Alternative
Medium-depth chemical peel (TCA)[a]
Red-light 5-aminolevulinic acid photodynamic therapy (ALA-PDT)

Modified from Kouba et al. 2006

[a]Trichloroacetic acid

Topical Treatments

Topical Steroids

Highly potent steroid creams are usually prescribed for localized disease. Topical steroids are successful in approximately 50 % of the cases.

Calcipotriol

It is the synthetic analogue of calcitriol and the bioactive form of vitamin D3. It has got immunomodulatory effects, regulates keratinocyte differentiation, and inhibits proliferation of keratinocytes. It is used alone or in combination with topical steroids such as betametasone ointment. Another vitamin D3, tacalcitol, has been reported as effective in a case report of GD.

Systemic Treatments

Oral Vitamin A

Oral vitamin A, 50,000 1U, may be administered three times per day for 2 weeks. The dosage is then reduced to 50,000 IU daily for a maximum of 12 weeks.

Corticosteroids

Systemic steroids suppress inflammation and pruritus. After the control of the disease, a minimum maintenance dose is recommended. Relapses may occur after cessation of systemic steroids.

Retinoids

Isotretinoin 40 mg/day has been used for 2–12 weeks. After improvement, it is suggested to taper the dose to 10 mg/day. Acitretin 0.5 mg/kg/day has been prescribed alone or in combination with calcipotriol ointment.

Methotrexate (MTX)

MTX 25 mg/week has been used. It has been found effective in some refractory cases.

Phototherapy

Psoralen-UVA, bath PUVA, and medium-dose UVA1 cold-light irradiation therapy have been used with success in GD. However, flare may be observed during the phototherapy.

Etanercept

Etanercept has been used 50 mg subcutaneously, twice weekly in a patient of GD for 6 weeks with success.

Alternative Treatments

Alternative treatment approaches should be used when the systemic therapies fail for the recalcitrant cases of GD. This includes trichloroacetic acid (TCA).

TCA

This method is based on the ablation of the affected epidermis to clear the pathologic process by reepithelialization. The standard concentration of TCA, 20–30 %, has been used successfully for the treatment in a recalcitrant GD patient.

ALA-PDT

Red-light 5-aminolevulinic acid photodynamic therapy has treated a recalcitrant case of GD after a single treatment session.

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Hailey-Hailey Disease (Familial Benign Pemphigus)

35

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Key Points

- Hailey-Hailey disease is a rare autosomal dominant skin disease due to mutations in the *ATP2C1* gene.
- The diagnosis is sustained by the clinical manifestations (recurrent erythematous plaques with erosions and fissures in the intertriginous areas) and the histopathological elements (acantholysis, "dilapidated brick wall" structure of epidermis).
- Topical antibiotic/antifungal therapy and topical corticosteroids are indicated in the mild form of the disease. In severe cases systemic antibiotics/antifungals and systemic corticosteroids can be used. Other treatments include: botulinum toxin injections, retinoids and laser CO_2 ablation.
- The patients have a poor quality of life, and in spite of different treatment attempts, both topical and systemic, the results are unsatisfactory.

Definition

Hailey-Hailey disease (familial benign chronic pemphigus, familial acantholytic dermatosis) is a rare skin disease with autosomal dominant transmission characterised by recurrent eruption of acantholytic blisters manifested in early adulthood.

Basic Concepts of Pathogenesis

ATP2C1 is the defective gene in Hailey-Hailey disease. This gene, located on 3q21-24, encodes the related human secretory pathway Ca^{2+}/Mn^{2+} ATPase (hSPCA1). hSPCA1 is located in the Golgi apparatus and is involved in the cytosolic and intra-Golgi Ca^{2+} and Mn^{2+} homeostasis. The decrease of Ca^{2+} or Mn^{2+} concentrations in the Golgi apparatus is inducing alterations in the construction of desmosomal components and other proteins involved in keratinocyte adhesion. More than 80 mutations in the ATP2C1 gene were described, but there is no correlation between genotype and phenotype.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_35,

Clinical Presentation

The disease debut is in early adulthood and consists of oval erythematous plaques covered with vesicles and post-vesicular lesions (erosions, fissures), scales and yellow crusts. The lesions are distributed symmetrically on the flexures (mainly involving the axillae and the groin) and friction sites. The flexural lesions are wet and can become hypertrophic and malodorous (Figs. 35.1 and 35.2) – a sign of secondary infection with bacteria or fungi. At the beginning the lesions are itchy and become painful when erosions and fissures develop. The lesions occur in recurrent eruptions, more severe during the hot seasons. Longitudinal white lines are formed on the fingernail plate (Fig. 35.3). Oral or genital eroded lesions can rarely occur. Few cases were described with segmental lesions (e.g. along Blaschko lines).

The disease is autosomal dominant with variable phenotypic expression, from mild forms (e.g. limited eczematous lesions, nail changes only) to severe forms (e.g. multiple painful flexural lesions).

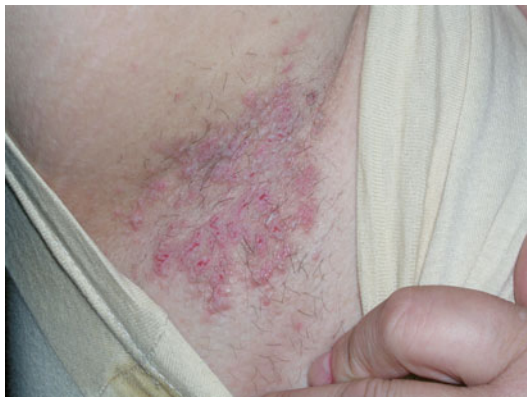

Fig. 35.1 Hailey-Hailey disease: right axillary area

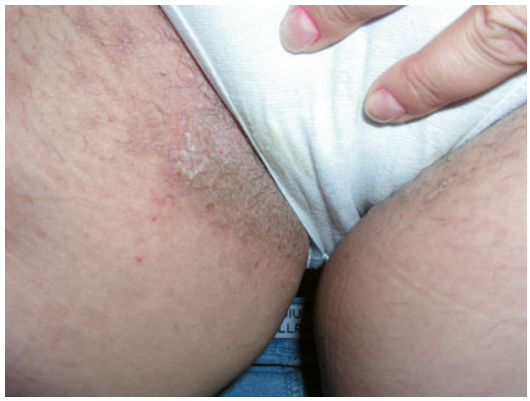

Fig. 35.2 Hailey-Hailey disease: right groin

Diagnosis: Histopathology

The histopathologic examination of the skin shows suprabasal clefting with acantholytic cells. Keratinocytes in stratum malpighii show few intercellular connections, mimicking a "dilapidated brick wall". Also present are discrete dyskeratosis and moderate perivascular lymphocytic infiltrate in the superior dermis (Fig. 35.4). The direct immunofluorescence examination is negative.

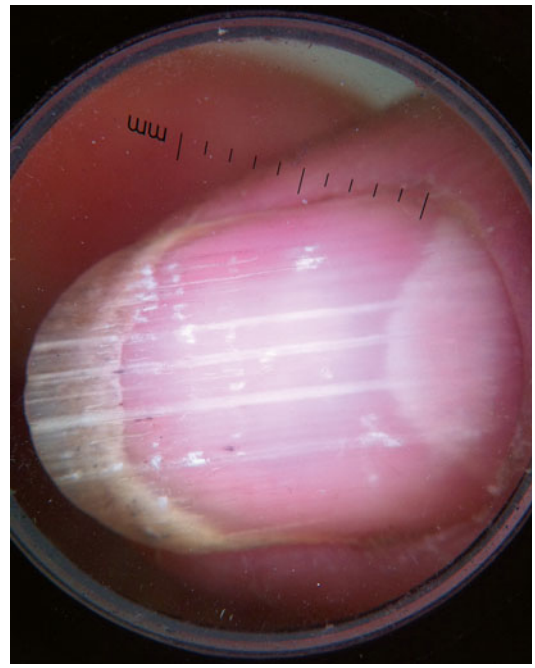

Fig. 35.3 Hailey-Hailey disease: fingernail plate with longitudinal *white lines* – dermatoscopic view

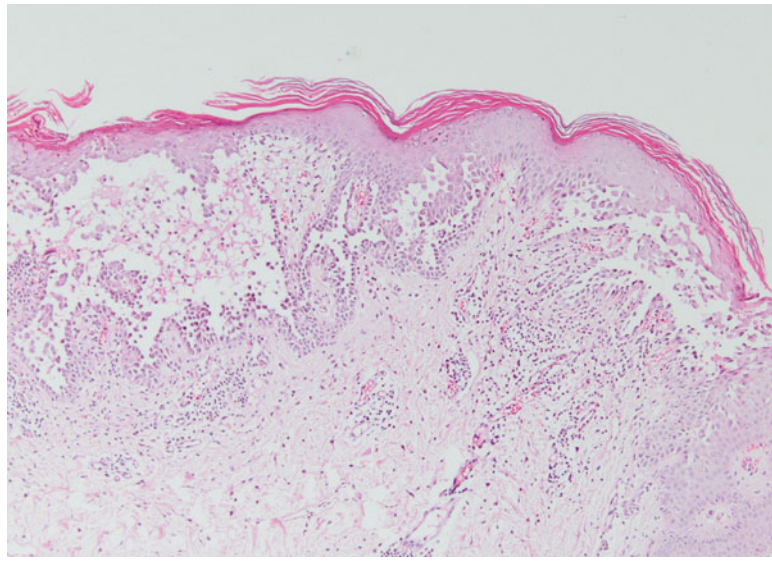

Fig. 35.4 Hailey-Hailey disease: "dilapidated brick wall" aspect (H-E, 10×) (Courtesy of A/Prof. Sabina Zurac, "Carol Davila" School of Medicine, Bucharest)

Differential Diagnosis

The autosomal dominant transmission of the disease and the adult onset of acantholytic blisters in the flexures are guiding elements for a positive diagnosis. Hailey-Hailey disease should be differentiated from:

- Darier-White disease
- Galli-Galli disease
- Eczema (contact dermatitis)
- Bacterial infection (impetigo, erythrasma)
- Fungal infection (dermatophytic or *Candida* spp. intertrigo)
- Viral infection (herpes simplex, varicella-zoster virus)
- Pemphigus vulgaris
- Pemphigus vegetans
- Epidermolysis bullosa simplex
- Inverse psoriasis vulgaris
- Extramammary Paget disease

General Principles of Treatment

Hailey-Hailey disease has no specific treatment. Most of the literature reports are limited to small series of cases. The Hailey-Hailey patient has a reduced quality of life and must constantly avoid mechanical trauma, skin maceration in the folds and exposure to ultraviolet light. Maintaining a normal weight and wearing comfortable clothing are recommended for moisture and friction prevention.

Topical Treatments

In patients with a mild form of Hailey-Hailey disease, the topical therapy is efficient for the remission of the inflammatory plaques and concomitant infection. Disinfectant measures (compresses or baths) can be used daily for the infection control: $AgNO_3$ 1 % solution, chlorhexidine, diluted bleach, etc. Local antibiotics will better treat the bacterial infection: gentamicin (also proven of value in selected patients with nonsense mutation in *ATP2C1* due to the read-through inducing capacities of aminoglycosides), clindamycin, neomycin and bacitracin. Azoles (clotrimazole, bifonazole, ketoconazole) are also recommended for controlling the mycotic infection.

Topical corticosteroids of mild potency (e.g. betamethasone dipropionate, fluticasone propio-

nate, mometasone furoate, triamcinolone acetonide, fluocinolone acetonide) are recommended for treating the inflammation. Combination of topical products including corticosteroids, antifungals and antibiotics can also be used when secondary infection is suspected.

In patients with frequent limited recurrences or in low-response cases, benefits can be obtained from topical retinoids or tacrolimus cream or calcipotriol cream.

Systemic Treatments

Systemic treatments are useful in severe forms of Hailey-Hailey disease. Systemic antibiotics are used according to the culture results. Long cures of erythromycin or cyclines (tetracycline, doxycycline, minocycline) can also be used for the anti-inflammatory effect. Systemic acyclovir will be used in case of herpes simplex virus infection. Systemic corticosteroids (e.g. prednisone 0.5–1 mg/kg) in short cures can reduce the skin inflammation. Systemic retinoids are not as effective as in Darier-White disease. Acitretin (25 mg/day) and also isotretinoin, etretinate and alitretinoin were reported as useful in some patients.

Other systemic treatments that can be used in severe or recalcitrant cases with different efficacy results are cyclosporine (2.5–3.5 mg/kg*day), dapsone (100 mg/day), thalidomide, methotrexate, systemic calcipotriol and etanercept.

Other Treatment Options

The reduction of sweating by botulinum toxin local injection was reported by many authors as beneficial in Hailey-Hailey patients. Surgical excision and skin grafting were also a successful treatment option for some patients. Of benefit in the case of patients with localised recalcitrant Hailey-Hailey disease was the destruction of lesions by dermabrasion with sterile sandpaper or CO_2 laser or selective tissue removal with Alexandrite laser or erbium:YAG laser. Photodynamic therapy with 5-aminolevulinic acid was reported as efficient in some patients.

Treatment Algorithm for Hailey-Hailey Disease Treatment (Fig. 35.5)

Future Perspectives

The developments in Hailey-Hailey disease pathogenesis can generate personalised therapy in selected patients. Aminoglycosides and non-aminoglycoside compounds that induce read-through of nonsense mutations can be of benefit in Hailey-Hailey patients with this type of mutation. As a disease produced by a single gene mutation, Hailey-Hailey disease is a candidate for gene therapy.

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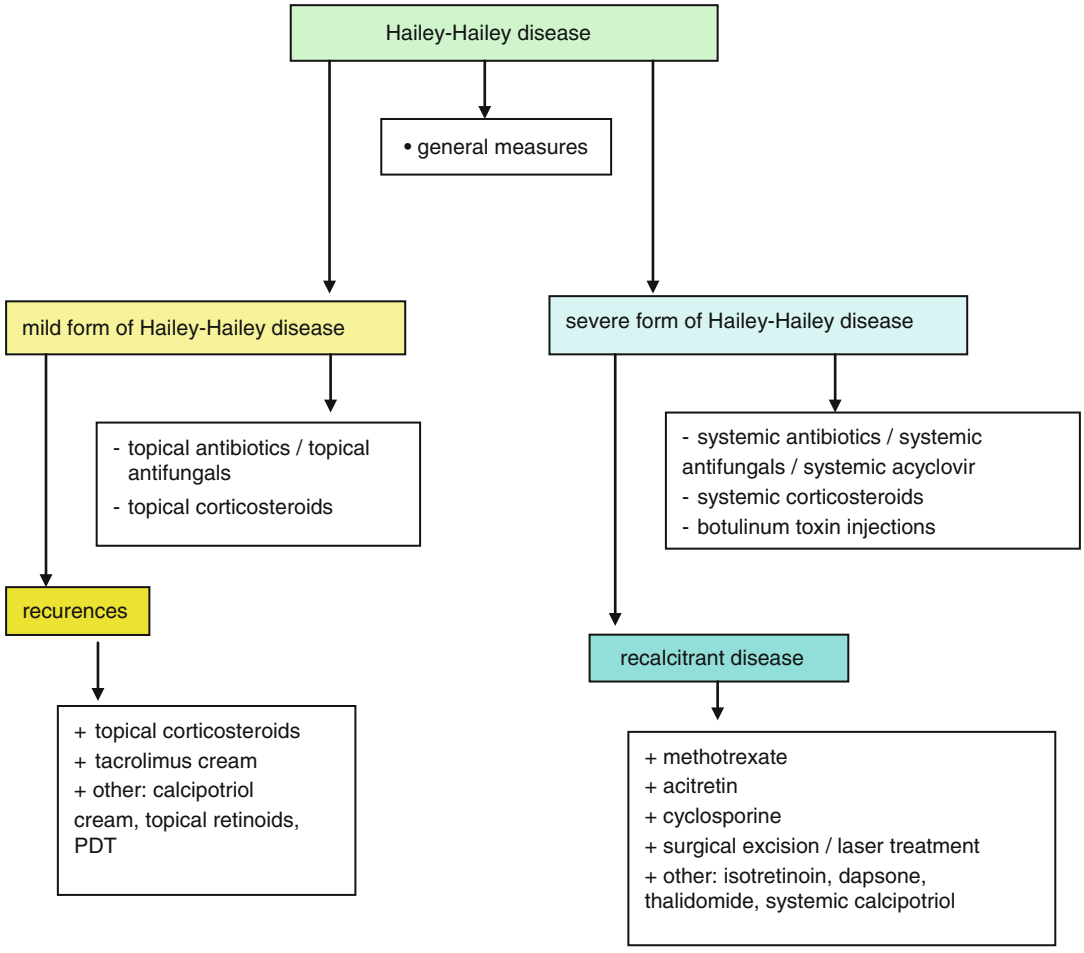

Fig. 35.5 Hailey-Hailey disease treatment algorithm

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Hand Dermatitis

36

John English, Angelo Massimiliano D'Erme, and Massimo Gola

Key Points

- Hand dermatitis, also known as hand eczema (HE), is the most common skin disorder affecting the hands. It is not a homogeneous disease, and it can occur in many and various forms either for clinical presentation or for severity.
- As shown in multicenter studies, (chronic) HE is associated with an inability to work and job loss, and the quality of life (QoL) is clearly compromised.
- Usually HE may be triggered by the contact with exogenous factors, and depending on them, it is possible to distinguish *irritant* and *allergic* contact dermatitis, or the influence of phenotypic factors, as in atopic dermatitis, can be predominant. During the normal practice, it is very common to observe mixed forms where development of HE involves multiple factors that may be present at the same or at different times.
- Chronic hand eczema (CHE) is not a uniform disease. It can be described as persistent HE (with own etiology and clinical manifestation) over 3 months or returns twice or more within 12 months.
- Successful basic therapy requires proper skin hydration; use of emollients; identification and avoidance of irritants, allergens, and specific trigger factors; antimicrobial treatment; skin protection measures; and educational programs. They have to be personalized according to the features of HE.
- The specific and proper use of topical corticosteroids (TCS) remains the first-line anti-inflammatory treatment of HE. They are fast acting and very effective in the short term (few weeks) for controlling the disease when the disease severity is mild to moderate.
- Phototherapies (mainly UVA1 and narrowband UVB) can be useful in moderate to severe forms, as well in HE unresponsive to TCS, including also very potent TCS.
- The management of severe *chronic hand eczema* (CHE) is often *challenging*, difficult, and unsatisfactory, further worsen by a not adequate response to local therapy. The therapeutic options for these

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_36, © Springer-Verlag Berlin Heidelberg 2015

patients are extremely limited. There is a clear medical need for an effective intermittent, long-term therapy to treat this chronic condition.

- Alitretinoin (9-cis-retinoic acid) has been specifically developed for the (long-term) management of CHE. The efficacy, safety, and tolerability of alitretinoin have been proved by multicenter trials and physician experiences. There are two traded formulations of alitretinoin: 10 and 30 mg. A 75 % improvement of clinical scores of CHE after 24 weeks was observed (48 % of patients achieve "clear" or "almost clear" hands within 12–24 weeks). The highest response was obtained in cases of hyperkeratotic CHE.

Definition and Epidemiology

Hand dermatitis, also known as hand eczema (HE), is the most common skin disorder affecting the hands. It is not a homogeneous disease, and it can occur in many and various forms either for clinical presentation or for severity. A wide range of clinical presentation has been reported: from mild, acute, and self-limiting forms to chronic and severe, refractory to treatment.

The clinical presentation includes scaling, lichenification, vesiculation/blistering, erythema, edema, hyperkeratosis, fissures, pruritus, and pain.

For these reasons a comprehensive differential diagnosis is often necessary.

The annual prevalence of hand eczema (HE) in the general population is between 7 and 12 % in Central and Northern Europe and the incidence at about 5 per 1,000.

Studies have reported a higher incidence of HE in female patients, which is most likely because of environmental factors.

The commonest causative factors and/or cofactors are a combination of irritants, mainly in domestic or working environment, and contact allergens with phenotypic factors (i.e., atopy, barrier deficit (i.e., filaggrin), and psoriasis).

A lot of affected people are workers and use their hands in their jobs.

High-risk professions are those where the job is made in a wet work environment: hairdressers, bakers, florists, healthcare workers, barman, metal workers, etc.

The annual rate of new hand eczema(s) is about 0.7 new cases per 1,000 workers in Germany: probably this rate may be higher due to the unreported cases.

Chronic hand eczema (CHE) has been defined as either a long-lasting, relapsing course of HE or HE unresponsive to standard treatment with topical corticosteroids (and basic therapy).

The proportion of chronic severe hand eczema (CHE) is estimated to be 5–7 % of all cases of HE, and 2–4 % are those refractory to topical treatment.

CHE has a poor long-term prognosis. It is very costly (most of the affected people are workers), and it has negative repercussion on people's quality of life.

Thus CHE is a very important issue in health economics and social medicine, as pointed out by several studies in the last years.

As shown in multicenter studies, (C)HE is associated with an inability to work and job loss. As a consequence, the (C)HE has a considerable economic impact on the patient, his or her employer, and the responsible insurers.

For example, painful rhagades, fissures, and erosions can severely restrict manual activities, causing significant impairment at work, in daily activities, and in social interactions. In Sweden up to 8 % of patients suffering from CHE have been forced to change jobs because of their disease. In Europe, the economic impact of HE has been estimated at €11 billion per year, only considering direct medical costs (cost for treatment, medication, visit, etc.). The direct nonmedical costs (as travel, informal care, etc.) and the indirect nonmedical costs (as loss of productivity, reduced performance at work, worsening of quality of life) were not considered in the total amount.

Furthermore, the quality of life (QoL) is clearly compromised. Hands are needed for a proper communication, expression, and working.

A lack of understanding of the disease and a suspicion of the people that the disease is contagious contribute further to the problem. HE is associated to psychological repercussions as shame, low self-esteem, anxiety, depression, withdrawal, and phobias.

Pruritus can increase the psychological stress (and vice versa), and they can lead to sleeplessness.

It has been shown that severe CHE is associated with a significant lowering of quality of life on par with that of generalized eczema or psoriasis.

About 50 % of all patients with hand eczema receive dermatological treatment, and about 5 % of them are off work due to the disease.

Basic Concepts of Pathogenesis

There is currently no universally accepted classification for HE. There is no single "hand eczema," but it includes different forms of disease.

HE is an inflammatory, noninfectious skin eruption whose pathogenesis can involve a combination of constitutional factors and exogenous factors. Undoubtedly, the impaired skin barrier function is a key factor in the pathogenesis of eczema. The dysfunction can be caused by a genetic predisposition (e.g., atopic skin diathesis, skin barrier component dysfunction, etc.) and environmental factors as irritants (low humidity, low or high temperatures, sweating, long-term application of topical corticosteroids, etc.), allergens, and exogenous proteases from house dust mites and *Staphylococcus aureus*.

Skin barrier dysfunction further increases the risk of penetration of irritants and allergens and the inflammation among the time.

During a clinical history, it is often possible to observe several causes (from exogenous to endogenous), heterogeneous morphological appearances (i.e., acute to chronic eczema, dyshidrosiform, hyperkeratotic-rhagadiform or "psoriasiform," nummular, etc.), and different manifestation sites (e.g., dorsal, palmar, interdigital, localized only at hands or more diffuse, etc.).

Usually HE may be triggered by the contact with exogenous factors, and depending on them, it is possible to distinguish *irritant* and *allergic* contact dermatitis, or the influence of individual factors, as in atopic dermatitis, can be predominant. During the normal practice, it is very common to observe mixed forms where development of HE involves multiple factors that may be present at the same or at different times. Thus the classification of hand eczema is challenging and it can be carried out according to etiological and morphological criteria as well as the affected location as reported in Table 36.1.

Severity can be evaluated according to the physician global assessment (PGA) (Table 36.2).

Table 36.1 Classification of hand eczema

Etiology (types of hand eczema)
Irritant HE
Allergic HE
Atopic HE
Other (vesicular/pompholyx type, protein contact dermatitis, idiopathic hyperkeratotic-rhagadiform, etc.)
Location
Dorsal surface of hands
Palmar surface of hands
Lateral margins of fingers
Fingertips
Interdigital folds
Wrists
One hand involved (or more involved than the other one)
Morphology
Redness, scaling
Acute exudative
Lichenified
Dyshidrosiform (vesicular)
Hyperkeratotic-rhagadiform (or psoriasiform)
Nummular
Severity (PGA)
Clear
Almost clear
Mild
Moderate
Severe
Duration
Acute
Chronic (>6 months or two relapse in 12 months)

From Diepgen et al. (2009) modified

Table 36.2 Physician global assessment (PGA)

PGA severity	Features	Intensity	Area involved
Severe	Erythema, scaling, hyperkeratosis/lichenification	At least one moderate or severe	>30 % of affected hand surface
	Vesiculation, edema, fissures, pruritus/pain	At least one severe	
Moderate	Erythema, scaling, hyperkeratosis/lichenification	At least one mild or moderate	10–30 % of affected hand surface
	Vesiculation, edema, fissures, pruritus/pain	At least one moderate	
Mild	Erythema, scaling, hyperkeratosis/lichenification	At least one mild	Less than 10 % of affected hand surface
	Vesiculation, edema, fissures, pruritus/pain	At least one mild	
Almost clear	Erythema, scaling, hyperkeratosis/lichenification	At least one mild	Less than 10 % of affected hand surface
	Vesiculation, edema, fissures, pruritus/pain	Absent	
Clear	Erythema, scaling, hyperkeratosis/lichenification	Absent	Not detectable
	Vesiculation, edema, fissures, pruritus/pain	Absent	

From Ruzicka et al. (2008)
The area involved does not apply to patients with eczema localized to fingertips. In the evaluation, the surface that refers to the surface area of the more severely affected side of the more affected hand has to be considered

Another commonly used scale is the modified total lesion symptom score (mTLSS).

HE varies in severity. Especially for CHE, a validated photographic guide has been carried out to better classify the CHE together, the PGA, and mTLSS scales.

Almost clear to mild HE heals quite quickly. Moderate eczema can persist for several weeks despite adequate dermatological therapy and cooperation of the patient. Severe eczema of the hands can be very difficult and challenging to treat.

At the moment, we can distinguish four main types of HE: irritant (subtoxic-cumulative) HE, allergic HE, atopic HE, and other forms of HE.

All these kinds of eczemas can become chronic with a chronic relapsing course (chronic hand eczema, 5° type).

The etiopathogenesis and clinical features of the "five main" types and of the CHE are reported in Table 36.3.

Table 36.3 Characteristics of irritant, allergic, and atopic hand eczema, other forms, and chronic hand eczema

1. Irritant (subtoxic-cumulative) hand eczema (IHD) (Fig. 36.1)
Etiopathogenesis
It is the result of repeated irritating harmful substances over a longer period of time in concentrations too low to produce an acute and immediate reaction
When the irritant is within the work environment, an improvement during the weekend (and healing possible with extended periods away from work) has been reported
Constitutional factors, as atopic skin diathesis and hyperhidrosis, promote its development
Location
Backs of the hands, fingers, exposed areas of the forearms, and, later, the inner surfaces of the hands are the most commonly involved areas
Skin symptoms are limited to the hands
Morphology
At the beginning, skin is raw, dry, and scaly. Acute manifestations are usually rare
After prolonged or repeated exposure to one or more irritants, there is development of redness, infiltration, and lichenification
Lastly, painful rhagades development and hyperkeratotic plaques interspersed with rhagades (hyperkeratotic-rhagadiform eczema)
Lesions present relatively well-defined borders and are not so itchy (as in allergic contact dermatitis)
2. Allergic hand eczema (AHD) (Fig. 36.2)

Clinical Presentation

Chronic Hand Eczema (CHE)

Chronic hand eczema (CHE) is not a uniform disease. There is no universally accepted

Table 36.3 (continued)

Etiopathogenesis
It is the result of delayed contact hypersensitivity (type IV hypersensitivity) to one or more allergens in a sensitized individual (verification with patch test is mandatory)
Protein contact dermatitis is also reported (rarely)
In occupational causes, the development and exacerbation occur in the working environment. An HE improvement during the weekend, up to a good improvement to healing on vacation, and a new relapse within days of returning to work are often reported
Location
The affected site corresponds to the area of exposure to the allergen
Involvement of exposed areas is typical (airborne dermatitis)
Spread of the dermatitis around the site of the exposure (d.d. irritant hand eczema)
Morphology
Acute exudative phase: it is possible to observe redness, vesicles, exudation, and excoriation. Severe pruritus is often reported
Chronic stage: hyperkeratosis, scaling/lichenification, infiltration, rhagades
Irregular border around the exposure sites (different from IHD)
3. Atopic hand eczema (Fig. 36.3) (AE)
Etiopathogenesis
Result of atopic eczema or atopic skin diathesis
Quite common involvement of hands in adult atopic dermatitis(AD)
Frequently unrelated to occupation but it is worthy to remember that irritant or occupational factors can trigger skin manifestation
Location
Often involves the backs of the hands (especially the dorsal site of the fingers)
Involvement of the nails can be present
Hand eczema can be the only site of AD involvement, or the hand can be a site of an AD spreader involvement (as flexor surfaces, face, neck)
Involvement of the wrist and of the "snuff box"
Morphology
Vesicles (dyshidrosiform morphology) in palmar and interdigital surfaces
Poorly bordered lichenified patches at the backs of the hands, mainly fingers and flexor surfaces of wrists
Scaling and rhagades in the lichenified patches on backs of the fingers
Sometimes nummular lesions on backs of hands

Table 36.3 (continued)

4. Other forms of eczema
Vesicular (dyshidrosiform), hyperkeratotic-rhagadiform (discussed in CHE), and nummular eczema
In this group it is possible to highlight an irritant, allergic, and/or atopic etiology or a combination of thereof
4.1 Vesicular (dyshidrosiform)
An atopic skin diathesis is common to observe
Location
Solitary blisters (pompholyx) mainly in the interdigital lateral spaces
Severe itching
Morphology
Solitary blisters (pompholyx) accompanied by severe inflammatory redness around and severe itching
4.2 Nummular eczema (Fig. 36.4)
An atopic skin diathesis and a history of AD are common to observe
Location
Dorsum of the end
Other lesions can be present on the wrist and arms and spread on the body
Morphology
Round-to-oval erythematous plaque on the back of the hands
5. Chronic hand eczema (CHE) (Fig. 36.5)
It can be the result of the IHD, AHD, AE, or other forms becoming chronic
Differences in etiology, morphology, and course explain the heterogeneity in the clinical manifestation and in the course of CHE
The hyperkeratotic-rhagadiform, vesicular, and mixed pattern HE are the most common manifestation
Location
Palmar and dorsum site
Tendency to recur at the same site
Morphology
Irregularly bordered, symmetrical, hyperkeratotic, lichenified lesions with painful rhagades
Absence or mild pruritus
The absence of vesicular eruptions is characteristic

classification for etiologically and clinically heterogeneous disease group. It can be described as persistent HE (with own etiology and clinical manifestation) over 6 months or returns twice or more within 12 months.

Differences in etiology, morphology, and severity make accurate diagnosis difficult and challenging.

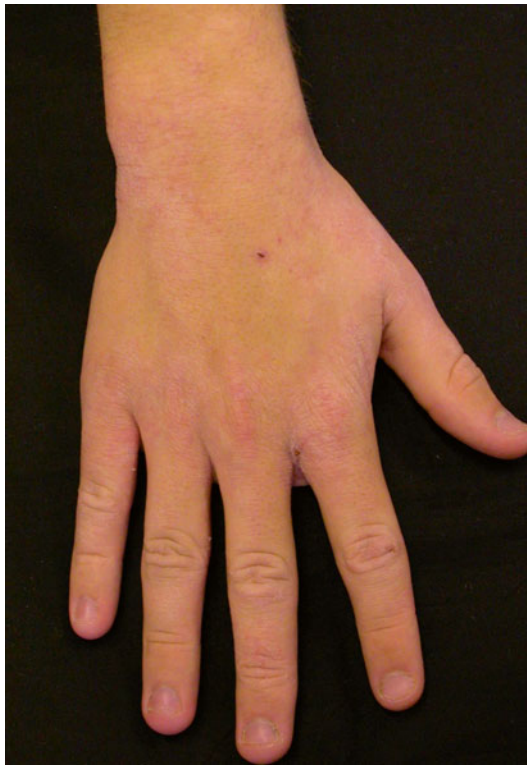

Fig. 36.1 Irritant contact eczema

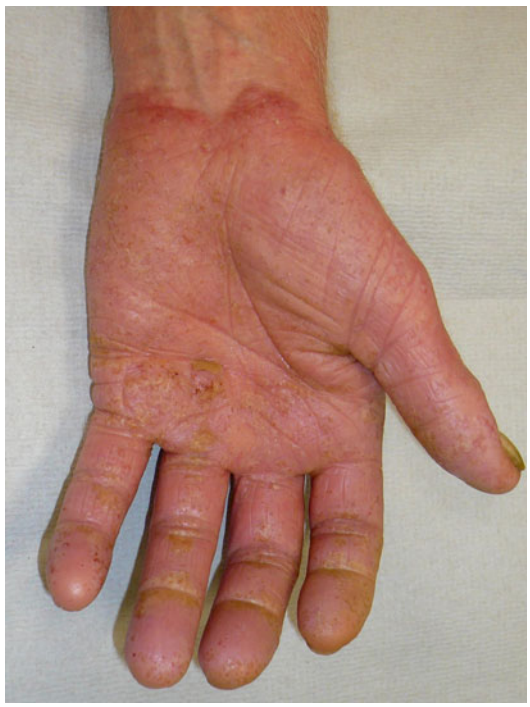

Fig. 36.2 Allergic contact eczema

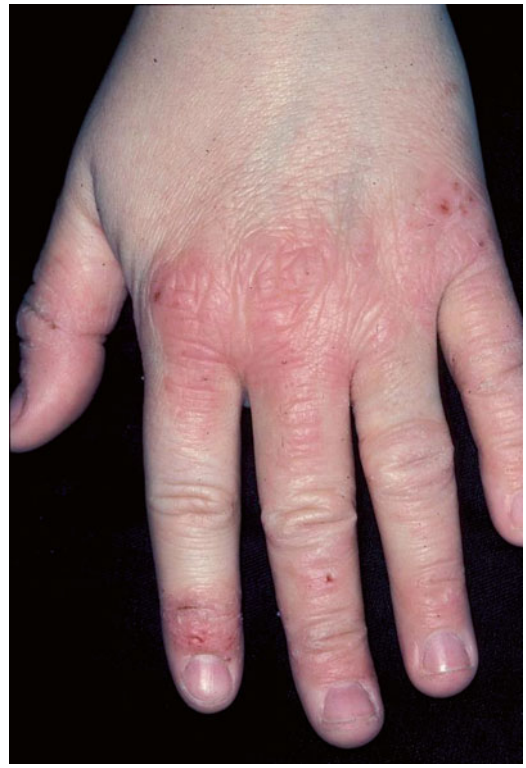

Fig. 36.3 Atopic dermatitis of the hands

The environment and individual factor interactions explain the different manifestations during the course.

The correct diagnosis is further hampered by the lack of a systematic classification system. It is based on etiology when possible and morphology when necessary.

Foot involvement is considered a distinguishing feature for idiopathic eczema if no other criteria (allergic or irritant contact dermatitis or atopic eczema) explain the plantar involvement.

Diagnosis

Given these limitations, accurate diagnosis of the disease is challenging and should be based on a careful patient history and on clinical examination (morphology and distribution of the lesions) (Fig. 36.6). Differential diagnoses, as psoriasis, infections, or other causes, must be excluded.

Diagnostic patch testing with the standard series, supplemented with additional specific

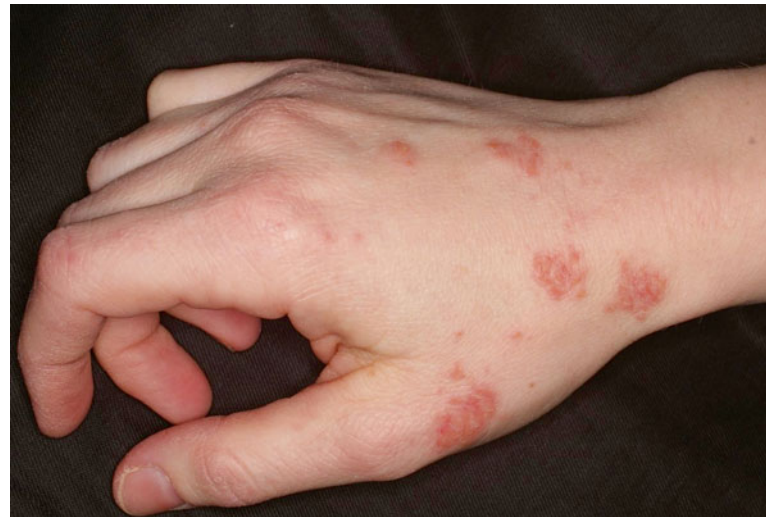

Fig. 36.4 Nummular eczema of the hands

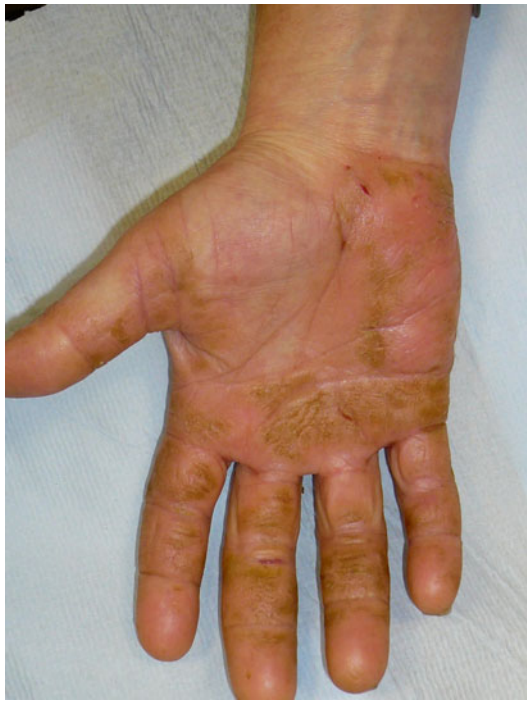

Fig. 36.5 Chronic (hyperkeratotic) hand eczema

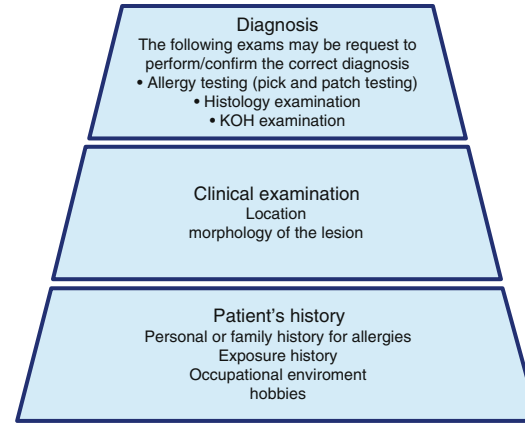

Fig. 36.6 Diagnosis of HE

series, other relevant allergens, and products used by the patient, according to the patient's exposure should be considered as a mandatory step.

The positivity of patch test(s) has to be relevant for the disease activity of CHE (as emerged from careful clinical history). Thus the diagnosis of allergic contact hand eczema can be made.

In a small studied group (22 patients with CHE and positive patch tests), the most common allergens are nickel (6), fragrance (3), medicaments (3), chromium (2), preservatives (2), permanent hair dye (2), and *Compositae* (1).

If no contact allergy is found and the patient has had relevant exposure to irritants (emerged from careful medical history), the dermatitis can be classified as irritant contact dermatitis. To confirm the diagnosis, an improvement of dermatitis with education and irritant avoidance has to be registered.

Lastly, a history of atopic dermatitis and other AD involvement can help in the diagnosis of AE.

The combination of irritant, allergen factors and atopic constitution contributes to led the

disease severe and chronic, the diagnosis difficult, and the management challenging. The clinical presentation varies greatly, making allergic and irritant types of eczema of the hands difficult to distinguish clinically and histologically.

Especially the correct diagnosis of hyperkeratotic-rhagadiform eczema can be very difficult due to its clinical and histological similarity to acral psoriasis.

It is important to remember that allergen avoidance may improve the eczema considerably but rarely leads to a complete cure underlying the multifactorial causes and features of HE. Even with the individualization and the avoidance of irritant/allergen factors, HE develops into a chronic condition as other dermatological skin diseases. Moreover the treatment is challenging and often unsuccessful despite adequate dermatological therapy and patient compliance.

Differential Diagnosis

Psoriasis, lichen ruber, and tinea manuum, in particular, can often be difficult to differentially diagnose and are sometimes mistakenly treated as eczema. Secondary infection of hand dermatitis with *S. aureus* is common.

Histological analysis is suggested in any skin disorder of uncertain cause or where the clinical diagnosis is doubtful.

Unfortunately, also histological examination cannot represent a valuable tool for the physician to distinguish clinically acral psoriasis from hyperkeratotic-rhagadiform eczema (whose similar clinical features are reported in Table 36.4). Table 36.5 lists diseases which should be considered as differential diagnoses. An accurate diagnosis of hand eczema leads to better management.

Table 36.4 Different features of psoriasis and hyperkeratotic-rhagadiform eczema. The clinical manifestations can be similar to each other

Psoriasis	Hyperkeratotic-rhagadiform eczema
Not usually itchy	Often itchy
Painful fissuring	Painful fissuring
Dry, silvery scale	Vesicular, scaly
Well-defined lesions	More diffuse lesions (border)
Nail and knuckle involvement	Nail can be involved
Koebner phenomenon	No Koebner phenomenon
Can be symmetrical	Often symmetrical
Often the palmar site is first involved	The palmar and dorsal site can be involved
Chronic relapsing	Often chronic relapsing

From English et al. (2009) modified

General Principles of Treatment

Although there are different therapeutic strategies for each group of HE, all patients should be educated and should adhere to skin protection measures and lifestyle changes to minimize exposure to allergens or irritants.

Allergen avoidance may also be beneficial, but not all contact allergies are clinically relevant. Table 36.6 lists measures that should be considered.

In Fig. 36.7 the general recommendation for HE according to its severity is reported.

Despite that HE is not a uniform disease, the basic therapy represents the first step in the long-term management of HE.

The treatment of hand eczema must take into account the following features in order to perform the correct management and therapy:

- Disease etiology (atopic, allergic, irritant, vesicular)
- Acuteness (acute vs. chronic eczema)
- Morphology (redness, scaling, lichenification, blistering, hyperkeratosis, rhagades, pruritus, etc.)
- Location (dorsal aspects of hands, interdigital spaces, palms)

Despite lots of literature data and clinical experience with various therapies, randomized controlled trials (RCT) are still lacking.

HE of recent onset should be treated promptly and vigorously in order to prevent the vicious circle of CHE. In fact the barrier damage and inflammation favor the penetration of irritants and allergens that further damage the skin barrier.

Table 36.5 List of diseases which should be considered in differential diagnosis with HE

Disease	Differential diagnoses	Notes
Psoriasis vulgaris	Personal or family history and clinical examination	Patch test and histological examination can help sometimes
Psoriasis pustulosa	Personal or family history and clinical examination. Sterile pustules	Neutrophils in the pustules
Acrodermatitis continua of Hallopeau	Personal or family history and clinical examination	
Tinea manuum	KOH examination	
Lichen planus	Different location (wrist) and morphology lesions (papules)	
Mycosis fungoides	Personal or family history and clinical examination	
	Histological examination	
Dermatitis (striata) pratensis	Personal history. Dermatitis bullosa and striata	
Palmar (and plantar) keratoderma	Personal or family history and clinical examination	
Scabies	Pruritus and clinical examination	
Fixed drug eruption	Personal or family history and clinical examination	
	Histology	
Pityriasis rubra pilaris	Other body sites affected	
	Histology	
Lupus erythematosus	Personal or family history and clinical examination	
Dermatomyositis	Personal or family history and clinical examination	
	Dorsum of the hand: Gottron papules	

Table 36.6 List of skin protection measures and lifestyle changes to minimize exposure to allergens or irritants

Short-term prophylactic measure of using gloves; however, do not use gloves for a long time as this will induce sweating of the hands. Use cotton liners or loosely fitting neoprene gloves
Short-term use of disposable gloves to avoid contact with irritants: washing powder, shampooing, dishwashing liquid, cleaning liquid such as toilet cleaner, etc.
Even the gloves themselves can sometimes aggravate the condition
Wash hands with mild, non-perfumed soap to reduce amount of skin bacteria
Avoid contact with certain food items: tomatoes, peeling of oranges, citrus fruits, and such like. Avoid juice from fish, meat, and certain vegetables. The patient's own experience will show what must be avoided
Reduce the amount of manual work at home and discuss where the partner could and should help, e.g., cleaning, dishwashing, helping the children with their baths, changing of the nappies, etc.
Avoid hair dying and potent allergens (i.e., *p*-phenylenediamine, acrylic compounds, nickel, etc.)
Complete avoidance of the triggering agent in patients who are sensitized to one or more allergens. Patients must be educated about the relevant contact allergens and where they are present and how to avoid or protect their skin with appropriate care measures
Emollient creams are the standard therapy, and they should be used alone or with all other treatments

Generally, *mild hand eczema* should be treated with anti-inflammatory drugs (topical corticosteroids (TCS)) together with a proper skin protection measures. This therapy, if performed quickly, is effective in controlling the symptoms in lots of these patients. Then a long-term management has to be performed with basic therapy. The short- and long-term management aims to prevent new relapses and to avoid the condition becoming chronic (which happens

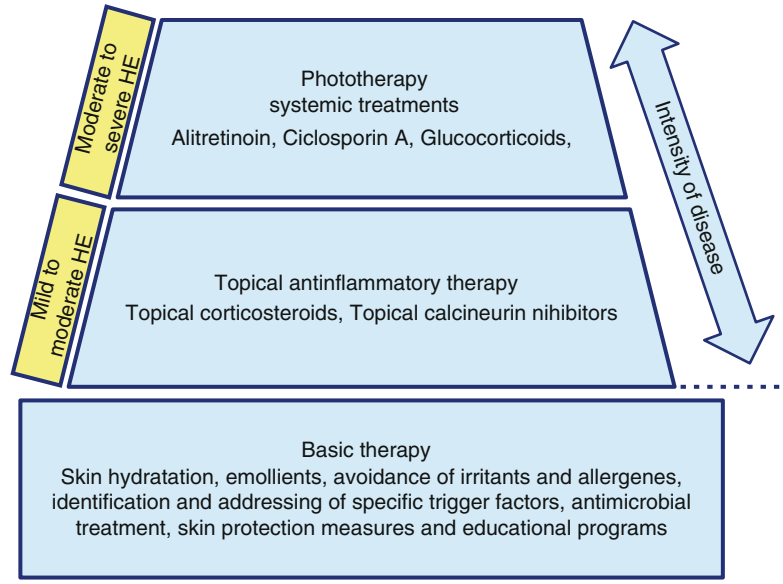

Fig. 36.7 General recommendation for HE according to its severity

in a considerable number of cases despite basic therapy and potent TCS).

It is important to note that a complete functional regeneration of the epidermal barrier requires several weeks or months after healing.

Chronic hand eczema is very difficult to treat and manage. They should be referred immediately and the treatment should not be delayed.

A successful management requires treatments that restore the skin barrier and control the inflammation.

Basic Therapy

Successful basic therapy requires proper skin hydration; use of emollients; identification and avoidance of irritants, allergens, and specific trigger factors; antimicrobial treatment; skin protection measures; and educational programs (as reported in Table 36.6).

Cleansing and Bathing

Patients with HE should follow a correct cleansing of the hands. As for atopic dermatitis, oil bath has to be preferred. The patient's washing habits have to be investigated. In fact excessive number of hand washing can be irritating for the hands.

Emollients

Consistent use of a moisturizing and emollient agent is key component in basic therapy. In particular, preparations should be free of any preservatives, fragrances, and perfumes (as well as for bath oils).

They should contain few ingredients (few or no potential allergens) in order to minimize a contact sensitization.

The vehicle of emollient is also important: In acute disease, dressings, lotions, or creams are preferred. On the other hand, in subacute, lichenified, and chronic stages, ointments are used with better efficacy.

Keratolytic substances can be useful in lichenified and in hyperkeratotic-rhagadiform eczema.

Salicylic acid (up to 20 %) and urea can be used with different concentration. Urea, at a concentration of 5–10 %, has a smoothing and water-binding effect, and it can be useful in lichenified and hyperkeratotic eczema. Sodium lactate, glycerol, sodium chloride, and other molecules can represent an alternative for water-binding and stratum corneum regulation.

Table 36.7 Topical therapy in hand eczema by morphology. They can be combined with the more appropriate pharmacological treatment

Morphology presumed effect of topical therapy (examples)
Vesicular ("*dyshidrosiform*")
Astringent solutions (i.e., potassium permanganate 0.025 %, eosin 2 %, boric acid 3 %)
Pasta exsiccans, zinc oxide barrier cream
When combined with hyperhidrosis, possible used aluminum chloride hexahydrate
Weeping/superinfection
Moisturizing (containing glycerol, urea 5–10 %, coal tar, etc.)
Astringent solution
Disinfectant and antibacterial (chlorhexidine, polyhexanide, povidone iodine, hydrogen peroxide, silver sulfadiazine, triclosan, etc.)
Treat immediately the superinfection (when it is clinically manifest) with pharmacological treatment
Hyperkeratosis
Keratolytic agents (salicylic acid-based ointments, ointments containing sodium chloride or urea)
Rhagades/fissures
Hydrocolloid dressings (rhagades)
Subacute eczematous reaction/lichenification
Anti-inflammatory substances (polidocanol (macrogol lauryl ether), glyceric acid, etc.)
Moisturizing (containing glycerol, urea 5–10 %, coal tar, etc.)
Dry, *scaling*
Moisturizing (containing glycerol, urea 5–10 %, coal tar, etc.)

From Diepgen et al. (2009), modified

Creams containing these molecules have to be used properly, because excessive or incorrect dosages can cause skin irritation and burning. They are also poorly tolerated on the rhagades.

A list of the emollient recommendation has been reported in Table 36.7.

Lastly, as for atopic dermatitis, educational programs and psychological counseling aim to improve the adherence in eczema management, the itch/scratching cognition, and the clinical and psychological condition.

Basic Therapy at Glance

Successful basic therapy requires proper:

- Skin hydration
- Use of emollients
- Identification and avoidance of:
  - Irritants
  - Allergens
  - Specific trigger factors
- Antimicrobial treatment
- Skin protection measures
- Educational programs

They have to be personalized according to the features of HE.

Topical Treatments

The specific and proper use of topical corticosteroids (TCS) remains the first-line anti-inflammatory treatment of HE.

They are fast acting and very effective in the short term (few weeks) for controlling the disease when the disease severity is mild to moderate. The use is limited by rebound flare-ups, tachyphylaxis, and lack of efficacy in severely affected patients. Despite their efficacy in the short term, long-term TCS use should be avoided because of their side effects. In particular, skin atrophy may contribute to further weakening of the skin barrier and further inflammation.

The choice of the potency of corticosteroids and the duration of treatment depend on the morphology, location, and severity of hand eczema.

As reported above (see atopic dermatitis chapter), corticosteroid concentration and its efficacy may be different when the preparation and the vehicles change.

It is commonly suggested to use immediately a potent to very potent steroid (according to the severity of the disease and the age of the patient) once or twice a day, followed by a less potent preparation for few days.

In case of chronic hyperkeratotic-rhagadiform hand eczema, the first treatment recommended is a high-potency corticosteroid (as clobetasol).

In mild to severe forms of HE, TCS have to be combined with the basic therapy. It is worthy to remember that the hand barrier is not restored at all after the end of the treatment. Thus a continued use of a nonsteroidal topical therapy (emollient) is necessary together with a basic education

of the hand skin care in order to achieve a long-term remission.

The possible utility of proactive therapy in the long-term management of HE (mainly chronic) has not been evaluated yet.

Before starting a TCS therapy, the correct diagnosis has to be performed. Other diseases, especially contact sensitivity (also to topical steroids, mainly when the symptoms get worse) and fungal infection, must be ruled out.

Other Topical Treatments

Topical calcineurin inhibitors (TCI) have been studied long in atopic dermatitis, and they can be used in atopic HE. TCI are not licensed for, but have been investigated in, the treatment of mild to moderate CHE. Studies investigating their efficacy in HE are still lacking.

Despite their safe profile (atrophy and other corticosteroid side effects are not reported with TCI), their use in HE is considered a second-line treatment in patients refractory to topical corticosteroids (TCS) or where the TCS use is contraindicated.

Topical Therapy at Glance

- The specific and proper use of topical corticosteroids (TCS) remains the first-line anti-inflammatory treatment of HE.
- They are fast acting and very effective in the short term (few weeks) for controlling the disease when the disease severity is mild to moderate.
- Despite their efficacy in the short term, long-term TCS use should be avoided because of their side effects. In particular, skin atrophy may contribute to further weakening of the skin barrier and further inflammation.
- The choice of the potency of corticosteroids and the duration of treatment depend on the morphology, location, and severity of hand eczema.
- Despite the safe profile of topical calcineurin inhibitors, their use in HE is considered a second-line treatment in patients refractory to topical corticosteroids (TCS) or where the TCS use is contraindicated.

Phototherapy

UVA1, topical PUVA, and UVB have been studied in HE. Narrowband UVB or UVA1 devices as well as excimer laser represent a valuable therapeutic option in these forms of hand eczema. The topical phototherapies have the advantage to limit therapy to the hands without a body irradiation. In this way some side effects (from erythema to potential carcinogenic risks) can be limited.

Since this treatment cannot be easily undertaken at home, one of the major disadvantages is that the patient has to go to the hospital from three to five times a week for the treatment. From 15 to 30 treatments are usually needed to achieve good results. This treatment can also be useful in combination with other topical or systemic therapies. In the literature, there are few studies evaluating the efficacy of phototherapy strategies. It can be a therapeutic option in moderate to severe forms, as well as in HE unresponsive to TCS, including also very potent TCS.

Phototherapy at Glance

- Narrowband UVB or UVA1 devices as well as excimer laser represent a valuable therapeutic option in HE.
- This treatment can also be useful in combination with other topical or systemic therapies.
- It can be a therapeutic option in moderate to severe forms, as well as in HE unresponsive to TCS, including also very potent TCS.

Systemic Treatments

The proportion of severe CHE is estimated to be 5–7 % of all cases, and approximately 2–4 % of patients with severe CHE are refractory to topical treatment.

The management of severe *chronic hand eczema* CHE is often *challenging*, difficult, and unsatisfactory, further worsened by a not adequate response to local therapy. It interferes with social and working life, and it has important and severe negative repercussion on the patients' quality of life. Moreover the majority of patients are workers, and high negative economic repercussion can be shown.

The therapeutic options for these patients are extremely limited. There is a clear medical need for an effective intermittent, long-term therapy to treat this chronic condition.

These patients may benefit (are candidate for) a systemic therapy.

Alitretinoin

Alitretinoin (9-cis-retinoic acid) is a drug approved from 2008 in several European countries for treating severe, chronic hand eczema that does not respond or with an unsatisfactory response to topical corticosteroids.

Alitretinoin, isomer of isotretinoin (13-cis-retinoic acid), is an endogenous physiological retinoid, panaagonist of both vitamin A acid receptors (retinoic acid receptors (RARs) and retinoid X receptors (RXRs).

It has been specifically developed for the (long-term) management of chronic hand eczema.

The exact mechanism of action of alitretinoin in the treatment of CHE is unknown.

Alitretinoin's anti-inflammatory and immunomodulatory properties have led to high response rates with a favorable safety profile over the long-term management.

There are two traded formulations of alitretinoin: 10 and 30 mg.

The efficacy, safety, and tolerability of alitretinoin have been proved by multicentral and national trials and experiences (BACH study and others).

A 75 % improvement of clinical scores of CHE after 24 weeks was observed (48 % of patients achieve "clear" or "almost clear" hands within 12–24 weeks). The highest response was obtained in cases of hyperkeratotic CHE.

A relapse has been observed in a third of cases. Studies have demonstrated that patients who had achieved "clear" or "almost clear" hands and had relapsed within 6 months responded to a second course of treatment.

Patients who had not responded to an initial 24 weeks of alitretinoin treatment achieved "clear" or "almost clear" hands in half of the cases when an additional treatment course of alitretinoin 30 mg for up to 24 weeks was carried out.

A small Italian experience has highlighted the positive impact of the alitretinoin treatment on the quality of life of patients with CHE. This data is of considerable importance considering that the study included 15 people whose jobs required the use of their hands. Eleven of those (73 %) reported moderately to severely impaired at work. Significant improvement of the point 7 of DLQI has been reported in this study. This point covers issues at work or studying, with scores ranging from 0 (no problem at work or studying) to 3 (severe difficulties at work or studying).

The recommended standard dose of oral alitretinoin is 30 mg daily for 12–24 weeks or until healing. Due to the possibility of increased triglycerides, cholesterol, and transaminases and thyroid side effects, some patients should begin with 10 mg once daily.

The most common reported side effect is headache (in about 20 % of cases), within the first 10 days of therapy.

It is very important to remember that alitretinoin, as any other vitamin A acid derivative, is a strong teratogen. Adherence to pregnancy prevention measures is strictly requested from before the beginning of the therapy up to 40 days after the end of the treatment for women of childbearing potential.

In conclusion alitretinoin is an effective, systemic, intermittent treatment for the long-term

management of chronic relapsing disease. The treatment has to be combined with topical therapies.

Systemic Corticosteroids

Systemic corticosteroids are commonly used to treat CHE. Despite their large use, their side effect profile and the lack of clinical studies do not allow to use them for the treatment of this disease. An acute relapse of CHE can benefit from a short period of oral corticosteroids.

Cyclosporine

Cyclosporine is approved for atopic dermatitis (of hands), and it can be used in severe, treatment-refractory HE, as a second-line treatment in patients unresponsive to alitretinoin or where the use of alitretinoin is not possible or is contraindicated. The use of cyclosporine in hand eczema is off-label.

Other Systemic Treatment

The use of other treatments such as methotrexate and azathioprine is reserved (off label) in patients unresponsive to other systemic treatments. Clinical large studies regarding the efficacy of these drugs are lacking.

Systemic Treatment at Glance

- The management of severe *chronic hand eczema* (CHE) is often *challenging*, difficult, and unsatisfactory, further worsened by a not adequate response to local therapy.
- The therapeutic options for these patients are extremely limited.
- There is a clear medical need for an effective intermittent, long-term therapy to treat this chronic condition.
- Alitretinoin (9-cis-retinoic acid) has been specifically developed for the (long-term) management of CHE.
- The efficacy, safety, and tolerability of alitretinoin have been proved by multicenter trials and physician experience.
- There are two traded formulations of alitretinoin: 10 and 30 mg.
- A 75 % improvement of clinical scores of CHE after 24 weeks was observed (48 % of patients achieve "clear" or "almost clear" hands within 12–24 weeks). The highest response was obtained in cases of hyperkeratotic CHE.
- The most common reported side effect is headache (in about 20 % of cases), within the first 10 days of therapy, followed by increase of triglycerides, cholesterol, and transaminases.
- Alitretinoin, as any other vitamin A acid derivative, is a strong teratogen.
- Cyclosporine is approved for atopic dermatitis (of hands), and it can be used in severe, treatment-refractory HE, as a second-line treatment in patients unresponsive to alitretinoin or where the use of alitretinoin is not possible or is contraindicated.
- Despite the large use of oral corticosteroids, their side effect profile and the lacking clinical studies do not allow to use them for the treatment of this disease.

Conclusion

The therapeutic approaches are summarized in Fig. 36.8a–e.

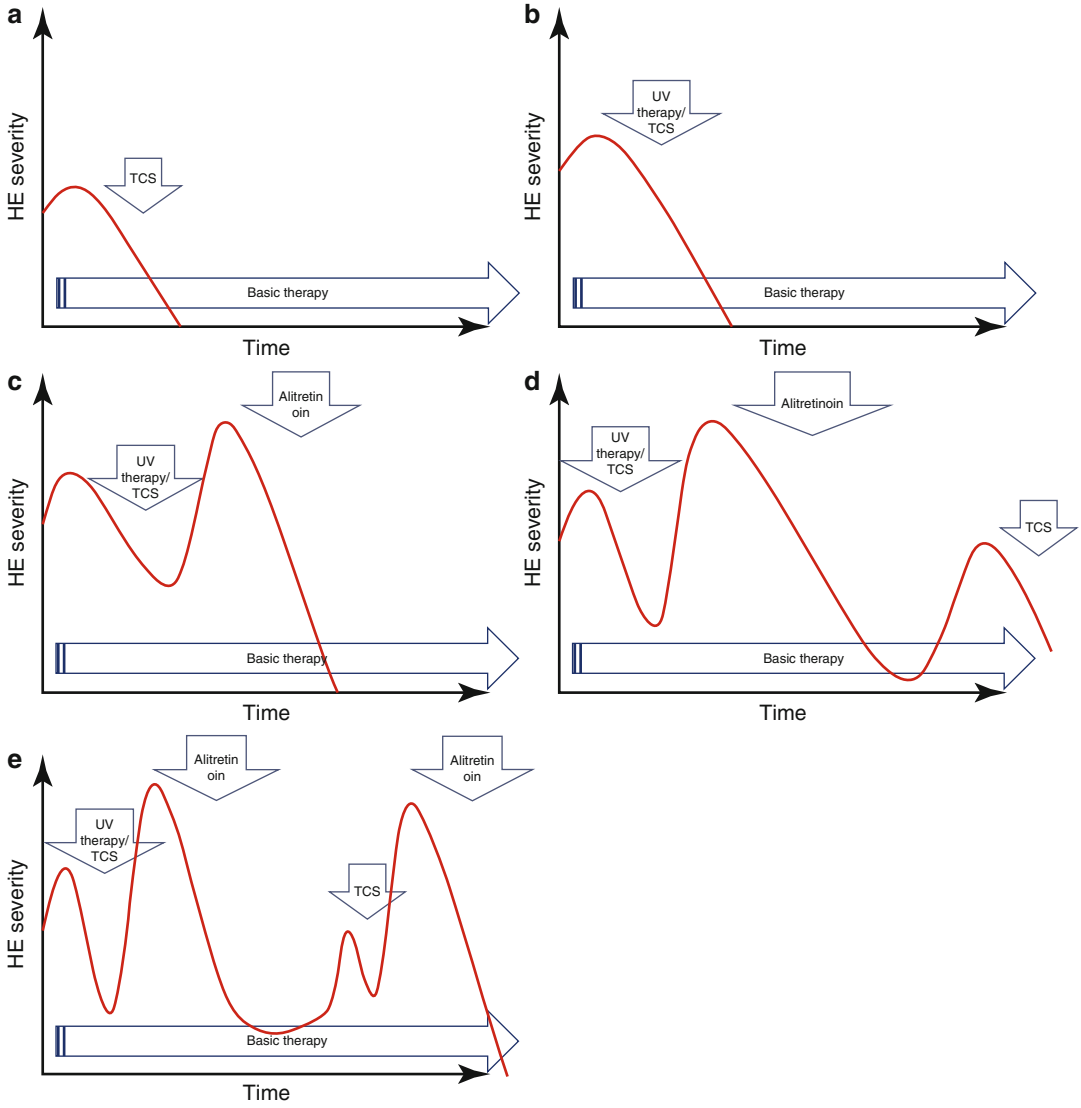

Fig. 36.8 (**a**) Mild and self-limiting HE, (**b**) moderate self-limiting HE, and (**c**–**e**) chronic moderate to severe HE. Topical and systemic treatments have to be combined during the time in order to achieve HE good improvement to remission

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Herpes Genitalis

37

Angelika Stary

Key Points

- Genital herpes is a chronic viral infection caused by two types of herpes simplex virus (HSV-1, HSV-2), most cases of recurrent genital herpes caused by HSV-2.
- Clinical diagnosis of genital herpes is often insufficient, and unclear manifestations should be confirmed by laboratory diagnosis in order to enable appropriate treatment and counselling for the patient.
- Cell culture, antigen detection, and PCR are the preferred tests for individuals with potential clinical lesions.
- Antiviral treatment with nucleoside analogues offers clinical benefit to symptomatic individuals with first-episode or primary genital herpes as well as for recurrent herpetic episodes.
- Transmission of HSV to the partner and newborn can occur by viral shedding and should be prevented by antiviral therapy.

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Definition and Epidemiology

Genital herpes is caused by the herpes simplex virus type 1 or 2 and is regarded as one of the most common sexually transmitted infections (STI) and the main cause of genital ulcer disease (GUD) in the developing world. HSV-2 infections are estimated to globally affect more than 500 million individuals with an annual incidence of 25 million cases among 15–50 years of age. It is a chronic infection and may last lifelong.

Herpetic lesions in the genital region have already been observed in the ancient period and were described by Greek scholars for a disease with creeping lesions. During the late eighteenth century, oral and genital herpetic lesions were recognised to be eventually associated with the same pathogenesis. Studies in the last century were able to demonstrate type-specific differences in the antigenic pattern between both HSV-1 and HSV-2.

Although most infections are mild or even subclinical, frequent recurrences are a persistent health and psychological burden for the individual with uncertainness concerning the danger of transmission to the sexual partner and newborn. In addition, erosive and ulcerative lesions have an impact on the transmission rate of the human immunodeficiency virus (HIV) and may lead to dangerous manifestations and treatment problems in immunocompromised persons. Only 10–25 % of persons infected with HSV-2 are aware of a genital HSV infection, mostly acquired

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_37, © Springer-Verlag Berlin Heidelberg 2015

from asymptomatic partners. The risk of sexual transmission correlates mainly on viral shedding in the large number of asymptomatic than symptomatic individuals. The risk of transmission of HSV infection to the neonate is high for infants born to mothers with clinical manifestations of first-episode genital herpes. Monitoring of first-episode or recurrent genital herpes during pregnancy is therefore an important preventive strategy for neonatal HSV infections. Potent antiviral agents offer clinical benefits in the treatment of first and recurrent episodes of genital herpes and have proven to reduce the frequency of recurrences when used as daily suppressive therapy. However, they cannot eradicate the latent virus infection and influence the transmission risk or recurrence rate after discontinuation.

Biology of HSV

Over 100 herpesviruses have been isolated in human beings who are the only known reservoir host. The herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are listed among the group of *Alphaherpesvirinae* (Table 37.1).

The typical structure of herpesviruses is characterised by the double stranded linear DNA genome, an icosahedral capsid of approximately 120 nm, and an envelope with glycoprotein spikes called tegument. The DNA genome codes for about 80 different genes, which are either important for viral growth or infection and replication. The spikes on the tegument express a large number of viral enzymes, and some glycoproteins are responsible for the interaction with the host cell and the cytopathic effect on the infected cells as well as the ability to establish latent infections in the host.

Table 37.1 Classification of human herpesviruses

Alphaherpesvirinae:
Herpes simplex virus (HSV-1 and HSV-2)
Varicella-zoster virus (VZV)
Betaherpesvirinae:
Cytomegalovirus (CMV)
Human herpesvirus 6 (HHV-6)
Human herpesvirus 7 (HHV-7)
Gammaherpesvirinae:
Epstein-Barr virus (EBV)
Human herpesvirus 8 (HHV-8)

Basic Concept of Pathogenesis

Both virus types of the HSV enter the human body by the oral or genital mucosa or occasionally by small lesions in the skin.

The infection of the cell occurs by the binding of the virus to the cell surface followed by the activation of a viral-membrane-fusing complex of glycoproteins (gB, gH, gL), which play a major role in the initial binding to heparan sulphate chains on cell surface proteoglycans. After the initial infection the virus invades the sensory nerve endings within the epidermis and is then retrogradely transported along the axon to the sacral ganglion with production of the virus or restriction of viral replication entering an immediate state of "latency" within neurons. Latency can occur if the viral genome is maintained in the cell and only a small number of the DNA is replicated without protein expression during the period of latency (latency-associated transcripts, LATs). The detection of LATs is a good marker for latency of HSV in the cells. Activation of latent viral genomes to the replicating state can be induced by in vitro cultivation of the latently infected tissue after explantation.

The cells are not automatically killed by the virus, as it occurs in cell culture. A virion shut-off protein which is also introduced to the cell at the time of viral entry causes degradation of pre-existing cytoplasmic mRNAs and inhibits cell protein synthesis. It is assumed that cell fusion, typical for the presence of procaryocytes in infected epithelia, may be a different method for viral spreading and facilitate evasion from the immune response of the host.

In human beings, latent infections can be converted to productive infection by factors or stimuli, which have not yet been fully defined, and the mechanisms underlying reactivation are still a tool for investigation. Exposure to stress,

fever, colds, sunlight, pneumococcal infections, menstruation, mechanic stimuli, tissue damage, immunosuppression, etc. is known to reactivate the virus from the sensory neurons. However, sometimes the occurrence of productive infection does not depend upon inducing stimuli, and the reason for reactivation is inevident. The virus is subsequently transported along the axon to the nerve endings and crosses into the epidermis at the site of initial infection on the dermis or mucous membranes. There it causes the typical vesicular herpetic lesions which may also be inapparent or hardly recognised. The frequency and clinical manifestation of the recurrent lesion depends on the immunocompetence of the host and the severity of the primary infection. Interestingly, HSV-1 reactivates more readily from the cervical sensory ganglia, whereas HSV-2 recurs from the sacral ganglia.

It is an assumption that this might be in connection with differences in the cell type and the viral proteins needed for reactivation. The replication of HSV in the epidermal cell layers has a cytopathic effect on keratinocytes followed by destruction and the occurrence of clinical lesions. The lesions, mostly vesicles, contain a high number of viral DNA, interferons, and other cytokines. Macrophages and CD4 lymphocytes can control the viral replication after 2–4 days, when the viral titres in the vesicle decline. It depends on the interaction of the immune response of the host and the inoculum of the herpesvirus whether the infection results in an asymptomatic relapse and how often asymptomatic shedding occurs between clinical visible lesions. Obviously HSV is able to evade different host-dependent immune mechanisms: it has the capacity to downregulate MHC class I antigen expression on the surface of infected cells. It can also bind and inactivate complement and immunoglobulins by interactions with glycoproteins C, E, and I.

In summary, after the invading virus has caused a productive primary mucocutaneous infection with an infection of the ganglia, the basic pathogenesis of HSV-1 and HSV-2 follows the sequence of latency, reactivation, and recurrent infection.

Epidemiology of Genital Herpes

The incidence and prevalence of genital herpes vary considerably in countries and population groups, affecting 20–40 % of adults in the developed and in an even higher percentage of individuals in the developing world. The cumulative lifetime incidence of HSV-2 reaches 80 % in African-American women and 60 % in African-American men. Several reports showed an increase of the incidence during the last decades. In the USA, however, the most recent data show a decrease from 21.7 % in 1991 to 17 % in 2004 (Fleming et al. 1997).

In most cases, infected individuals have acquired the HSV infection subclinically and can be identified only by antibody detection. It is therefore difficult to make exact calculations about the infection rates in different population groups worldwide. Reported data differ according to the presence and detection of clinical symptoms and are dependent on the technology used for the diagnosis of an infection. Type-specific serology assays provide information on the occurrence of type-specific HSV-2 and HSV-1 infections. The predominant cause of genital ulcers is HSV-2 accounting for up to 80 % of diagnosed aetiologies of GUD. The frequency of HSV-2 antibodies is higher among persons from STI clinics or MSM compared with the general population. In the last decade, an increase of genital lesions caused by HSV-1 has been reported in the developed world. A shift from HSV-2 to HSV-1 has been reported predominantly in young women and MSM. Reasons for that are unclear and can only be assumptions like an increase of oral sex or a decrease of HSV-1 infections during childhood. In a study on the cause of HSV-1 in genital herpes and its impact on surveillance and prevention, it was demonstrated that genital HSV-1 may often be acquired through receptive oral sex.

Infections with HSV-2 types are nearly always sexually acquired, while HSV-1 is already acquired in most individuals during childhood.

However, these infections do not protect against an infection with type 2. HSV-1 is causing a high proportion of first episodes in young women and MSM, while recurrences and subclinical viral shedding are more frequently observed for HSV-2.

Risk factors associated with transmission of genital herpes include age (15–30 years), the number of sexual partners, black or Hispanic race, female gender, homosexuality, HIV positivity, and social status measured by lower income and education levels. HSV-2 is spread primarily by sexual contact through infected secretions via inoculation onto susceptible mucosal surfaces.

The overall risk of HSV-2 transmission to a seronegative partner is estimated to be 3–12 % per year and seems to be higher for women (17 %) than for men (4 %) and higher when clinical lesions are present compared to subclinical genital herpes. The reason for a higher risk for women is probably dependent on anatomic differences and a greater mucosal surface area compared with men. There is conflicting data on whether a past infection with HSV-1 has a protecting effect concerning the acquisition of an infection with HSV-2. The DNA of HSV could also be detected in the semen of men with genital HSV-2 infection which might also play a role in transmission of infection.

Clinical Presentation

Genital herpes infections have a wide range of clinical features and may occur subclinical or asymptomatic in most of the cases. Clinical manifestations are influenced by viral and host factors and differ between primary infections and recurrences.

Primary or First-Episode Genital Herpes Infection

In primary infections, symptoms typically occur within 3–7 days after exposure often with a prodrome of tender lymphadenopathy, malaise, anorexia, and fever with localised pain and burning, followed by typical clinical lesions with vesicles and erosions (Figs. 37.1 and 37.2). Primary genital herpes has prolonged local and systemic symptoms which usually reach a peak within the first 3–4 days after onset of lesions with massive local pain and edema. In women, lesions may involve the cervix and cause vaginitis, vulvitis, and dysuria. Genital lesions in men caused by a primary HSV infection are usually not as dramatic as in women. A history of primary genital herpes is often unknown and only reported in 50 % of symptomatic infections in individuals with HSV-2 seropositivity.

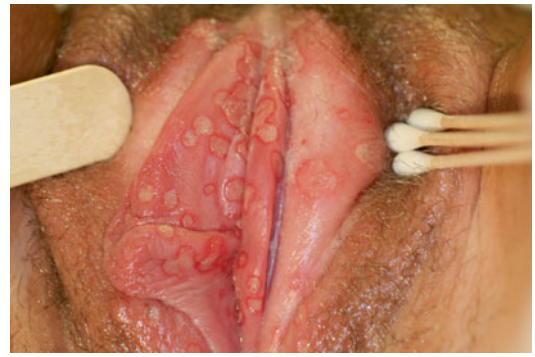

Fig. 37.1 First-episode genital herpes HSV type 1 in a 14-year-old adolescent, multiple erosions in the vulva region with urinary retention

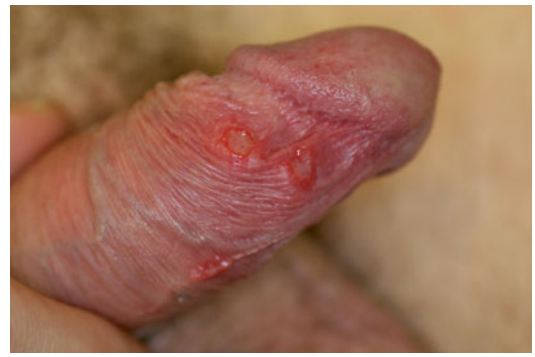

Fig. 37.2 First-episode genital herpes type HSV-2 in an 18-year-old adolescent, multiple erosions on the penile shaft

HSV Cervicitis and Proctitis

Cervical herpetic lesions are clinical features which are seldomly observed and are therefore easily overseen and often underdiagnosed. They may be asymptomatic or may result in vaginal discharge. Cervical HSV is a possible site of shedding and important for transmission of the virus to newborns or the sexual partner.

HSV is the most frequent pathogen isolated in men with nongonococcal proctitis and is commonly associated with fever, bloody rectal discharge, and severe rectal pain. Both HSV-1 and HSV-2 have been isolated from the rectal area of MSM but can also occur in women and may result in subclinical viral shedding due to reactivation in latent sacral ganglia.

Recurrent Genital Herpes

The major problem of genital herpes is the reactivation of the virus resulting in recurrences over months or years with varying frequency. Reactivation of HSV-2 from the sacral nerve root ganglia is widespread over a large anatomic area. It is less frequently observed with HSV-1 compared with HSV-2 infection and occurs in about 60 % in the first year and 30 % in the second year after first-episode HSV-1 infection. In contrast to HSV-1 relapses, about 90 % of individuals with HSV-2 infections develop recurrences in the first year with a higher frequency in men than in women.

The frequency of recurrences correlates directly with the severity of primary infection with varying time intervals between relapses. Usually, recurrences are less severe, and a limited number of blisters will appear on the genitalia which will resolve within a week. Lesions may even be subclinical and unobserved (Fig. 37.3).

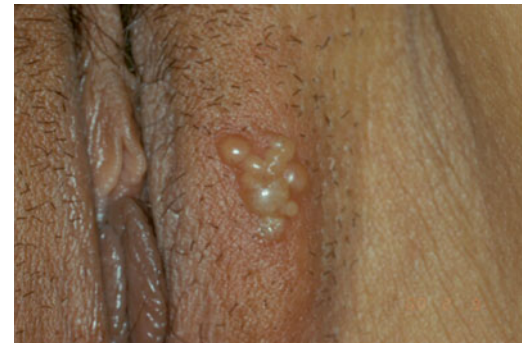

Fig. 37.3 Recurrent genital herpes with blisters on the labium major; HSV-2 positive

Genital Shedding of HSV

Asymptomatic viral shedding in patients with genital herpes is important for the understanding of transmission to the partner or newborn. It has been shown that besides shedding during symptomatic episodes of genital herpes, additional asymptomatic viral shedding occurs intermittently, mostly within a week of clinical recurrence. Individuals with more frequent recurrences had also more frequent subclinical shedding, as well as those who had recently acquired genital herpes. Viral DNA could be detected by PCR from the vulva, cervix, and rectum. These results may explain the viral transmission to partners of infected but asymptomatic individuals, unaware of eventually being a risk for their sexual partner. This has an important implication in terms of current or future relationships of individuals with genital herpes. In a multicentre study in the USA among individuals with symptomatic and asymptomatic genital HSV-2 infections, the frequency of genital shedding was evaluated (Tronstein et al. 2011). It could be demonstrated that persons with asymptomatic infections shed virus in the genital tract less frequently than persons with symptomatic infections, mainly because of a less frequent shedding from genital lesions. Even among persons with asymptomatic infection, shedding occurred in 10 % of days. The issue of infectivity is of concern for partner management and public health: The DNA load necessary for transmission is unknown, but there is an estimation that even a quantitatively moderate shedding may result in transmission. It is important to actively inform and advise the infected individual and offer methods such as condom use or daily antiviral medication to decrease the risk for transmission.

Diagnosis

In many infected individuals clinical symptoms of genital herpes may present as classical manifestations without the need of laboratory diagnosis. However, clinical diagnosis of atypical genital herpes should be confirmed or established by laboratory testing. Diagnostic procedures enable nowadays many more possibilities for both diagnosis of an acute infection and insight in the incidence and prevalence of HSV-1 and HSV-2 infections in different risk groups and in the general population. Multiple diagnostic methods are available for the detection of the virus, viral DNA, or viral antigen (Fig. 37.4). They include culture, direct fluorescent antibody assays (DFA), or molecular biological technology (Table 37.2). The Tzanck test is still often performed for rapid diagnosis in atypical clinical manifestations, but DFA is more sensitive and distinguishes between HSV and VZV. Cell culture had been used in the past for viral detection and is useful for resistance testing, but compared with molecular biological methods, the sensitivity is low and declines rapidly when the lesions start to heal. PCR is the most sensitive and the preferred method for the diagnosis of severe cases of HSV infections such as herpes simplex encephalitis or infections in newborns. It is recognised as the reference method for the detection of HSV in the cerebrospinal fluid and in brain biopsies and should be the method of choice for special questions concerning immediate treatment recommendations. This might be the case at the term of labour for decisions concerning caesarean section or for the diagnosis of HSV infection in the neonate. However, even amplification technology does not provide a 100 % sensitive test, and since viral shedding is intermittent, a negative result at the time of PCR testing does not exclude herpetic infections.

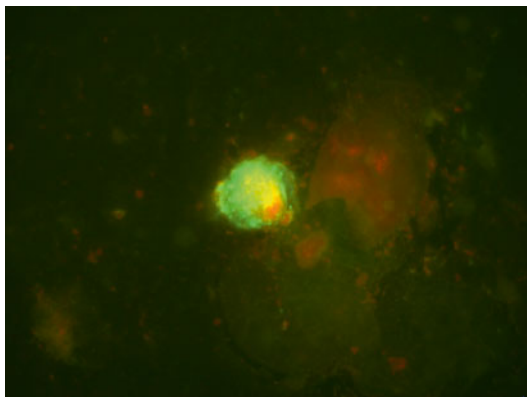

Fig. 37.4 Smear from the genital area of first-episode genital herpes. Direct fluorescence antibody assay: HSV-1 positive

Antibody detection for the differentiation between HSV-1 and HSV-2 antibodies in serological tests may be used for a better epidemiological insight. Type-specific antibody tests distinguish between both HSV types and are based on the type-specific glycoprotein gG-1 for HSV-1 and gG-2 for HSV-2 antibody detection. For prevalence or incidence studies and for prognosis and counselling, several reliable type-

Table 37.2 Diagnostic procedures for genital herpes

	Sensitivity	Specificity	Advantage	Disadvantage
Nucleic acid amplification NAATs	High	High, up to 100 %	Rapid different material	No resistance proof
				Expensive assays cross reactions
				Contamination
Virus culture	High, dependent on age of lesions	High	Allows sensitivity testing	Labour intensive
				Difficult transport
				Difficult storage
				Less sensitive
Antigen detection (EIA)	High, up to 80 %	High	Speed, costs	Less sensitive
				No viral typing
Antigen detection (immunofluorescence)	Lower, up to 50 %	High	Inexpensive	Less sensitive

Table 37.3 Differential diagnosis of genital herpes

Syphilitic chancre
Chancroid
LGV
Scabies with excoriations
Erosive genital candidiasis
Traumatic lesions
Fixed drug eruption
Genital aphthae
M. Behcet
LRP
Ulcus vulvae acutum Lipschuetz
Inflammatory bowel disease (M. Crohn)

and non-type-specific antibody detection assays are available. The Western blot represents the gold standard for serologic methods and is both highly sensitive and specific. However, it is still seldomly performed.

The use of diagnostic methods is especially recommended to exclude other infectious or non-infectious reasons for genital erosions or ulcerations (Table 37.3). In asymptomatic partners, CDC recommends type-specific serologic testing for HSV infection (2010).

General Principles of Treatment

The management of sex partners includes clinical and anamnestic evaluation, treatment recommendation, and counselling. Management and treatment of genital herpes have different targets which should be approached after the diagnosis is established and the patient had the opportunity for counselling.

In primary genital herpes it is of upmost importance to shorten the time of lesions and local and systemic symptoms and to prevent possible complications such as aseptic meningitis or urinary retention. After first genital episode or primary infection, the prevention of latency and the development of recurrences are further tools. In case of already established latency, the reduction or prevention of subsequent recurrences as well as the transmission of the disease to the partner or newborn is required. What has research contributed to these goals?

Antiviral drugs against HSV can partially control and reduce acute symptoms and the frequency of recurrent episodes. However, despite major advantages during the last 25 years, it is not possible to prevent latency or eradicate the latent virus from the ganglion or to reduce the frequency of episodes and the possibility of transmission after the preventive treatment is discontinued.

Antiviral treatment

Nucleoside Analogues

Antiviral treatment with nucleoside analogues offers clinical benefit to symptomatic individuals with first-episode or primary genital herpes as well as for recurrent herpetic episodes. Nucleoside analogues are also efficient in suppressing recurrent genital herpes in individuals with frequent episodes and are therefore recommended for long-term suppression in those with >6 episodes per year. Among FDA-approved oral antiviral drugs, acyclovir, valacyclovir, and famciclovir are the drugs of choice for the treatment of genital herpes. Oral administration is more efficient than locally applied antiviral creams.

1. Acyclovir
2. Valacyclovir
3. Famciclovir

Acyclovir (ACV)

ACV was the first guanosine analogue that was introduced as antiherpetic agent. It selectively inhibits the replication of HSV-1 and HSV-2 and of the VZV. It is phosphorylated by the virus-specific thymidine kinase in HSV-infected cells to acyclovir monophosphate and then by cellular enzymes to the active component, acyclovir triphosphate, which inhibits viral DNA synthesis by competing with guanosine triphosphate as a substrate for the viral DNA polymerase. ACV has potent in vitro activity against both serotypes of HSV and markedly reduces the duration and severity of lesions in animal models. It can be administered topically, orally, and intravenously, and all three options lead to reduction of viral

shedding and a quick healing of lesions and to a reduction of the duration of symptom. However, only the systemic treatment offers the benefit of accelerated improvement of general symptoms and avoids the development of new lesions. Therefore, oral treatment for both first-episode and recurrent genital herpes is recommended and eventually intravenous administration in acute primary genital herpes with severe general symptoms.

Numerous studies in primary and recurrent herpes have shown ACV to efficiently decrease the duration of symptoms and viral shedding, and in primary or first-episode infection, it rapidly reduces fever and systemic symptoms within 48 h. It is important to initiate the antiviral treatment as early as possible to have an immediate effect on viral shedding. The oral administration of 400 mg ACV twice daily has shown similar antiviral effect as a dosage of 5 × 200 mg. Higher dosage does not offer more benefit.

For recurrent genital herpes, the influence of ACV has also been studied concerning the frequency of recurrent episodes: daily ACV prevention reduces the number of recurrences and the rate of HSV detection on genital mucosa. However, it has no influence on the rate of recurrences if not permanently administered.

Beside the efficient impact of ACV on herpetic lesions in the introital region of the genital tract, it has also shown an improvement of herpetic proctitis in men having sex with men (MSM) and on cervical lesions in women with herpes cervicitis.

ACV has an excellent safety profile. Side effects are seldomly reported and might include nausea, headache, and rash. In case of renal dysfunction, the treatment schedule has to be modified. Resistance is seldomly observed and mostly only occurs in immunocompromised individuals. HSV resistance to ACV has been described in immunosuppressed individuals (mainly HIV-positive persons) in 2–9 %. In those cases, resistance is not restricted to ACV only, but also includes treatment with valacyclovir and famciclovir.

Valacyclovir

The main disadvantage of ACV is the low bioavailability of ACV with only a small fraction of the drug is absorbed. Valacyclovir, the L-valyl ester of acyclovir and a prodrug of ACV, is almost completely converted in the gastrointestinal tract by hepatic and intestinal enzymes, which increases the bioavailability of ACV from 10 to 20 % to more than 50 %. A dosage of 1,000 mg daily is similarly effective as intravenous ACV.

Valacyclovir and ACV have been compared in numerous studies, demonstrating a similar profile of activity in primary, first-episode, and recurrent genital herpes with a more convenient dosage frequency.

Different schedules of dosage for valacyclovir have been evaluated and compared with placebo or with ACV.

For the treatment of first-episode herpes, the recommendation of antiherpetic therapy with 1 g valacyclovir twice daily was similarly efficient as 200 mg ACV five times daily. However, in individuals with first-episode or recurrent herpes episodes, even the lower dosage of 500 mg valacyclovir twice daily was equally effective in the reduction of lesions and viral shedding as 1,000 mg twice daily and also comparable with 200 mg ACV five times daily or 400 mg daily (Gupta et al. 2004). Both drugs decreased the risk of viral isolation by 95 % and the rate of HSV detection by about 75 %.

Valacyclovir is also recommended for prevention of recurrent episodes in individuals with genital herpes.

It has been compared with placebo for the prevention of recurrences in genital herpes and viral suppression in 382 patients with at least eight recurrences per year for a period of 4 months: while about 70 % of drug recipients were recurrence-free, the corresponding data in the placebo group was about 10 %. Valacyclovir 500 mg once daily is therefore recommended for persons with nine or fewer recurrences per year. A different schedule of 250 mg twice daily or a higher dosage of 1,000 mg is recommended in individuals with ten or more recurrences per year.

Valacyclovir has also been evaluated whether it has an impact on viral shedding and the transmission of HSV-2 in between sexual partners: 500 mg once daily was able to reduce transmission of HSV-2 by 48 % (Corey et al. 2004).

To summarise, both drugs, ACV and valacyclovir, are equal in their profile of efficacy and side effects, with the advantage for valacyclovir of a more convenient dosage frequency. An early onset of therapy within 24 h is essential for a successful influence of the clinical course of genital herpes.

Famciclovir

Famciclovir is the prodrug of penciclovir, which inhibits the replication of both HSV types. It needs the viral thymidine kinase for phosphorylation to penciclovir monophosphate and – similar to ACV – is converted in the intestinal wall and liver to the active form penciclovir triphosphate. It has a high bioavailability of about 77 % and a much longer intracellular half-life (10 h versus 1 h). The antiviral drug is well tolerated with a very low profile of adverse effects. A reduced dosage is recommended in case of impaired creatinine clearance.

For the treatment of first-episode genital herpes, famciclovir showed comparable results with ACV, concerning symptom resolution, viral shedding, and lesion healing (Loveless et al. 1995). The efficacy of 125 mg famciclovir twice daily was evaluated in recurrent genital herpes and showed a significant difference to placebo with a shorter duration of lesions and a reduced viral shedding in all immunocompetent patients. A higher dosage did not show additional benefit. Famciclovir has also demonstrated to be effective in suppressing recurrent genital herpes in individuals with frequent episodes when compared to placebo (up to 90 % without episode within 4 months compared to 48 % in placebo group). Compared with valacyclovir, the first recurrences were reported earlier and suppression was not as efficient (Wals et al. 2006). The result of this study supposes that famciclovir was not as successful in HSV suppression and sexual transmission when compared to valacyclovir.

Resistance to Acyclovir

Resistance of HSV to ACV depends mainly on the deficiency of the viral thymidine kinase (TK) but can also be the result of altered TK or DNA polymerase. TK-deficient viral strains are less virulent but eventually can develop latency in the ganglion. ACV-resistant HSV are observed in about 3 % of isolates in immunocompetent individuals and may be detected even in persons who have never been treated with ACV and together with ACV-sensitive strains at the same time. It is interesting that despite the fact that ACV was used already for about 30 years, the frequency of in vitro resistance has not changed and does not happen more often in individuals treated over several years with this antiviral drug. It seems that in individuals treated with ACV, in vitro resistance of HSV may occasionally appear but is rapidly cleared by the immunocompetent host.

The majority of ACV-resistant strains have been isolated from immunosuppressed people undergoing multiple courses of ACV treatment in recurrent genital HSV infections. Patients with HIV infection or on immunosuppressive therapy for bone marrow or organ transplantations are especially exposed to severe HSV infections, and treatment failures are usually due to ACV-resistant HSV strains. The frequency of in vitro ACV resistance correlates with low CD4 count and topical ACV therapy. Since this is only described in about 5 % of isolates, routine testing for ACV resistance is not recommended.

Therapy in patients with ACV-resistant HSV strains may include high-dose oral or intravenous ACV or alternative drugs such as foscarnet, cidofovir, or other antiviral agents. As famciclovir is based on a similar antiviral mechanism, most ACV-resistant strains are also resistant to famciclovir.

Alternative Antiviral Therapy of ACV-Resistant Genital Herpes

The clinical management of genital herpes caused by ACV-resistant strains remains a challenge and needs to substitute ACV with alternative antiherpetic drugs.

Foscarnet

Foscarnet is a viral DNA polymerase inhibitor and is used in case of ACV resistance. Administration of foscarnet is usually intravenously or topical because of its poor oral absorption. Treatment is recommended by CDC (2010) as intravenous infusion (40 mg/kg every 8 h) until clinical resolution is observed. This dosage provides a high rate of clinical resolution in severe genital herpes and has proven to be more efficient than vidarabine (Safarin et al. 1991). Adverse reactions are frequent and may lead to renal insufficiency and metabolic disturbances but only rarely requires discontinuation of therapy.

Cidofovir

Cidofovir is an acyclic nucleoside phosphonate and is phosphorylated by cellular enzymes. It can therefore be implemented as alternative therapy in case of deficiency of viral TK. It is usually applied topically due to the potential of renal toxicity with IV administration. Since in long-term studies in animal models the development of tumours is reported as additional side effect, the drug is recommended only as an alternative drug in immunocompromised individuals.

Resiquimod and Imiquimod

Both drugs have partly shown a healing effect in herpetic lesions but have not proven substantial efficiency on the frequency of episodes in recurrent genital herpes. The antiherpetic potency was reported in few studies, but results were inconsistent.

There are several drugs tested for genital herpes but have demonstrated inefficiency against HSV: vidarabine, idoxuridine, isoprinosine, ether, 2-deoxy-D-glucose, BCG vaccine, chloroform, povidone iodine, topical surfactants, photodynamic dyes, topical IFN-alpha transfer factor, lysine, and nonoxynol-9. The long list reflects that despite the improvement in knowledge of management of genital herpes, treatment of recurrent genital herpes is still a management problem in this field of medicine.

A New Drug on the Horizon?

Pritelivir has been recently evaluated as a potential alternative antiherpetic agent in patients with a history of HSV-2 genital herpes (Wald et al. 2014). It is an inhibitor of the viral helicase-primase complex and has proven antiviral activity in vitro and in animal models. Pritelivir was administered in different schedules either daily in different dosages (5, 25, 75 mg) or weekly (400 mg). Compared with placebo, pritelivir administered in doses of 25 mg or more and once weekly, respectively, significantly reduced both the frequency of HSV shedding on the genital mucosa and the quantity of the virus detected. Also subclinical shedding of HSV was significantly reduced in both men and women. In addition the effect of pritelivir on genital lesions was evaluated, and a dose-related significant difference was observed between the antiviral drug and placebo group. It had an impact on the reduction of number of days of genital lesions at doses of 75 mg daily and the weekly administration with fewer recurrences. The drug was well tolerated, and adverse events were rare without safety problems and with no evidence of resistance. Although this was a short-term study of only 28 days, the outcome assumes that pritelivir provides a new alternative to the nucleoside therapeutic agents and may have the potential for combination therapy (Whitley and Prichard 2014).

Treatment of First Clinical Episode

Initial episodes of genital herpes include both anti-HSV-1/anti-HSV-2 antibody-negative primary herpes and anti-HSV1 or anti-HSV-2 antibody-positive first-episode genital herpes infection. First herpetic manifestations can cause prolonged clinical illness and concomitant systemic symptoms. Antiviral oral treatment should start as soon as possible after assumed diagnosis.

Recommended Regimens (CDC) (2010)

Acyclovir 400 mg orally three times a day for 7–10 days

Acyclovir 200 mg orally five times a day for 7–10 days
Famciclovir 250 mg orally three times a day for 7–10 days
Valacyclovir 1 g orally twice a day for 7–10 days

Recommended Regimens (IUSTI Europe)
Acyclovir 400 mg orally three times a day for 5 days
Acyclovir 200 mg orally five times a day for 5 days
Famciclovir 250 mg orally three times a day for 5 days
Valacyclovir 500 mg orally twice a day for 5 days

All drugs have shown to be effective, and the length of therapy should be extended if healing is incomplete, new lesions develop, or severe systemic complications are observed. Hospitalisation and intravenous application of antiviral drugs may be required with extraordinary clinical symptoms or if the patient is unable to tolerate oral treatment.

Concomitant counselling should include information on the natural course of the disease with the potential subclinical shedding, partner transmission, and recurrences. Screening on other STIs may be considered.

Treatment of Recurrent Episodes

Recurrent episodes are usually self-limited and require early initiation within 1 day of onset of lesions or prodromes. The reduction of healing of lesions may be 1–2 days. The patient should be provided with the drug with instructions for treatment to be started eventually, patient-initiated within the first hours of onset of symptoms. Treatment schedules differ in length and dosage. All antiviral drugs are effective for treatment of episodes, and head-to-head studies show no difference between the antiviral agents and length of therapy. Famciclovir may be less effective in the suppression of viral shedding. If symptoms are mild, patients may decide not to have antiviral therapy and may only need supportive advice.

Recommended Regimens (CDC)
Acyclovir 400 mg orally three times a day for 5 days
Acyclovir 800 mg orally twice a day for 5 days
Acyclovir 800 mg orally three times a day for 2 days
Famciclovir 125 mg orally twice a day for 5 days
Famciclovir 1,000 mg orally twice a day for 1 day
Famciclovir 500 mg orally once, followed by 250 mg twice a day for 2 days
Valacyclovir 500 mg orally twice a day for 3 days
Valacyclovir 1 g orally once a day for 5 days

Recommended Regimens (IUSTI Europe)
5-day therapy schedules:
Acyclovir 200 mg orally five times a day for 5 days
Acyclovir 400 mg orally three times a day for 3–5 days
Valacyclovir 500 mg orally twice a day for 5 days
Famciclovir 125 mg orally twice a day for 5 days
Short-course therapies:
Acyclovir 800 mg orally three times a day for 2 days
Famciclovir 1,000 mg orally twice a day for 1 day
Valacyclovir 500 mg orally twice a day for 3 days

Suppressive Therapy of Recurrent Genital Herpes

Suppressive therapy reduces the frequency of episodes by 70–80 % in patients with frequent relapses and is recommended in individuals with frequent and/or troubling recurrences. The decision for initiating suppression of genital herpes by the continuous treatment is very subjective and based on considerations including the frequency of relapses, the association with significant symptomatology and major psychosexual problems in the sexual relationship, costs, and the inconvenience of permanent drug administration. Suppressive treatment of recurrent genital herpes may lead to a significant improvement of life quality.

Where relapses are less frequent (<3–5 per year), intermittent episodic treatment may be preferable.

The safety and resistant data has been documented with ACV over 18 years and with other drugs for several years, and routine blood examination is not required.

The optimal dosage of ACV should be 800 mg daily. Breakthrough episodes may occur in approximately 20 % of patients and may lead to a modification or doubling of the schedule.

Individuals may experience at least a reduction of episodes compared to the situation without suppression and should be advised to include two recurrences to allow a view about discontinuation or change of dosages. Patients should be informed that despite treatment, viral shedding may occur and viral transmission to the partner may still be a risk. Suppressive therapy should be periodically discontinued and may be modified or stopped after 6–12 months to reassess the frequencies of relapses, since the frequency of recurrences decline over time.

Recommended Regimens (CDC)
Acyclovir 400 mg orally twice a day
Famciclovir 250 mg orally twice a day
Valacyclovir 500 mg orally once a day
Valacyclovir 1 g orally once a day

Recommended Regimens (IUSTI Europe)
Acyclovir 400 mg orally twice a day
Valacyclovir 250 mg orally twice a day
If >10 recurrences per annum
Valacyclovir 500 mg orally once a day
If <10 recurrences per annum
Famciclovir 250 mg orally twice a day

Management of Genital Herpes in Pregnancy

The therapy of genital herpes in pregnancy is complex and mainly concentrated on genital herpes near delivery in order to avoid transmission to the neonate. All women should be asked during pregnancy and at the onset of labour whether they ever had an episode of genital herpes. The incidence of neonatal herpes among asymptomatic women with the history of recurrent genital herpes or with genital herpes in the first half of pregnancy is low (<1 %) but increases to 30–50 % among women who acquire genital herpes near delivery (30–50 %) (Brown et al. 1997). Prevention of neonatal herpes is therefore concentrated on both avoiding first episode of genital herpes during late pregnancy and transmission of the virus during delivery.

Management of pregnancy with first-episode genital herpes during early pregnancy in the first and second trimester:

- Treatment of genital herpes of the pregnant woman in case of clinical symptoms
- Daily suppressive therapy with 400 mg acyclovir twice daily from week 36 to prevent recurrence
- Vaginal delivery if no lesions are present at the onset of labour

Management of pregnancy with first-episode genital herpes during late pregnancy in the third trimester:

- Treatment of genital herpes of the pregnant woman in case of clinical symptoms.
- Daily suppressive therapy with 400 mg acyclovir twice daily from week 36 to prevent recurrence.
- Intrapartal administration of intravenous acyclovir may be considered.
- Caesarean section should be considered in those with symptoms within 6 weeks of delivery.
- In case of vaginal delivery: no use of scalp electrodes and avoidance of prolonged membrane rupture.

Caesarean section in women without symptoms is under debate, and the risk to acquire herpes or the risk of a caesarean section has to be balanced from case to case.

Management of pregnancy with recurrent genital herpes:

- Vaginal delivery is indicated if no clinical lesions are present at onset of delivery.
- Daily suppressive therapy with 400 mg acyclovir twice daily from week 36 is recommended to avoid caesarean section in women with frequent recurrences.
- Caesarean section is only indicated if there are lesions at the onset of labour.

- Cultures or PCR diagnosis at term are not indicated.
- In early pregnancy continuous or episodic antiherpetic therapy is not recommended for women with recurrent genital herpes and should only be provided in case of severe and complicated recurrences.

General recommendations for pregnant women:

- Women without known genital herpes should abstain from sexual intercourse with partners known or suspected of having genital herpes.
- Information, whether a history of genital herpes is available.
- Careful clinical examination for herpetic lesions.
- ACV treatment late in pregnancy reduces the frequency of recurrences and – in consequence – the need for caesarean section.
- Antiviral treatment is not indicated among HSV-seropositive women without a history of genital herpes.

Neonatal Herpes Infection

Neonatal herpes infection is defined as infection in a newborn within 28 days after birth. Untreated, it is associated with a 40 % survival rate and can lead to long-term consequences in survivors (Corey and Wald 2009). Most neonatal infections result from exposure to HSV during delivery, although in utero and postnatal infections may also occur. The highest risk for the transmission of HSV to the neonate occurs from women who acquire genital HSV-1 or HSV-2 infections near term (50–80 %). It is remarkable that there is a discrepancy between a high shedding rate among women with HSV-2 infection and the low neonatal transmission rate with less than 1 % of neonates of mothers shedding the virus during delivery. This suggests a protective role of transplacental antibodies.

Congenital neonatal HSV infections are rare events with microcephaly, hydrocephalus, and chorioretinitis as the most common manifestations.

In neonatal infection, three different clinical pictures can be differentiated:

1. Manifestations of the skin, eyes, and mucous membranes account for about 45 % and need to be treated with high-dose intravenous ACV and have a good prognosis. Recurrences may occur in early childhood.
2. CNS-associated infections occur in about 30 % of infected neonates, and morbidity is higher in HSV-2 than in HSV-1 infections and may be associated with high rates of developmental problems and neurological abnormalities.
3. Disseminated HSV infections in neonates have a very bad prognosis with at least 30 % death despite ACV treatment. High-dose intravenous treatment with ACV is the drug of choice and has been systematically evaluated for neonatal infections.

Genital Herpes in HIV-Positive Individuals

Genital herpes plays a major role in HIV-positive persons, and with 60–90 % it is the most common cause of genital ulcer disease in this special risk group. Clinical manifestations range from minimal erosions to severe ulcerative symptoms. The infection may even stay unrecognised. Immunocompromised individuals may have prolonged or severe episodes of genital, anal, or oral herpes with often painful or atypical lesions. Viral shedding – independent from clinical symptoms – is increased and occurs on up to 30 % of days in HIV-infected individuals. Several studies reported the interaction of both viruses in immunocompromised individuals. It was demonstrated that in persons infected with both HIV and HSV, asymptomatic or symptomatic reactivation of HSV is associated with an increased level of HIV in the blood as well as in the genital tract (Schacker et al. 2002). Continuous suppressive therapy with ACV in persons with recurrent HSV infection reduces the severity and frequency of symptomatic recurrences and can also reduce the HIV levels. The initiation of retroviral therapy may worsen the clinical manifestations of genital herpes as part of the immune reconstitution syndrome.

In a study of the Prevention HSV/HIV Transmission Study Team performed in more than 3,400 heterosexual HIV-serodiscordant couples in Africa, it was investigated whether the ongoing suppression of HSV-2 with 400 mg ACV twice daily for 24 months may reduce the risk of HIV-1 transmission (Celum et al. 2010). It was disappointing that despite a significant reduction of the plasma level of HIV and a reduction in the occurrence of genital ulcers, daily ACV therapy did not reduce the risk of HIV-1 transmission to the sexual partner. The authors assumed that the lack of efficacy of ACV on the transmission rate may demonstrate that a greater reduction of HIV-1 plasma levels may have to be achieved.

Although resistance to nucleoside analogues is very rare, and the introduction of antiretroviral therapy has decreased the frequency of in vitro resistant HSV strains among HIV-infected individuals, it develops occasionally in HIV-positive individuals. This may lead to a difficult situation for the suppression of recurrences or the treatment of acute HSV infection, since treatment options for ACV-resistant strains of HSV are limited. However, new drugs on the horizon may be successfully implemented.

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Herpes Simplex Virus Infection (Orofacial)

38

Theognosia Vergou

Key Points

- Herpes simplex virus type 1 (HSV-1) is among the most common human pathogens worldwide. Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are responsible for orofacial and genital herpes, respectively. Transmission takes place through direct contact with skin lesions, mucous membranes, and secretions (i.e., saliva). Transmission of HSV can occur during both asymptomatic and symptomatic periods of viral shedding.
- The symptoms of primary infection start 3–7 days after exposure. The prodromal symptoms are tender lymphadenopathy, malaise, myalgia, fever, burning sensation, localized pain, tenderness, and inability to eat. The most common clinical presentation of primary HSV-1 infection is gingivostomatitis in children and young adults.
- Most of the patients that develop a recurrent infection have some common prodromal symptoms, such as itching, pain, or burning sensation. The clinical symptoms start with a group of vesicles on an erythematous base, most commonly at the mucocutaneous junction of the lips. Other less common sites are the nasal mucosa, the cheek, the coccyx area, the buttock, and the upper surface of the fingers.

Definition and Epidemiology

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are responsible for orofacial and genital herpes, respectively. Worldwide it has been shown that almost 80 % of the adult population has antibodies against HSV-1. In children, 80–90 % of herpes simplex infections are attributed to HSV-1. HSV-2 is responsible for 70–90 % of genital herpes infections, even though HSV-1 might also be the cause of a genital infection, due to oral-to-genital transmission. HSV infections of both types are common in both the industrialized and developing worlds. The virus has the ability to successfully avoid the host immune system by entering a non-replicating state known as latency. This establishes a lifelong infection with periods of reactivation that are stimulated by various environmental cues. Prevention of infection is particularly difficult, as transmission between individuals often occurs during unrecognized and asymptomatic shedding during latency in the host individual.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_38, © Springer-Verlag Berlin Heidelberg 2015

Basic Concepts of Pathogenesis

In the majority of cases, orofacial HSV infections are caused by HSV-1, but HSV-2 have also been reported in sexually active persons and in HIV patients. Transmission takes place through direct contact with skin lesions, mucous membranes, and secretions (i.e., saliva). Transmission of HSV can occur during both asymptomatic and symptomatic periods of viral shedding. Replication of the virus takes place at the site of infected surface (i.e., mucocutaneous), and then it establishes latency until reactivation, after traveling to the sensory dorsal root ganglia (the trigeminal for orofacial HSV). The period of latency varies in individuals, and in most cases there are some factors that trigger the reactivation process, such as stress, cold weather, fever, immunosuppression, and ultraviolet light. The HSV viral envelope is composed of about a dozen viral glycoproteins in a lipid bilayer, many of which have the ability to use multiple alternative host cell receptors. In addition, the virus has multiple strategies to enter the cell, including using fusion or different forms of endocytosis.

Clinical Presentation

Primary Infection

It is very rare to have a newborn with herpetic primary infection, due to the fact that most babies have antibodies to HSV-1 at the time of delivery. After the first year of life, as soon as the antibodies titers start to decrease, the primary infection can occur. The symptoms of primary infection start 3–7 days after exposure. The prodromal symptoms are tender lymphadenopathy, malaise, myalgia, fever, burning sensation, localized pain, tenderness, and inability to eat. The most common clinical presentation of primary HSV-1 infection is gingivostomatitis in children and young adults. It may present together with pharyngitis. Multiple ulcers may appear on the anterior parts of the mouth and also significant edema and pain. In young adults, primary infection is most commonly characterized by the initial development of multiple, painful vesicles on an erythematous base that may progress to pustules and/or ulcerations. Resolution occurs within 2–6 weeks. The mouth and lips are most commonly involved in orofacial HSV-1 infection and the buccal mucosa and oropharyngeal membranes as well.

Recurrent Infection

Some of the most common triggering factors for reactivation have already been mentioned above. Most of the patients that develop a recurrent infection have some common prodromal symptoms, such as itching, pain, or burning sensation. The clinical symptoms start with a group of vesicles on an erythematous base, most commonly at the mucocutaneous junction of the lips. Other less common sites are the nasal mucosa, the cheek, the coccyx area, the buttock, and the upper surface of the fingers (Figs. 38.1 and 38.2). The vesicles in 3–4 days crust (Fig. 38.3), and after 7–10 days total healing will occur.

In most cases, three to four times/year is the common number of relapses, but some patients experience a recurrence even more often. Complications of recurrent orofacial HSV infection are eczema herpeticum (in patients suffering from severe atopic dermatitis), recurrent erythema multiforme, and disseminated HSV infection (in patients with Darier's disease, mycosis fungoides, ichthyosis vulgaris, pemphigus, or

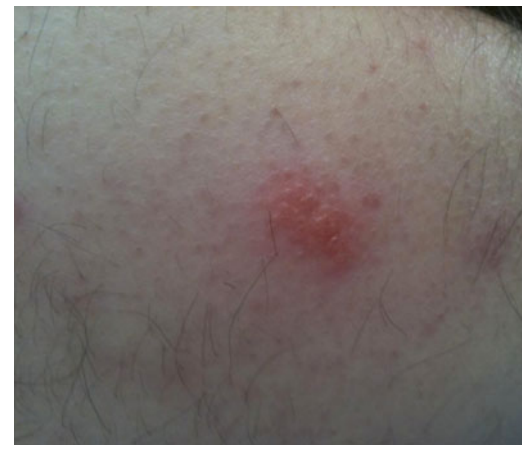

Fig. 38.1 The characteristic group of vesicles on an erythematous base of HSV infection

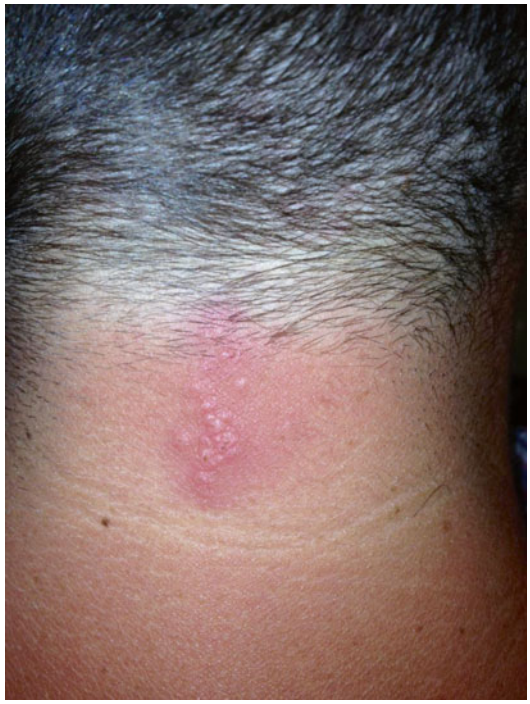

Fig. 38.2 HSV infection on the neck

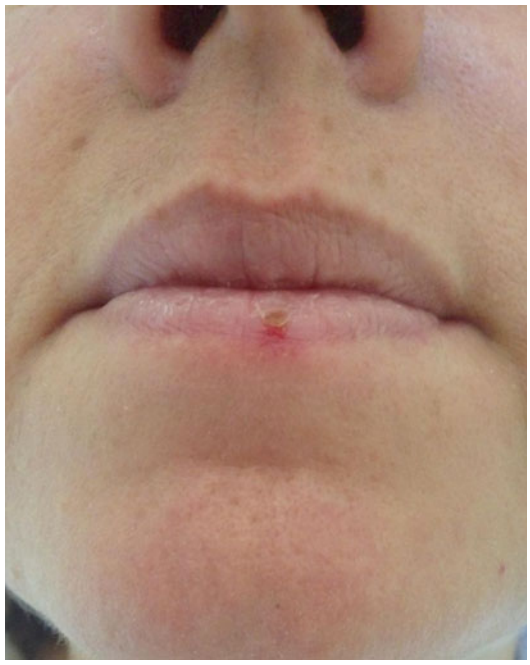

Fig. 38.3 Crusting of the HSV vesicles after 3–4 days of recurrent infection

Sezary's syndrome or in immunocompromised patients, such as HIV patients).

Keratoconjunctivitis is a situation that needs an ophthalmologist evaluation as soon as possible. Primary infection presents unilateral or bilateral, with significant eyelid edema, photophobia, tearing, and lymphadenopathy. Recurrent episodes with unilateral involvement are common.

Herpes encephalitis has a rate of mortality over 70 %, in untreated patients.

In immunocompromised patients, the lesions are larger, with persistent ulceration and crusting. In many cases, the infection is disseminated and severe.

Diagnosis

The Western blot method, for the detection of HSV antibodies, has very high sensitivity and specificity (99 %) and is one of the most valuable laboratory tests in order to diagnose HSV infections. Reliable serologic tests distinguish HSV-1 and HSV-2 antibodies. Tzanck smear reveals characteristic multinuclear, epithelial, giant cells (the technique is scraping the surface of early lesions). Viral cultures, PCR, and direct immunofluorescence for the detection of HSV antigens (very quick and reliable test, from the content of vesicles) are also available laboratory tests.

The histopathology reveals ballooning of the cytoplasm of keratinocytes, and this is a very characteristic and early sign of HSV infection. Another histopathology finding is the intranuclear inclusion bodies inside the degenerated nuclei. Spongiosis occurs in the epidermis, and intraepidermal vesicles are seen within the epidermis and dermis. Acantholytic keratinocytes are present, and a dense infiltration of lymphocytes, neutrophils, and eosinophils are seen in the dermis.

Differential Diagnosis

- Aphthous stomatitis
- EBV infections (i.e., pharyngitis)
- Stevens-Johnson syndrome
- Oral candidiasis
- Drug-induced mucositis

General Principles of Treatment

Primary infection with clinical symptoms in seronegative children and adults can be treated with oral antivirals as shown in Table 38.1. The dose for children is 15 mg/kg, five times/daily, for 7–10 days. In the majority of cases, only symptomatic, topical or oral antiviral treatment is enough for recurrent episodes. Patients with very frequent (more than six episodes/year) or severe and prolonged recurrences (including atopic patients) can be treated with suppressive oral antivirals, as shown in Table 38.1. Intravenous acyclovir is indicated for neonatal HSV infection, severe infections in immunocompromised hosts, and patients with systemic complications.

The fact that most current therapies target HSV-1 replication is not surprising, given that the initiation of replication is a very important process and any disturbance to this process adversely affects viral propagation. Acyclovir (ACV) is one of the oldest antiviral drugs used for HSV-1 treatment. ACV functions as a substrate for viral DNA polymerase, competing with deoxyguanosine triphosphate for incorporation into the elongation chain. It is a nucleoside analog with potent inhibitory effects and relatively low toxicity. ACV is selectively phosphorylated in virally infected cells by viral thymidine kinase, a process required for the activation of ACV. Valacyclovir, as a prodrug of ACV, enhances the bioavailability of ACV to levels threefold to fivefold higher than that obtained with oral ACV. Another drug developed during this period of antiviral development was famciclovir. Famciclovir, a synthetic acyclic guanine derivative, is a prodrug that, after oral administration, is rapidly metabolized to the highly bioavailable antiviral compound penciclovir via a two-step process of enzymatic hydrolysis and oxidation. Table 38.1 presents all therapeutic regimens for both HSV primary infection and recurrence.

Table 38.1 Therapeutic regimens for all oral antivirals for primary infection, recurrent episode, and suppressive treatment

Primary infection[a]/recurrent episode
Acyclovir: 200–400 mg, 5 times/day for 5 days
Valacyclovir: 500 mg, 2 times/day for 5 days or for recurrent episode 2 g, 2 times/day for 1 day
Famciclovir: 250 mg, 2 times/day for 5 days
Symptomatic therapy: topical antibiotics, NSAIDS
Recurrent infection (suppressive treatment)
Acyclovir: 400 mg, 2 times/day for 6 months
Valacyclovir: 500 mg, 1 time/day for 6 months
Famciclovir: 250 mg, 2 times/day for 6 months

[a]For primary infection, the therapeutic schedule can extend to 10 days, depending on the severity

N-Docosanol is an HSV-1 fusion inhibitor, and it functions by targeting the cell membrane and modifying the regions that many viruses utilize for entry. Through this modification, the fusion between a virus and its host cells is inhibited. Docosanol not only functions as an entry inhibitor, but also it interferes with the replication of HSV-1 and some other viruses. It is also administered in topical form and is mainly used for treating herpes labialis.

The entry of HSV into host cells is an intricate process that relies heavily on the ability of the viral glycoproteins to bind host cellular proteins and to efficiently mediate fusion of the virus envelope with the cell membrane. Acquisition of HSV-1 results in a lifelong latent infection. Because of the cycles of reactivation from a latent state, much emphasis has been placed until now on the management of infection through the use of DNA synthesis inhibitors as already mentioned above. However, new methods are needed to provide more effective treatment at earlier phases of the viral infection and to prevent the development of drug resistance by the virus. One of the most attractive candidates to assume this greater role in antiviral therapy is the targeting of glycoprotein-receptor interactions to inhibit the initial steps of viral entry, attachment, and fusion.

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Herpes Zoster

39

Uwe Wollina

Abbreviations

BW	Body weight
DNA pol	DNA polymerase
HZ	Herpes zoster
TK	Thymidine kinase
VZV	Varicella-zoster virus (VZV)

Key Points

- Herpes zoster (HZ) is a common infectious disease caused by varicella-zoster virus (VZV).
- Diagnosis is primarily a clinical one. Cutaneous and extracutaneous manifestations of HZ are known.
- Treatment of choice is systemic acyclovir.
- Other antiviral drugs are available.
- For elderly people, VZV vaccine is an option in secondary prevention.

Definition and Epidemiology

Herpes zoster (HZ) is an acute segmental eruption of herpetiform-grouped vesicles due to endogenous reactivation of varicella-zoster virus (VZV) infection of nerval segments. In Germany the annual incidence is 5.8 per 1,000 patient years. The incidence of HZ increases with age: from 6.2 in the age group of 50–54 years to 13.2 for people ≥90 years. Similar figures have been reported from other European countries like Italy, Denmark, and the UK. There is no gender prevalence.

Patients at risk for HZ are those with inherited or acquired immunodeficiencies, immunosuppression, and lymphoproliferative disorders. HZ is low contagious.

Basic Concepts of Pathogenesis

The causative agent of HZ is VZV or herpes virus type 3 – an α herpes virus. Primary infection leads to varicella. During the viraemic period of primary infection (chickenpox), VZV infects sensible dorsal spinal nerve ganglia and/or cephalic nerve ganglia. VZV lies dormant in the nervous system – neurons and glia satellite cells – for years. Endogenous reactivation of viral infection occurs after impairment of immune surveillance. Trigger factors are immunosuppressive treatment, malignancy, trauma, and emotional stress. Approximately 70 % of solid organ transplant patients suffer from HZ. The risk for

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_39, © Springer-Verlag Berlin Heidelberg 2015

HZ is 4.8 times higher in patients with haematological malignancies. VZV spreads antidromically with secondary cutaneous involvement classically limited to unilateral dermatome(s). Destruction of the ganglion causes characteristic HZ pain. Neuronophagia results in sensible deafferentation and postherpetic neuralgia.

Clinical Presentation

After a prodromal phase of 1–5 days with malaise, fever, segmental pain, hyperesthesia, itch, and burning sensations, erythematous lesions develop. Within the erythema, multiple umbilicated vesicles arise with a diameter usually <5 mm. After a couple of days, vesicles evolve to pustules which desiccate within a week leaving crusts (Fig. 39.1). Extended prodromal phase has been observed up to 18 days (Zerngast et al. 2013). Aberrant vesicles are not uncommon, but bilateral or generalized HZ is less common and points to a more severe underlying pathology (Fig. 39.2a, b).

A necrotic variant is seen more often in the head and neck region leaving scars (Fig. 39.2c). When HZ affects not only the sensible but motoric nerves, palsy may result. HZ does not always produce cutaneous symptoms – HZ sine herpete. A late complication of HZ is Wolf's isotopic response, i.e. the appearance of other cutaneous disorders in the previously affected dermatome(s).

HZ can occur in various variants that run a peculiar course with characteristic symptoms.

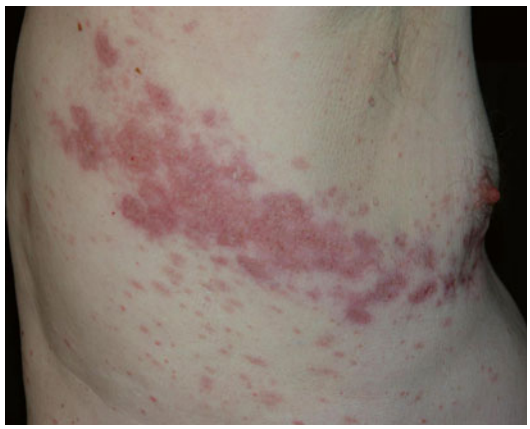

Fig. 39.1 Typical herpes zoster. Cutaneous findings are limited to a unilateral dermatome

- Zoster ophthalmicus (first trigeminal branch) with affection of the forehead, capillitium, and eye. These patients need an urgent ophthalmological investigation. Bell's palsy is a possible delayed complication.
- Zoster of the second and third trigeminal branch can involve oral mucosa and tongue with aphthoid lesions and gingivitis.
- Cranial HZ may cause headache, neck stiffness, and nuchal lymphadenopathy.
- Central nervous (CNS) HZ is a severe complication developing meningitis, encephalitis, or CNS vasculitis.
- Zoster oticus with the risk of peripheral paresis of the facial nerve.
- Ramsay Hunt syndrome is due to affection of N. facialis and N. vestibulocochlearis. Typical manifestations include tinnitus, vertigo, and deafness. Patients with incomplete eye closure and dry eye at the beginning have a worse prognosis.
- Perineal HZ with severe pain, obstipation, and urinary retention.
- Visceral dissemination of HZ is a rare manifestation not restricted to immunocompromised hosts. These patients may develop multiple ulcers in the gastrointestinal tract.

HZ can cause cutaneous vasculitis and erythema multiforme. In rare cases postherpetic keloids may develop in former HZ lesions.

The neuropathic pain syndrome – postherpetic neuralgia – is a greatly feared complication leading to severe chronic pain over more than 4 weeks. The incidence of postherpetic neuralgia is between 0.4 and 1.3 per 1,000 patient years for individuals of ≥50 years. Other complications include loss of vision in zoster ophthalmicus and vasculitis that may require hospitalization.

Patients receiving tumour necrosis factor-α inhibitor therapy may run a protracted course with severe postherpetic neuralgia.

HZ-related mortality is estimated as 0.21 per 100,000 patient years.

Diagnosis

The diagnosis of HZ is primarily clinical based on rash and segmental distribution. In case of HZ

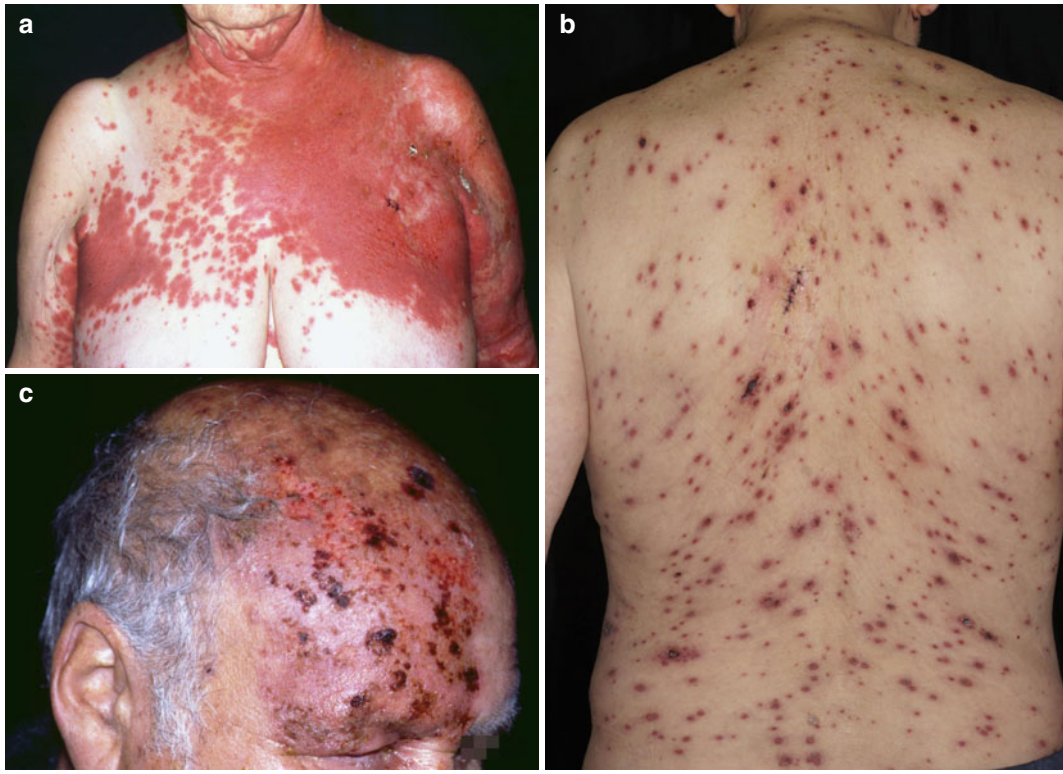

Fig. 39.2 More severe clinical types of herpes zoster. (**a**) Involvement of several dermatomes with haemorrhagic lesions. (**b**) Disseminated vesicles in generalized herpes zoster due to immune dysfunction of malignancy (here chronic lymphatic leukaemia). (**c**) Necrotic herpes zoster of the first trigeminal nerve branch

without rash, diagnosis is more complicated. Polymerase chain reaction has the best specificity (99 %) and sensitivity (95 %) compared to direct immunofluorescence staining (76 and 82 %) or virus culture (99 and 20 %). Tzanck test from vesicles or bullae is positive. Electron microscopy cannot differentiate VZV from herpes virus type 1 and 2.

Differential Diagnosis

The most important differential diagnosis is zosteriform herpes simplex. Other possible differential diagnoses include acute (contact) dermatitis, autoimmune bullous disease, bullous erysipelas, and eczema herpeticatum. Pain can be mistaken for intervertebral disc prolapse, myocardial infarction, pleurisy, abdominal disease, migraine, etc.

General Principles of Treatment

HZ needs to be treated systemically with antiviral drugs within 72 h of onset of the rash. If necessary, antibiotics, analgesics, and antipruriginous treatments may be added.

Systemic Treatments

HZ needs to be treated by systemic antiviral drugs. First-line treatment is acyclovir at a dosage of 10 mg/kg body weight (BW) three to five times a day for 5–7 days. The treatment should be 10 days in case of immunosuppressed patients. Orally applied acyclovir has a limited bioavailability. In children the dosage is 10 mg/kg BW three times a day with a maximum daily dosage of 2,500 mg. In patients with renal insufficiency, dose reduction is necessary. Nephrotoxicity is a rare but possible complication.

Acyclovir resistance of VZV has been reported in rare cases of immunocompromised patients. Both thymidine kinase (TK) and DNA polymerase (pol) gene mutations have to be considered in resistance testing. In a number of patients, resistance cannot be verified by virological methods.

Alternative oral drugs in immunocompetent adults include brivudine (125 mg once a day), famciclovir (3×250 mg/day), and valaciclovir (3×1,000 mg/day) for 7 days. In immunosuppressed adult patients, famciclovir can be used at doses of 3×500 mg/day. A multicentre, randomized, open trial in Japanese immunocompetent HZ patients suggested that famciclovir is superior to valaciclovir for acute pain relief (Ono et al. 2012). Another trial demonstrated equivalent efficacy of brivudine and famciclovir in HZ regarding resolution of symptoms and signs as well as prevention of postherpetic neuralgia (Wassilew et al. 2005). In contrast to acyclovir, brivudine has no nephrotoxicity. Brivudine is absolutely contraindicated in patients receiving 5-fluorouracil or other 5-fluoropyrimidines currently or within the last 4 weeks. The major active metabolite of brivudine, bromovinyl uracil, is a strong inhibitor of dihydropyrimidine dehydrogenase that can lead to a life-threatening accumulation of 5-fluoropyrimidines (Tables 39.1 and 39.2).

Table 39.1 Pharmacological treatment options in postherpetic neuralgia

Drugs	Examples
Tricyclic antidepressants	Amitriptyline (starting dosage 25 mg/day) Clomipramine 25–100 mg/day Desipramine – 150 mg/day Nortriptyline – 150 mg/day
Anticonvulsants	Carbamazepine 400–1,600 mg/day Gabapentin 900–3,600 mg/day Pregabalin 150–900 mg/day
Opiates	Oxycodone 10–400 mg/day Tramadol 200–600 mg/day
Topical anaesthetics	0.025 % capsaicin cream 5×/day 5 % lidocaine patch maximum 3 patches a day 8 % capsaicin patch (1 h with supervision)

Table 39.2 Treatment algorithms

Treatment algorithm for herpes zoster (HZ) in adults		
Uncomplicated HZ in immunocompetent hosts		
1st line	Acyclovir 800 mg five times a day for 7 days	
	Or brivudine 125 mg once a day for 7 days	
2nd line	Valaciclovir 1,000 mg three times a day for 7 days	
	Or famciclovir 500 mg three times a day for 7 days	
Uncomplicated HZ in immunocompromised hosts, complicated HZ in immunocompetent hosts		
1st line	Acyclovir intravenously 10 mg/kg three times a day	
Additional treatment for all patients: pain control		
Acute pain	1st line	NSAID like ibuprofen, aspirin, paracetamol or acetaminophen
	2nd line	Oxycodone
	3rd line	Opioids like tramadol

Topical Treatments

Topical treatment is symptomatic and includes soothing, drying, and antipruriginous effects. Typical ingredients are zinc oxide, cornstarch, clioquinol, menthol, or alcohol.

Crusted lesions benefit from ointments and wet dressings. Secondarily infected skin lesions may be treated with topical antibiotics like fusidic acid and antiseptics.

Topical acyclovir eye ointment is often used in zoster ophthalmicus although an add-on effect has never been established.

Vaccination

In Europe and the USA, a live attenuated vaccine for prevention of HZ and HZ complications has been approved for immunocompetent adults ≥50 years of age. The US Advisory Committee on Immunization Practices recommends vaccination for immunocompetent adults ≥60 years. A single vaccination results in HZ and postherpetic neuralgia incidence by 51 and 67 %, respectively. A booster may be necessary after 20–30 years. Depressed patients have a diminished VZV response to vaccination that can

Table 39.3 Treatment algorithm for postherpetic neuralgia

Line of Rx	Drugs	Examples	Dosage
1st line	Tricyclic antidepressants	Amitriptyline Nortriptyline Desipramine	10–75 mg at night
	Gabapentin		300–1,200 mg 3 time a day
	Pregabalin		50–300 mg twice daily
	Topical 5 % lidocaine patch		One patch every 12 h
2nd line	Opioids	Tramadol	50–400 mg/day
	Capsaicin cream		3 times a day
	8 % capsaicin patch		4 patches for 60 min every 3 months
3rd line	Centrally acting opioids	Morphine	30–360 mg/day

be improved with antidepressant therapy. Breakthrough HZ after active vaccination is possible but very rare.

Alternative and Experimental Treatments

FV-100 is a prodrug of the highly potent anti-VZV bicyclic nucleoside analogue CF-1743. Pharmacokinetics and safety have been evaluated in several trials. Oral doses of 400–800 mg/day were well tolerated.

KAI-1678 is an inhibitor of protein kinase C. The compound has shown no efficacy in acute postherpetic neuralgia in contrast to subcutaneous infusions of lidocaine.

Topical S-ketamine 1 % ointment has been evaluated in a double-blind, placebo-controlled, cross-over study to treat postherpetic neuralgia in 12 patients. After 15 days, pain-related findings improved with S-ketamine, but further investigations are necessary.

Intravenous vitamin C (7.5 g/50 ml) used as an adjuvant treatment for 2 weeks in an open trial seems to exert beneficial effects on fatigue, number of dermatomes and lesions, and pain. CNS vasculitis due to VZV infection may respond to intravenous pulses of cyclophosphamide.

Management of Postherpetic Neuralgia

The frequency of postherpetic neuralgia is reduced by early antiviral therapy and active vaccination. Elderly patients with deep pain at initial visit are at risk for this complication. Since its aetiology is complex and involves peripheral and central mechanisms, the combination of pharmacological treatments often is more efficacious than single agents.

The addition of short-term systemic corticosteroids to antiviral treatment is controversial, and a recent Cochrane review found no evidence for corticosteroids to prevent postherpetic neuralgia (Chen et al. 2010).

First-line treatments of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, and topical 5 % lidocaine patch. Second- and third-line therapies include opioids, tramadol, capsaicin cream, and 8 % capsaicin patch (Table 39.1). Invasive procedures like sympathetic blockade, intrathecal steroids, and implantable spinal cord stimulators can be used in patients refractory to conservative pharmacological interventions (Table 39.3).

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Hirsutism and Hypertrichosis

40

Clio Dessinioti and Andreas D. Katsambas

Key Points

- Hirsutism is defined as the excessive growth of terminal hairs in androgen-dependent areas in females.
- Hypertrichosis is defined as the generalized excessive growth of hair that is not limited to androgen-dependent hair.
- The causes of hirsutism and hypertrichosis include heritable factors, endocrine disorders (usually the polycystic ovary syndrome (PCOS) and more rarely nonclassical adrenal hyperplasia, androgen-secreting ovarian, or adrenal tumors), or medications.
- An effective management of hirsutism should aim to diagnose and treat any underlying hormonal disease while reducing excessive hair.
- Evidence-based data regarding the use of systemic treatments for hirsutism is lacking.
- As idiopathic hirsutism is mainly a cosmetic problem, topical treatments and hair removal methods are preferred.
- Combined oral contraceptives are a first-line therapy for hirsute women with PCOS.
- Eflornithine hydrochloride 13.9 % cream is an FDA-approved treatment indicated for the reduction of unwanted facial hair in women.
- Different cosmetic and hair removal methods include chemical depilation, bleaching, physical methods, electrolysis, thermolysis, and laser hair removal/photoepilation.
- An interdisciplinary approach comprising a dermatologist, an endocrinologist, and/or a gynecologist may provide optimal management to the hirsute woman.

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Definition and Epidemiology

Hirsutism is defined as the presence of excessive terminal hair in females in androgen-dependent areas such as the mustache area, chin, neck, arms, upper and lower abdomen, upper and lower back, and inner aspect of the thighs. In these body areas, hair growth is controlled by androgens that transform vellus to terminal hairs. In particular, the androgen dihydrotestosterone (DHT) acts in the skin via androgen receptors in the dermal papilla and increases the hair follicle size.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_40, © Springer-Verlag Berlin Heidelberg 2015

Hirsutism, together with acne, seborrhea, and alopecia, represents cutaneous manifestations of hyperandrogenism. Hirsutism affects approximately 5–10 % of women of reproductive age in the general population. Also, 70–80 % of patients with androgen excess demonstrate hirsutism, with the most common cause of androgen excess (hyperandrogenemia) being the polycystic ovary syndrome (PCOS). The prevalence of hirsutism in PCOS has been reported to be 40–92 % in European and American women. The prevalence of nonclassical congenital adrenal hyperplasia (CAH) among women with hirsutism varies from 1 to 12 %, depending on the ethnic group. On the other hand, in less than 20 % of hirsute women, hirsutism may be idiopathic, with normal serum androgen levels and normal ovulatory function. Idiopathic hirsutism may be due to the hypersensitivity of the hair follicle to androgens.

In contrast to hirsutism, hypertrichosis is defined as the generalized excessive hair growth that is not limited to androgen-dependent hair. Hirsutism and hypertrichosis may have considerable psychological consequences, causing severe distress and a significant negative impact on the quality of life.

Basic Concepts of Pathogenesis

The hair follicle is only found in mammals, and its growth cycle is regulated by hormones, mainly androgens. There are three main types of hair: lanugo, vellus, and terminal. Lanugo hair is the fine hair covering the fetus that is shed during the neonatal period. Vellus hair is the nonpigmented fine hair. Terminal hair shafts are coarser and darker. Vellus hair changes to terminal hair at puberty, while terminal hair changes to vellus hair in androgenic alopecia. Hirsutism usually results from the transformation of vellus hair into terminal hair in androgen-sensitive body areas.

Hirsutism is often the result of an underlying ovarian, adrenal, or central endocrine abnormality. Also, increased bioavailability of testosterone and increased sensitivity of hair follicles to androgens can contribute to the pathogenesis of hirsutism. The primary androgen involved in the development of hirsutism is dihydrotestosterone, which is synthesized from testosterone by the enzyme 5α-reductase type 2 in the hair follicle. Hirsute women have increased 5α-reductase activity in their hair follicles, which is stimulated by hyperandrogenemia and by high levels of insulin and/or insulin-like growth factors. The most common endocrine cause of hirsutism is PCOS which is characterized by ovarian androgen excess.

Hypertrichosis may be related to familial factors, metabolic disorders (such as hypothyroidism, anorexia nervosa, and malnutrition), or medications (including glucocorticoids, phenytoin, minoxidil, diazoxide, and cyclosporine).

Clinical Presentation

Hirsutism presents with excess hair on androgen-sensitive body areas, such as the face (Fig. 40.1), chest, abdomen, and/or thighs. In hypertrichosis, hair growth is not mediated by androgens, and the excess hairs are not distributed in an androgen-sensitive (male) pattern.

The degree of hirsutism in most studies is objectively quantified by a modified Ferriman–Gallwey (F-G) scoring system (Fig. 40.2), first introduced in 1961. Nine regions are assessed and given a score of 0 (no terminal hair) to 4 (extensive terminal hair). Hirsutism is generally

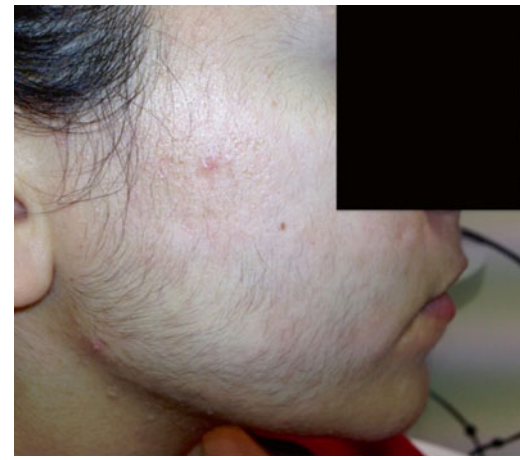

Fig. 40.1 Hirsutism of the face in a 22-year-old woman

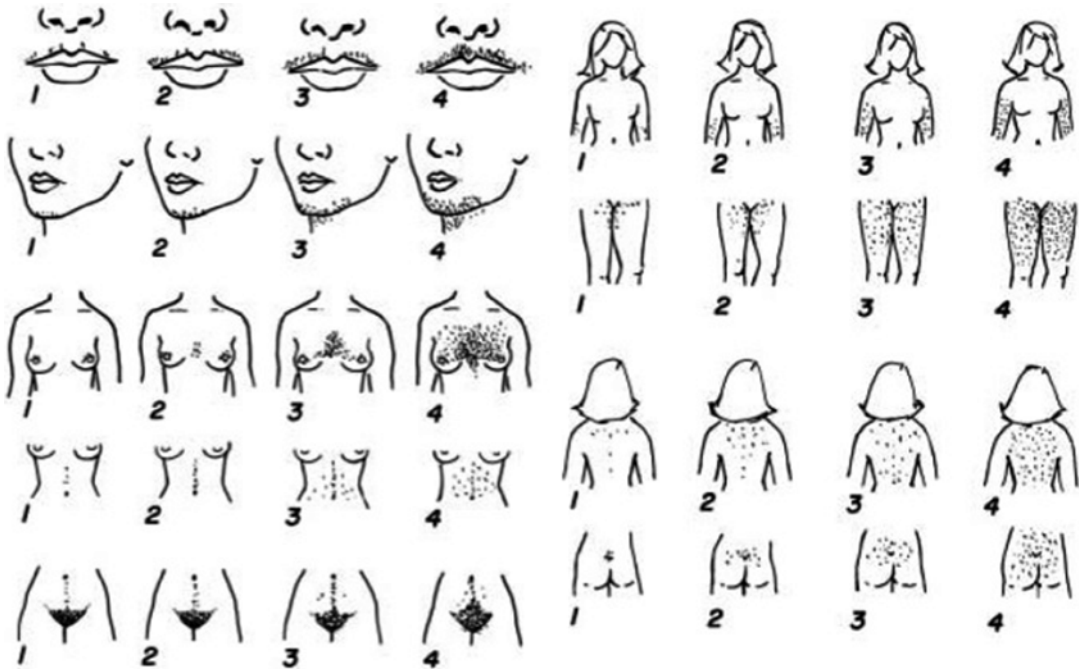

Fig. 40.2 Modified Ferriman–Gallwey hirsutism scoring system. Each of the nine body areas is assigned a score from 0 (no hair) to 4 (frankly virile) (Reproduced with permission from Hatch et al. (1981). ©Elsevier)

defined as a score of 8 or above. Mild hirsutism is defined as an F-G score of 8–15, moderate hirsutism as an F-G score of 16–25, and severe hirsutism as an F-G score >25.

Hirsutism can be a presenting sign of PCOS, nonclassical CAH, Cushing's syndrome, or androgen-secreting tumors.

PCOS is a multifactorial polygenic disorder of unknown etiology. It is the most common cause of hirsutism, even in the presence of normal menstrual cycles. It has therefore been suggested that the presence of hirsutism in women should prompt the evaluation for PCOS. The diagnosis of PCOS is currently based upon an international agreement (the 2003 Rotterdam Consensus Group) and is defined by the presence of at least two out of three of the following criteria: (1) oligomenorrhea or amenorrhea, (2) clinical hyperandrogenism or serum androgen excess, and (3) polycystic ovaries by a pelvic ultrasound. Cutaneous signs of hyperandrogenemia in PCOS include hirsutism, acne, seborrhea, and androgenic alopecia. In particular, the following symptoms or signs indicate high risk for PCOS and should prompt further evaluations:

- Moderate or severe hirsutism
- Resistant acne
- Menstrual irregularities
- Acanthosis nigricans and obesity
- Mild hirsutism, acne, or acanthosis nigricans associated with any other feature of PCOS

CAH is an autosomal recessive disorder with a reported prevalence for nonclassical (late-onset) CAH ranging from 0.6 to 10 % depending on the ethnic group. CAH can present with premature pubarche (appearance of sexual hair before 8 years of age in girls and 9 years in boys), hirsutism, acne, adult-type apocrine odor, tall stature in children, and advanced skeletal maturation. Growth can be assessed by review of growth charts, and skeletal maturation can be assessed by a bone age X-ray (X-ray of the left hand in children ≥2 years and hemi-skeleton in children <2 years of age). Nonclassical CAH is a progressive disorder, with the prevalence of hirsutism increasing with age in individuals >10 years old. Among 270 Spanish

women with hirsutism, acne, androgenic alopecia, or irregular menses, nonclassical CAH was diagnosed in six women (2.2 %).

Idiopathic hirsutism (hirsutism without hyperandrogenemia) accounts for about half of mild hirsutism and for a smaller fraction of moderate/severe hirsutism.

The term "SAHA syndrome" was coined in 1982 by Professor Orfanos to characterize the association of seborrhea, acne, hirsutism, and androgenic alopecia in women. In approximately 20 % of patients, all four major signs of SAHA syndrome are present; seborrhea is always present and androgenic alopecia occurs in 21 %, acne in 10 %, and hirsutism in 6 % of patients. The SAHA syndrome is classified into idiopathic, ovarian, adrenal, and hyperprolactinemic types, depending on the underlying associated disorder.

Diagnosis

The diagnostic evaluation of the hirsute woman should include a detailed medical history of the time of onset and rate of progression of hirsutism and of menstruation and fertility and a family history of PCOS, diabetes, obesity, and hyperandrogenism. The physical exam should include evaluation for hirsutism, androgenic alopecia, acne, seborrhea, galactorrhea (a sign of possible hyperprolactinemia), and acanthosis nigricans; signs of virilization (such as clitorimegaly, deepening of voice, or increasing muscularity) suggest marked hyperandrogenemia due to androgen-secreting adrenal or ovarian tumors. Also, hormonal evaluations and a pelvic ultrasound examination should be performed in patients suspected to have PCOS (Table 40.1). Referral to an endocrinologist to exclude PCOS and other hormonal causes should be considered.

The hormonal evaluations should be performed in the early follicular phase. In women under hormonal contraception, this should be ideally discontinued for at least 8–12 weeks before the hormonal evaluation. There is some disagreement as to whether hormonal evaluations are necessary in women with mild hirsutism. The 2008 Endocrine Society Guidelines by Martin et al., on the evaluation and treatment of hirsutism in premenopausal women, do not recommend this testing, whereas Barbieri and Ehrmann, as well as Escobar et al., suggest measuring testosterone (as a marker of ovarian androgens) and DHEA-S (as a marker of adrenal androgens) in all hirsute women. 17-Hydroxyprogesterone can assist in the diagnosis of NCCAH. Very high levels of testosterone (>150 ng/dl or 5.2 nmol/l) or DHEA-S (>700 μg/dl or 18.9 μmol/l) should raise suspicion of an ovarian or adrenal tumor, respectively, and should prompt referral to an endocrinologist for further evaluation including imaging.

Table 40.1 Diagnostic approach to hirsutism

Personal and family history: hirsutism (timing, rate, and psychological impact), menstruation, fertility, PCOS, diabetes, hyperandrogenism
Physical exam: hirsutism (modified Ferriman–Gallwey score), androgenic alopecia, acne, seborrhea, galactorrhea, acanthosis nigricans, and signs of virilization such as clitorimegaly, deepening of voice, and increased muscularity
Laboratory evaluations: LH, FSH, PRL, E2, DHT, SHBG, DHEA-S, 17-OH P, androstenedione, TSH
Pelvic ultrasound

LH luteinizing hormone, *FSH* follicle-stimulating hormone, *PRL* prolactin, *E2* estradiol, *DHT* dihydrotestosterone, *SHBG* sex hormone-binding globulin, *DHEA-S* dehydroepiandrosterone sulfate, *17-OH P* 17-hydroxyprogesterone, *TSH* thyroid-stimulating hormone

Differential diagnosis in patients with hirsutism or hypertrichosis includes the following:

- PCOS: diagnosis based on the Rotterdam criteria
- Nonclassical late-onset congenital adrenal hyperplasia: elevated 17-OH progesterone, diagnosis confirmed by ACTH stimulation test
- Cushing's syndrome: elevated and/or non-suppressible cortisol plasma or urine levels, hypertension, abdominal striae, and easy bruising
- Hyperprolactinemia: mild hyperandrogenism/hyperandrogenemia, oligomenorrhea/amenorrhea, and galactorrhea
- Primary hypothyroidism: elevated TSH, decreased thyroxine levels, menstrual irregularities, mild hyperandrogenism or/and hyperandrogenemia, cold intolerance, and goiter
- Acromegaly: elevated IGF-1 serum levels, non-suppressible growth hormone levels, oli-

gomenorrhea/amenorrhea, acral enlargement, coarse facies, prognathism, and macroglossia
- Virilizing adrenal or ovarian androgen-secreting tumors: rapid onset of hirsutism, extremely elevated plasma androgen levels, signs of virilization (clitorimegaly, deepening of voice, increased muscularity), and tumor confirmed with imaging (ultrasound or computed tomography)
- Drugs: androgens (danazol), glucocorticoids, minoxidil, valproate, and cyclosporine
- Hypertrichosis lanuginosa acquisita: rare, sudden appearance of long, fine, nonpigmented lanugo hairs that can grow to extraordinary length, mostly on the face and ears; occasionally associated with glossodynia or taste alterations; can be a paraneoplastic condition (breast and uterine adenocarcinomas, lymphomas, urinary bladder carcinomas), but may also be seen in anorexia nervosa and thyrotoxicosis

General Principles of Treatment

An effective management of hirsutism should aim to correct any underlying hormonal disease while reducing excessive hair. The management of women with hirsutism may require pharmacological systemic or topical treatments (Table 40.2), adjunct cosmetic methods of hair removal, and lifestyle modifications. The main rationale behind the medical treatment of hirsutism consists in suppressing ovarian or adrenal androgen secretion or blocking androgen action at the hair follicle.

For mild hirsutism, simple, inexpensive methods, such as bleaching, shaving, and waxing may suffice. Eflornithine hydrochloride cream may be prescribed for the topical treatment of facial unwanted hair (or used off-label for focal hirsutism in other body areas). A combination of pharmacological treatment regimens and direct methods to reduce and remove hair including electrolysis and photoepilation (laser or intense pulsed light) can yield better results.

Several factors should be taken into account during the therapeutic approach to hirsutism, including efficacy, safety, convenience, potential pain, and expense. The choice of therapy should be based on the degree of hirsutism, potential underlying hormonal disorders, the impact on the individual's quality of life, and the desired degree of unwanted hair reduction.

Table 40.2 Overview of systemic and topical pharmacological treatments for hirsutism

Systemic treatments	Topical treatments
Combined oral contraceptives[a]	Eflornithine hydrochloride
Antiandrogens	
Spironolactone, cyproterone acetate, finasteride[b], flutamide[b]	
Insulin-lowering drugs	Finasteride[b]
Metformin[b], rosiglitazone[b]	
Glucocorticoids[b]	

[a]EE 35 μg/CPA 2 mg is the only contraceptive pill approved by the European Medicines Agency (EMA) for the treatment of hirsutism
[b]The 2008 Endocrine Society Guidelines suggest against the routine use of these treatments for hirsutism

As idiopathic hirsutism is mainly a cosmetic problem, topical treatments and hair removal methods are preferred. A consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society published by Escobar-Morreale et al. mentions that the subjective perception of the patient, and not only the absolute extent of hair growth, may also be taken into account to guide the decision for appropriate treatment.

Specific recommendations and suggestions for and against certain drugs and other treatment methods by the 2008 Endocrine Society Guidelines (Martin et al.) on the evaluation and treatment of hirsutism in premenopausal women are outlined in the following section; for women with patient-important hirsutism despite cosmetic measures, either pharmacological therapy or direct hair removal methods were suggested (weak recommendation, very low quality evidence). Women with hirsutism should be adequately informed about the potential risks associated with COC use.

Healthy eating, regular exercise, and weight reduction are encouraged in all patients with PCOS to reduce the risk of cardiovascular disease and type 2 diabetes. By decreasing insulin

resistance, weight loss and exercise may also decrease androgen levels and normalize ovulation.

Systemic Treatments

Evidence-based data regarding the use of systemic treatments for hirsutism is lacking. Systemic treatments suggested by the Endocrine Society for patient-important hirsutism in premenopausal women include hormonal therapies (oral contraceptives and antiandrogens). However, this was a weak recommendation based on very low quality evidence.

Because with any systemic therapy it takes several months to reduce hirsutism, the efficacy should not be evaluated before 6 months of treatment, and no changes in dose or addition of second agents should be done before that time. In the meantime, concomitant adjunct treatment such as waxing, bleaching, electrolysis, and laser therapy may be beneficial.

Antiandrogens and insulin-sensitizing agents are not currently approved for the treatment of hirsutism by the European Medicines Agency (EMA).

Combined Oral Contraceptives

Combined oral contraceptives (COC) generally contain ethinyl estradiol (EE) and a progestin. The main progestins with antiandrogenic properties used in COC formulations are cyproterone acetate (CPA) and drospirenone.

The beneficial effects of COC for hirsutism are mediated by several mechanisms: (1) they inhibit FSH and LH release by the pituitary, thereby reducing ovarian androgen production; (2) they decrease the levels of free testosterone by stimulating the hepatic synthesis of SHBG; (3) certain progestins inhibit adrenal androgen production by inhibiting the activity of steroidogenic enzymes; and (4) certain progestins like CPA and drospirenone exert antiandrogenic actions as antagonists of the androgen receptor (antiandrogens).

COC are a first-line therapy for hirsute women with PCOS. COC containing cyproterone acetate and those containing drospirenone or desogestrel are generally effective in improving mild-to-moderate hirsutism in PCOS when used for more than 12 cycles. Of note, EE 35 μg/CPA 2 mg is the only COC approved by the EMA for the treatment of hirsutism in premenopausal women.

In a randomized, physician-blinded study, Batukan et al. showed a comparable improvement in hirsutism in 100 women with COC containing EE 30 μg/drospirenone 3 mg (median F-G score of 3 at 12 months compared to 15 at baseline) versus EE 35 μg/CPA 2 mg (median F-G score of 4 at 12 months compared to 16 at baseline) after 12 months.

A prospective randomized trial by Oner et al. reported similar efficacy of oral 0.03 mg ethinyl estradiol/3 mg drospirenone 21/7 regimen or 0.02 mg ethinyl estradiol/3 mg drospirenone 24/4 regimen, for 6 months, in 47 women with moderate-to-severe hirsutism ($p<0.05$). An improvement in the F-G scores for hirsutism was observed in Group 1 (mean ± SD) (17.3 ± 5.2 to 8.7 ± 2.5, $p<0.001$) and in Group 2 (17.5 ± 4.8 to 7.9 ± 2.8, $p<0.001$). There was a significant decrease of total and free testosterone in both groups.

Women should be counseled that it takes several months to obtain an improvement in hirsutism.

COC have potential serious side effects, including an increased risk of venous thromboembolism (VTE), stroke, and myocardial infarction. These risks are increased in patients with a history of hypertension, diabetes, or migraine and in cigarette smokers. There are contraindications to COC therapy, including women with a history of clotting disorder, thrombophlebitis, cerebrovascular disease, coronary occlusion, abnormal vaginal bleeding, impaired liver function, migraine, smokers over age 35, and women at increased risk of breast cancer. An evaluation by an endocrinologist or a gynecologist can be useful when the use of COC is contemplated for hirsutism, and women with hirsutism should be adequately informed about the potential risks associated with COC use.

Antiandrogens

Antiandrogens, or androgen receptor blockers, are defined as agents that inhibit directly the binding of dihydrotestosterone (DHT) to its receptor in a competitive way. They include cyproterone acetate, spironolactone, flutamide, and finasteride. Antiandrogen monotherapy without contraception should be avoided due to the teratogenic effect. So, antiandrogens are usually employed as second-line therapy, adjunctive to COC. If the response to COC is suboptimal after 6 months of treatment, an antiandrogen can be added.

A systematic review and meta-analysis by Swiglo et al. included 12 eligible studies of at least 6 months of antiandrogen therapy in women with hirsutism. Antiandrogens reduced F-G scores by 3.9 (95 % CI 2.3–5.4) compared to placebo. Spironolactone reduced hirsutism scores by 1.3 (95 % CI 0.03–2.6) compared to metformin. Spironolactone or finasteride combined with contraceptives (1.7, 95 % CI 0.1–3.3) was superior to monotherapy with contraceptives. The authors concluded that weak evidence suggests antiandrogens are mildly effective for the treatment of hirsutism.

Cyproterone acetate (CPA 10 mg, 50 mg) is a progestational antiandrogen that blocks the androgen receptor. CPA is the only antiandrogen that also has an antigonadotrophin action by inhibition of ovulation. It is used either as the progestin component of COC (at a low dose of 2 mg) or alone at higher doses of 12.5–100 mg given over the first 10 days of the menstrual cycle. A study by Kelekci et al. reported that the combination of 35 μg of EE/2 mg of CPA plus 100 mg of CPA daily for 6 months in 45 women showed the same improvement in hirsutism with 30 μg ethinyl estradiol (EE)/3 mg drospirenone plus 100 mg CPA ($n=45$) or 30 μg of EE/3 mg drospirenone plus 100 mg of spironolactone ($n=44$). The most frequent side effect of CPA monotherapy is amenorrhea or oligomenorrhea. Other side effects of CPA include nausea, vomiting, fluid retention, headache, liver dysfunction, and blood clotting disorders.

Spironolactone is an analogue of aldosterone that acts as an antagonist of the mineralocorticoid receptor but also of the androgen receptor, thus competing with dihydrotestosterone (DHT). In addition, it inhibits enzymes involved in androgen biosynthesis. A systematic review by Brown et al. reported that in two trials comparing 100 mg of spironolactone with placebo, there were significant differences in subjective improvement in hair growth (OR 7.18, 95 % CI 1.96–26.28), but not in the F-G score. The authors concluded that due to the scarce number of studies, the small number of included patients, and differences in study design, results cannot be generalized. Spironolactone may cause hyperkalemia, menstrual irregularity, breast tenderness, headache, and fatigue. It is contraindicated during pregnancy as it may lead to feminization of a male fetus (abnormalities of the male fetal genitalia, such as hypospadias).

Flutamide is a nonsteroidal antagonist of the androgen receptor used to treat prostate cancer. It has been associated with hepatotoxicity, for which reason its use for hirsutism is not recommended.

Finasteride has no direct effect on the androgen receptor or the pituitary. Rather, it inhibits in hair follicles the activity of 5α-reductase type 2, the enzyme that converts testosterone to the highly active DHT. However, of the two isoforms of the enzyme, finasteride targets only 5α-reductase type 2, thus exerting a partial effect. It is also more expensive than spironolactone and has a higher potential teratogenic effect; thus, its routine use for hirsutism is not recommended.

Antiandrogens are not currently approved for the treatment of hirsutism by the European Medicines Agency (EMA).

Insulin-Sensitizing Drugs: Metformin

Compensatory hyperinsulinemia is associated with insulin resistance in PCOS. Metformin is an insulin-sensitizer that reduces insulin resistance, insulin secretion, and hyperinsulinemia.

A double-blind placebo-controlled crossover study by Kelly et al. in 16 women with PCOS and hirsutism reported a significant improvement of hirsutism F-G score with metformin compared to placebo (F-G score 15.8 ± 1.4 vs 17.5 ± 1.2, $p=0.025$).

In the prospective randomized controlled trial of Rezvanian et al. in 70 women with PCOS, the addition of metformin 1,500 mg daily to intense pulsed light (IPL) therapy during 6 months resulted in significantly better control of hirsutism compared to five sessions of IPL alone ($p = 0.009$).

Adverse effects with metformin include nausea, vomiting, diarrhea, myalgia, palpitation, flushing, reduced vitamin B12 levels, and lactic acidosis. Metformin is contraindicated in case of renal disease/dysfunction due to increased risk for lactic acidosis.

Insulin-sensitizing agents are not currently approved for use in women with hirsutism or PCOS. There are no adequate evidence-based data regarding the effects of metformin for hirsutism, and the 2008 Endocrine Society Guidelines suggested against its routine use for hirsutism.

Studies Evaluating Metformin Compared to COC in Women with Hirsutism

Harborne et al., in a randomized study in 52 women with PCOS, compared metformin (500 mg, three times daily) to EE 35 μg/CA 2 mg, for 12 months. They reported that both treatments significantly reduced the F-G score, with metformin showing a significantly greater degree of reduction in the F-G score (25 %) compared with EE/CA (5 %) ($p < 0.01$).

Ibanez et al., in a randomized, open-label trial, compared the effects of 35 μg ethinyl estradiol/mg cyproterone acetate (EE/CA) versus a low-dose combination of pioglitazone (7.5 mg/day), flutamide (62.5 mg/day), and metformin (850 mg/day) (PioFluMet) for 18 months, in 34 nonobese adolescent girls with hyperinsulinemic androgen excess. After 18 months of treatment, the mean reduction in the hirsutism score compared to baseline was 6.5 with PioFluMet ($p < 0.001$) and 4.7 with EE/CA ($p < 0.001$). At 24 months follow-up, there was a more significant reduction with PioFluMet compared to EE/CA, with a mean reduction in the hirsutism score of 6.8 and 3.8, respectively ($p < 0.01$).

A Cochrane review of metformin versus oral contraceptives in PCOS evaluated 4 randomized controlled trials involving 104 subjects and reported no evidence of a difference in effect between COC and metformin on hirsutism, with both treatments resulting in a standardized mean difference of −0.18 ($p = 0.48$). The dose of metformin was 500 mg three times daily in one trial and 500 mg twice daily for the first 3 months increasing to 1,000 mg twice daily for the next 3 months for three of the trials. The COC type was EE 35 μg/CA 2 mg in all trials. The duration of trials ranged from 4 to 12 months.

Topical Treatments

Eflornithine Hydrochloride Cream

Hair follicles in the anagen (growth) phase are characterized by the highest activity of ornithine decarboxylase (ODC), the rate-limiting enzyme of polyamine biosynthesis. Eflornithine hydrochloride is an inhibitor of ODC, and eflornithine hydrochloride 13.9 % cream (Vaniqa) has been clinically shown to slow the growth of unwanted facial hair in women. It is FDA-approved for the reduction of unwanted facial hair in women; it is available by prescription and is applied twice daily. Eflornithine cream is not indicated for use during pregnancy (FDA pregnancy category C).

Eflornithine cream may be combined with laser hair removal methods. Smith et al. reported more rapid hair removal when eflornithine cream was combined with laser treatment (alexandrite or Nd:YAG) in 54 women with unwanted facial hair for 34 weeks. Hamzavi et al. reported higher rates of complete or almost complete hair removal in 31 women treated for unwanted hair on the upper lip, for 26 weeks with eflornithine cream combined with long-pulsed alexandrite laser (93.5 %) versus laser alone (67.9 %) ($p = 0.021$). The Endocrine Society Guidelines suggest the use of eflornithine cream for women who desire a more rapid response to laser therapy.

Finasteride

Stimulation of 5α-reductase in hair follicles causes male pattern hair to grow on the face and body and to be lost on the scalp. Topical finasteride (a type 2, 5α-reductase inhibitor) has been used for treating hirsutism with inconsistent results.

In a double-blind, randomized, placebo-controlled study of 77 women with excess facial hair, Farshi et al. reported that the addition of 0.5 % finasteride solution for 6 months to intense pulsed light/radiofrequency (four sessions) may result in greater reduction of facial hair (by 1/cm^2).

Given that the data overall show little or no benefit in hirsutism, the Endocrine Society Guidelines suggest against the use of topical finasteride.

Hair Removal Methods

Different cosmetic and hair removal methods include chemical depilation (removal of hair above the skin surface), bleaching (to lighten hair color), physical depilation (trimming), or epilation (removal of hair with its bulb by tweezing, by waxing, or by the use of electric rotating epilating devices), electrolysis, thermolysis, and laser hair removal or photoepilation.

Chemical and Physical Methods

With chemical depilation, chemicals such as sulfur compounds of calcium, arsenic, antimony, barium, and strontium are applied to dissolve the hair through reduction of disulfide bonds. The depilatory creams are mostly based on thioglycolates 2–4 %. Disadvantages include allergic or contact dermatitis. Bleaching lightens the color of excessive hair to make it less visible. Bleaching is quick, easy, painless, and inexpensive. Disadvantages include skin irritation due to peroxide/sulfates contained in bleaching products and possible sensitization. For any bleaching or chemical depilation, it is advised to first perform it on a small test area.

Trimming of hair is safe, and it does not accelerate hair regrowth. Tweezing or plucking is a temporary method of epilation that is used for small areas of excess hair. Disadvantages include pain, folliculitis, postinflammatory hyperpigmentation, and potential scarring. Waxing involves the application of melted wax to hair-bearing skin which, upon drying, is rapidly peeled away from the skin. Disadvantages include pain, folliculitis, sensitization (to the colophony resin), and the possibility of thermal skin burns caused by the hot wax. Electric rotating epilating devices for home use or waxing techniques are based on hair shaft epilation leading to longer-lasting hair-free effects (2–6 weeks). Disadvantages include pain, skin irritation, and folliculitis.

Electrolysis-Electroepilation

Electrolysis is performed by passing direct or galvanic current through an epilation probe introduced into the hair follicle opening, leading to a chemical reaction and destruction of the hair follicle. This is a time-consuming method. In thermolysis (electroepilation), high-frequency alternating current is used to destroy the hair follicle by heat. The "blend method" combines both types of currents. Disadvantages include pain, hyperpigmentation, risk of scarring, and transmission of infection if the electrolysis needles are not properly sterilized.

Laser/Photoepilation

Wavelengths in the red and near-infrared spectra (600–100 nm) are suitable for hair removal, providing sufficient energy absorption by melanin, and decreased absorption from other skin chromophores such as oxyhemoglobin, and by water. Lasers used to treat unwanted hair include the long-pulsed ruby laser (694 nm), the long-pulsed alexandrite laser (755 nm), the diode laser (800–810 nm), and the long-pulsed Nd:YAG laser (1,064 nm). The intense pulsed light (IPL) is a non-laser, polychromatic, noncoherent light (590–1,200 nm) used in photoepilation.

The effects of laser systems used for hair removal are based on the principle of selective photothermolysis to selectively cause thermal damage

to the target (pigmented hair follicles) by using the melanin of the hair shaft as a chromophore, without damaging the surrounding tissue. A component of photothermolysis is the thermal relaxation time. This is used to determine the pulse width for laser light, so that the heat generated within the target owing to absorption of photon energy does not cause damage to the surrounding tissue.

In the retrospective study of Kutlubay, the effect of a millisecond alexandrite hair removal laser (755 nm) in 2,359 subjects was evaluated. Patients were treated in 3–15 sessions per anatomic site. A mean hair reduction of 61–86 % was reported, with lighter skin types showing better results. Complications were reported in 2.2 % of subjects, including transient hyper- or hypopigmentation, folliculitis, blistering, pruritus, and excoriations.

In general, the reported short-term efficacy with lasers ranges between 30 and 70 % up to 6 months after the final treatment, depending also on the treatment settings. Long-term hair removal efficacy beyond 6 months postoperatively has been reported with the alexandrite laser, the diode laser, and the long-pulsed Nd:YAG laser, with an average of approximately 50 % hair reduction at 6–20 months after treatment.

Two studies (McGill et al. and Goh) compared IPL to either the long-pulsed alexandrite laser or Nd:YAG laser and reported the IPL to be inferior to laser devices for hair removal.

Treatment parameters that must be individualized include wavelength, pulse duration, spot size, fluence, and number of sessions. Other key components with laser hair removal include proper patient selection, informed consent, and understanding of the principles of laser safety. The treatment outcome depends on skin type, hair color and density, and hormonal status. Blond, red, and white hair is not suitable for laser epilation, whereas dark hair in a fair-skinned subject is the ideal scenario. To minimize the risk of skin pigmentation side effects in patients with darker skin type (Fitzpatrick phototypes IV), it is suggested to use lower fluences of alexandrite and diode laser wavelengths or a long-pulsed Nd:YAG laser. Complications include hypo- or hyperpigmentation and rarely scarring and paradoxical hypertrichosis, the latter defined as the induction of terminal hairs after treatment of vellus hairs, especially on the cheeks and chin.

Patients should be informed that permanent and complete hair removal is not likely, but that significant long-term reduction can be achieved with multiple treatments. In females with hirsutism owing to hormonal disorders, laser hair removal may have lower efficacy, and continued maintenance sessions may be required. As mentioned, concurrent hormonal treatment may be beneficial in this setting.

Topical anesthesia (lidocaine/prilocaine cream) may be applied in limited body areas 1 h prior to laser treatment. Protective eye goggles by the patient and the treating physician should be used during laser treatment, and it is advised not to treat a patient within the bony orbit. Sun exposure should be avoided after laser treatment to avoid postinflammatory hyperpigmentation.

Conclusions

In conclusion, an effective management of hirsutism should aim to diagnose and treat any underlying hormonal disease while reducing excessive hair. Evidence-based data regarding the use of systemic treatments for hirsutism is lacking. As idiopathic hirsutism is mainly a cosmetic problem, topical treatments and hair removal methods are preferred.

According to current official guidelines and accepted practices, combined oral contraceptives (COC) or laser/IPL epilation is suggested for premenopausal women with patient-important hirsutism. Combined oral contraceptives are the first-line therapy for hirsute women with PCOS. If COC are chosen, treatment efficacy should be evaluated after no less than 6 months. Women with hirsutism should be adequately informed about the potential risks associated with COC use. When laser/IPL epilation is chosen, it can be combined with eflornithine hydrochloride cream for a more rapid result. The routine use of other topical or systemic medications for hirsutism is not suggested.

An interdisciplinary approach comprising a dermatologist, an endocrinologist, and/or a gynecologist may provide optimal management to the hirsute woman.

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HIV Infection and AIDS: Antiretroviral Therapy

41

Vassilios Paparizos and Sofia Kourkounti

Key Points

- HIV infection is now considered to be a chronic disease with a long life expectancy.
- The treatment of HIV infection consists of newer drugs that have easy dosing schedules and fewer side effects.
- There are currently three regimens that drugs are co-formulated into a single tablet, administrated once per day, and more similar regimens are expected.
- Increased comorbidity, associated with the long-term survival, is a new therapeutic challenge.
- Initiation of treatment is recommended in earlier stages, even in asymptomatic patients with high levels of CD4 T-lymphocytes.
- Early treatment of HIV may help prevent or manage comorbidities and reduce risk of transmission.
- The high cost of treatment still remains a major obstacle.

Definition and Epidemiology

Human immunodeficiency virus (HIV) infection remains a major public health problem in Europe and around the world. Approximately 2.3 million people were living with HIV in Europe at the end of 2010, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS), and this number continues to grow. The prevalence of HIV/acquired immunodeficiency syndrome (AIDS) in different regions of the continent varies widely, from less than 0.1 % in parts of Central Europe up to more than 1 % in parts of Eastern Europe. Ongoing developments in antiretroviral therapy (ART) have provided the means for those affected to live longer and healthier lives than would have been possible in the first years of the epidemic. With new developments in therapy, however, have come new challenges, and, like the virus itself, HIV/AIDS treatment will continue to evolve and adapt.

Basic Concepts of Pathogenesis

HIV/AIDS is caused by a human retrovirus named human immunodeficiency virus-1 (HIV-1) and, in a very few cases (predominantly in West Africa, rarely in Europe), human immunodeficiency virus-2 (HIV-2). HIV-1, which was discovered in 1983, is a ribonucleic acid (RNA) virus with two RNA chains organized into nine genes. The virus contains enzymes such as

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_41, © Springer-Verlag Berlin Heidelberg 2015

reverse transcriptase, which enables the transcription of viral RNA into DNA; integrase, which aids the integration of viral DNA in the host cell's DNA; and proteases, which assist in the formation of structural and functional viral proteins from high molecular weight precursor proteins.

In the initial step in the interaction between HIV and cells, the viral surface glycoprotein, gp120, is bound to the CD4 receptor molecule and a co-receptor. The co-receptor is a chemokine receptor, usually CCR5 for macrophage-tropic strains (M-tropic or R5-tropic) or CXCR4 for T-cell line-tropic strains (T-tropic or X4-tropic). The complex of virus and receptors leads to exposure of the viral glycoprotein gp41 and then fusion of the viral and cellular membranes, allowing the virus to enter the target cell.

Each of these steps, and every other point in the life cycle of HIV and its enzymes, is a potential target for antiretroviral drugs.

General Principles of Treatment

In its first decade, beginning in 1987, the treatment of HIV infection depended on nucleoside analogue reverse transcriptase inhibitors (NRTIs), including 2,3-azidothymidine (AZT; also called zidovudine). In 1996, protease inhibitors (PIs) became available, and triple therapeutic combinations were introduced. Because HIV quickly and easily mutates, it would rapidly develop resistance to the administration of a single antiretroviral drug. Triple combinations, dubbed highly active antiretroviral therapy (HAART), were able to achieve strong suppression of viral replication, yielding much better and longer-lasting results than monotherapy had been able to achieve.

In order for HAART to achieve its main objective, that is, strong, long-lasting suppression of HIV, a patient's viral load, as reflected in the number of RNA copies per millilitre of blood plasma (plasma HIV RNA), must be reduced by more than 0.5 log copies/mL 4–8 weeks after therapy is initiated and to undetectable levels (<50 copies/mL) no later than 6 months after beginning treatment. According to the 2012 European AIDS Clinical Society (EACS) guidelines, a detectable HIV RNA level 6 months after initiation of treatment is the definition of virologic failure.

Successful treatment and strong viral suppression enable the reconstruction of the human immune response. Immune reconstitution is both quantitative and qualitative and includes an increase in the CD4 T-cell count and the restoration of these cells' repertoire. Such reconstruction is only partial, since HIV-specific responses, which shut down during the initial infection, do not reset. The degree to which CD4 T-cells increase during immune reconstitution depends on many factors, including the patient's viral load, treatment compliance, age, and lowest CD4 T-cell count (CD4 nadir) prior to treatment.

Although these improvements are incomplete, the vast majority of patients treated for HIV/AIDS experience viral load reduction and immune restoration. This enormous achievement has led to a significant reduction, in the affected population, of opportunistic infections such as Kaposi's sarcoma and other clinical manifestations of AIDS (AIDS conditions). These therapeutic successes have also led to a decreased need for hospitalization and an improvement in patients' quality of life and involvement in productive and social activities. According to several studies, the life expectancy of HIV patients has exceeded 30 years post infection. Life expectancy in the uninfected population is still higher, but patients with CD4 T-cell counts >500 cells/mm^3 who receive ART have mortality rates equal to that of the general population. In present-day Europe, most deaths in HIV-infected patients are not due to AIDS.

In addition to all of these treatment effects, ART is an important means of prevention, since the reduction in viral load reduces but does not

eliminate completely the infectivity of treated subjects. From a public health perspective, the reduction in the viral load of a community as a whole can lead to diminished virus spread. Thus, the main objectives of ART today can be summarized as follows:

- Maximum and long-term suppression of viral load
- Restoration of immune function
- Reduction of HIV-associated morbidity and prolongation of survival with improved quality of life
- Limitation of the transmission

Initiation of ART

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. New drugs, with their new mechanisms of action, improved efficacies, better safety, and fewer side effects, are broadening therapeutic horizons. Co-formulated, single-tablet, once-daily drugs are facilitating tolerance and improving patient adherence.

However, HIV/AIDS medications are meant to be taken for life, which means that the virus may develop resistance and patients will certainly endure side effects. As a response to these problems, intermittent therapy and 'drug holidays' have been trialled but have failed and are now contraindicated. Successful treatment, then, depends on the patient making a firm decision and committing to a course of action after appropriate counselling. Such counselling partly involves a discussion of the potential negative effects of each option and an investigation of potentially complicating factors, including health-related factors like comorbid depression, substance abuse, or other mental disorders, and system-related factors such as the restrictions of any relevant health insurance, the availability and cost of drugs, and the existence or lack of social support.

The best time to initiate ART remains controversial. The rapid reduction in viral load, subsequent reduction of infectiousness, and possible decrease in non-HIV comorbidity led some experts to advocate early initiation of treatment. The US Department of Health and Human Services (DHHS, USA) and the International Antiviral Society, USA (IAS, USA), panel recommended, in 2012, the immediate initiation of treatment in all patients, regardless of the CD4 T-cell counts. On the other hand, some experts have recommended tempering the rush into immediate ART, citing the need for lifelong commitment and the long-term toxicity and high cost of the drugs.

The EACS guidelines, meanwhile, recommend starting treatment in:

- All patients with clinical symptoms (stage B or C in the CDC classification system)
- All asymptomatic patients with a CD4 T-cell count <350 cells/mm^3

The EACS guidelines also recommend earlier initiation of treatment under specific conditions such as the presence of HIV-associated kidney disease, neurocognitive disorder, Hodgkin lymphoma, cancer associated with the human papillomavirus, hepatitis B requiring treatment, pregnancy, etc. (see Table 41.1).

Antiretroviral (ARV) Drugs

At present, there are many ARV drugs from six different classes used for the treatment of HIV/AIDS (see Table 41.2). These classes include:

1. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Integrase inhibitors
5. Fusion inhibitors
6. Entry inhibitors – CCR5 co-receptor antagonists

Table 41.1 Initiation of antiretroviral treatment

According to EACS guidelines 2013:
A. ART initiation is recommended in:
1. Symptomatic HIV disease (CDC B or C conditions)
2. All patients with CD4 count below 350 cells/mm^3
3. Regardless of CD4 T-cell count, HIV patients with:
HIV-associated kidney disease
HIV-associated neurocognitive impairment
Hodgkin lymphoma
HPV-associated cancers
Pregnancy
Hepatitis B requiring anti-HBV treatment
4. Patients with CD4 T-cell counts between 350 and 500 cells/mm^3 with:
Hepatitis C virus (HCV) co-infection
B. Use of ART should be considered in:
Asymptomatic patients with primary HIV infection
Non-AIDS-defining cancers requiring chemo- and/or radiotherapy
Patients at high risk for CVD (>20 % estimated 10-year risk) or history of CVD
Patients with hepatitis B not requiring anti-HBV treatment and CD4 count 350–500 cells/mm^3
Patients with CD4 count >500 cells/mm^3 and hepatitis C for which anti-HCV treatment is not feasible
Patients with CD4 count >350 cells/mm^3, to reduce HIV transmission
Patients with CD4 count >350 cells/mm^3, individualized, especially if patient is requesting ARV therapy and is ready to start
DHHS USA and IAS – USA panel, 2012, recommends initiation of antiretroviral therapy in all patients, regardless of CD4 T-cell count:
In order to reduce the risk of disease progression
For the prevention of transmission of HIV, through HIV RNA load reduction

Table 41.2 Antiretroviral medications in Europe

	Name	Main dosage forms	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)			
1	Zidovudine (AZT or ZDV)	Caps 100 mg Tabl 300 mg	
2	Abacavir (ABC)	Tabl 300 mg	
3	Didanosine (ddI)	Caps (ec) 400 mg Caps (ec) 250 mg	250 mg: body weight <60 kg
4	Lamivudine (3TC)	Tabl 150 mg Tabl 300 mg	
5	Emtricitabine (FTC)	Caps 200 mg	
6	Stavudine (d4T)	Caps 40 mg Caps 30 mg	30 mg: body weight <60 kg
Nucleotide reverse transcriptase inhibitors (NtRTIs)			
7	Tenofovir disoproxil fumarate (TDF)	Tabl 300 mg	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
8	Efavirenz (EFV)	Tabl 600 mg Tabl 100 mg	
9	Nevirapine (NVP)	Tabl 200 mg Tabl XR 400 mg	
10	Etravirine (ETR)	Tabl 100 mg Tabl 200 mg	

Table 41.2 (continued)

	Name	Main dosage forms	Comments
11	Rilpivirine (RPV)	Tabl 25 mg	
Protease inhibitors (PIs)			
12	Indinavir (IDV)	Caps 400 mg	
13	Fosamprenavir (FPV)	Tabl 700 mg	
14	Darunavir (DRV)	Tabl 400 mg Tabl 600 mg	
15	Atazanavir (ATV)	Tabl 300 mg Tabl 200 mg	
16	Lopinavir/r (LPV/r)	Tabl 200/50 mg	
17	Saquinavir (SQV)	Tabl 500 mg	
18	Nelfinavir (NFV)	Tabl 625 mg Tabl 250 mg	The only unboosted PI
19	Tipranavir (TPV)	Caps 250 mg	
Integrase inhibitors			
20	Raltegravir (RAL)	Tabl 400 mg	
21	Elvitegravir (EVG)	–	Only as co-formulated
CCR5 antagonists			
22	Maraviroc (MVC)	Tabl 150 mg Tabl 300 mg	Dose depending on concomitant ARVs
Fusion inhibitors			
23	Enfuvirtide (ENF)	Inj (sc) 90 mg	
Combination formulations			
	Trizivir (AZT/3TC/ABC)	Tabl 300/150/300 mg	
	Kivexa (ABC/3TC)	Tabl 600/300 mg	
	Truvada (TDF/FTC)	Tabl 300/200 mg	
	Combivir (AZT/3TC)	Tabl 300/150 mg	
	Atripla (TDF/FTC/EFV)	Tabl 300/200/600 mg	
	Eviplera (TDF/FTC/RPV)	Tabl 300/200/25 mg	
	Stribild (TDF/FTC/Cobi/EVG)	Tabl 300/200/150/150 mg	
Boosters			
	Ritonavir	Tabl 100 mg Caps 100 mg	Co-formulated with lopinavir in Kaletra
	Cobicistat	–	Co-formulated in Stribild

Drugs that no longer have approval or that are no longer used: Zalcitabine (ddC), Delavirdine (DLV), and Amprenavir (APV)

Antiretroviral Regimens for the Initiation of Therapy

The plethora of ARV drugs allows patients and clinicians to choose an optimal combination that is compatible with the needs and characteristics of the individual patient. The choice of regimen is usually based on guidelines developed by an expert panel, which recommend preferred medicines and offer alternative choices when the preferred medicines are not ideal or practicable for a given situation. Such guidelines, issued by international and national organizations, are frequently revised or updated (see Table 41.3).

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)

NRTIs and NtRTIs (also called nucleoside/nucleotide analogues or even 'nukes') inhibit HIV's reverse transcriptase function by preventing

Table 41.3 Initial combination regimen for antiretroviral-naive adult patients

According to EACS guidelines 2013:
A. Preferred regimens
The initial regimen consists of two NRTIs, preferably combinations of TDF/FTC or ABC/3TC, plus one of the following
NNRTI (recommended: EFV or RPV)
Ritonavir-boosted PI (recommended: ATV/r or DRV/r)
Integrase inhibitor (recommended: RAL)
B. Alternative regimens
Alternatively, the regimen may consist of two NRTIs – TDF/3TC, ZDV/3TC, ddI/3TC, and ddI/FTC – plus a third drug, such as:
Ritonavir-boosted PI (LPV/r, SQV/r, or FPV/r)
NNRTI (NVP)
CCR5 inhibitor (MVC)
Integrase inhibitor (EVG + Cobicistat)
According to DHHS guidelines 2013:
(a) Preferred NRTI regimen is only TDF/FTC and the only alternative combination is ABC/3TC
(b) Preferred NNRTI is only EFV. RPV is included in alternative regimens and NVP is not
(c) Preferred PIs are ATV/r και DRV/r. LPV/r is included in alternative regimens and SQV/r is not

transcription of the viral RNA into DNA. These act as alternative substrates that compete with physiological nucleosides/nucleotides. The integration of NRTIs/NtRTIs in the chain formation of viral DNA interrupts its composition, since the virus can no longer create phosphodiester bonds with the 'fake' nucleoside/nucleotide. In order to be incorporated into the DNA chain, NRTIs must first be phosphorylated in the cell with three phosphate groups (while NtRTIs, which already contain one phosphate group, require two more), forming triphosphate analogues, the active form of the molecules. NRTIs were the first antiretroviral drugs; AZT, introduced in 1987, was used as monotherapy for many years. Today, a combination of two NRTIs/NtRTIs forms the backbone of HIV/AIDS treatment, which is usually completed with a third drug from another class.

Although tolerance is very good, NRTIs/NtRTIs have been associated with long-term toxicity. Their main long-term side effects include myelotoxicity (particularly with AZT), hepatotoxicity, lactic acidosis, rhabdomyolysis, pancreatitis, peripheral neuritis (especially with stavudine [d4T] and didanosine [ddI]), and lipoatrophy. Many of these side effects are related to mitochondrial toxicity. The incorporation of false nucleosides leads to inhibition of mitochondrial DNA polymerase-c, resulting in impaired synthesis of mitochondrial enzymes that generate ATP by oxidative phosphorylation.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs inhibit HIV's reverse transcriptase activity by binding a hydrophobic pocket close to the enzyme's active site, locking the site in an inactive conformation. These drugs are very potent, but they have a low genetic barrier; a single primary mutation can create an HIV strain able to resist them. In many cases, a single mutation (e.g. the K103N mutation) can cause cross-resistance, making more NNRTIs ineffective. However, when patient adherence to treatment is very high, these mutations are not easily or quickly selected.

The main side effects of NNRTIs are hepatotoxicity, drug eruption (especially with nevirapine [NVP]), and central nervous system (CNS) disorders (associated with the use of efavirenz [EFV]). As these drugs are metabolized by cytochrome CYP3A4, particular attention to interactions with other drugs or substances (e.g. methadone) is required.

Protease Inhibitors (PIs)

PIs inhibit HIV proteases by binding to their active sites, preventing the cleavage of Gag and Gag-Pol precursor proteins. When proteolytic splicing is prevented, incomplete and non-infectious virions are produced. Since 1995, PIs inaugurated the HAART era, revolutionizing the treatment of HIV/AIDS. All PIs have strong antiviral activity and high genetic barriers; a sum of many mutations is required to develop resistance to them, especially to the newest drugs. PIs, however, have many side effects, both short-term and long term. Short-term side effects are mainly gastrointestinal disturbances such as nausea, abdominal upset, flatulence, and diarrhoea, while long-term side effects include lipodystrophy, metabolic disorders such as hyperlipidaemia, insulin resistance, atherosclerosis, and an increased risk of cardiovascular disease and osteoporosis-osteopenia. While these side effects affect the entire class, some additional side effects are specific to certain drugs: atazanavir and indinavir (IDV) are associated with hyperbilirubinaemia and nephrolithiasis, and IDV is associated with skin dryness and nail dystrophy.

PIs are metabolized in the liver and are potent inhibitors of cytochrome CYP3A4. PIs may interact with many other drugs so careful co-administration is required.

Meanwhile when ritonavir is co-administered with other PIs, it leads to a considerable increase in several pharmacokinetic parameters, including Cmax (maximum concentration) and Ctrough (trough levels). This phenomenon, known as 'boosting', is indicated on labels by the notation '/r' after the drug name and simplifies daily regimens by reducing dose frequency and pill burden.

Integrase Inhibitors

Integrase inhibitors are designed to inhibit one of the functions of the viral integrase. Integrase is involved in multiple steps of the path of the viral DNA, from the production in the cytoplasm to the transfer to the core and the final incorporation into the DNA of the host cell. The currently available integrase inhibitors (raltegravir and elvitegravir) inhibit the final step, the binding of the viral DNA into the cellular DNA (strand transfer inhibitors). Integrase inhibitors are well tolerated; their side effects are relatively rare and mild. The most common adverse events associated with these drugs are transient mild-to-moderate headaches and fatigue.

Because integrase inhibitors are metabolized by glucuronidation via UDP-glucuronyltransferase 1A1 (UGT1A1) and not by cytochrome p450, interactions with other drugs are minimal. Drugs that are strong inducers of glucuronidation enzyme UGT1A1 though, such as rifampicin, significantly reduce concentrations of raltegravir. Integrase inhibitors are considered to have a relatively low genetic barrier, and there is cross-resistance between raltegravir and elvitegravir. However, in clinical practice they have demonstrated superiority over other drugs as a first-line therapy.

Currently, two integrase inhibitors are available: raltegravir, which must be administered twice a day, and elvitegravir, which exists only as a co-formulation with emtricitabine, tenofovir, and cobicistat.

Entry Inhibitors: Fusion Inhibitors

The fusion of the HIV membrane with the membrane of the target cell is an essential step for the entry of the virus. After connecting the viral gp120 with the CD4 receptor and co-receptor (CCR5 or CXCR4), viral gp41 undergoes a conformational change that exposes the hydrophobic region of gp41 to the cell membrane. This allows the two heptad repeat sequences (HR1 and HR2) of gp41 to interact, resulting in the formation of a hairpin structure that brings the virus and cell membranes together, mediating the fusion of virus and cell.

At present, there is only one fusion inhibitor: enfuvirtide (T-20). T-20 exerts its action by binding to HR1 and disrupting its interaction with HR2, so that the fusion of the two membranes is

no longer possible and the virus cannot enter the cell.

T-20 is only available in the form of a twice-daily subcutaneous injection. Its most frequent adverse reactions are injection site reactions, including pain, erythema, itchiness, nodules, cysts, or granulomas. Other adverse reactions are rare but include coughing, dyspnoea, arthralgia, insomnia, depression, and infections, notably bacterial pneumonia. T-20 is a synthetic peptide with a high molecular weight (4,492 Kd), making it difficult to develop a non-injectable formulation.

Entry Inhibitors: CCR5 Co-receptor Antagonists

There is currently only one drug, maraviroc (MVC), in the class of co-receptor antagonists. MVC binds to the CCR5 co-receptor, which is a chemokine receptor, inducing conformational changes and leading to the inhibition of its binding to the viral gp120. MVC has no activity against HIV strains that use the CXCR4 receptor (X4-tropic strains) or those that can use both receptors (dual-tropic), and there are currently no CXCR4 co-receptor antagonists. However, in most patients, strains that bind to the CCR5 co-receptor (R5-tropic strains) prevail in the early stages of the disease; R5-tropic strains are found in 80–90 % of treatment-naïve patients; CCR5 antagonists, therefore, probably need to be given earlier in the course of the disease. X4-tropic strains of HIV, on the other hand, are almost exclusively found in advanced stages of the disease.

So far, a shift in virus tropism from R5- to X4- or dual-tropic during treatment with MVC has not been observed. In any case, before administering MVC, tropism testing should be performed to exclude patients with X4- or dual-tropic strains. MVC is very well tolerated, with usually few and relatively mild side effects, including gastrointestinal disorders, headaches, dizziness, and joint pain.

MVC is metabolized by cytochrome CYP3A and thus enzyme inhibitors such as PIs increase the level of MVC in the blood, while inducers, as EFV or etravirine (ETR), may substantially decrease maraviroc concentrations. In practice, the dosage of MVC depends on which antiretroviral drugs are co-administered.

Changing Antiretroviral Therapy

Change Due to Virologic or Immunologic Failure

As previously noted, virologic failure, according to EACS guidelines, is defined as HIV RNA levels >50 copies/mL 6 months after starting therapy (initiation or modification). ARV drugs should be changed in patients experiencing virologic failure, especially when there is resistance mutation substantiated by genotypic testing. The new regimen must contain at least two and preferably three fully active drugs. However, in all cases of virologic failure, the degree of the patient's adherence to therapy and possible factors affecting compliance should be investigated thoroughly. If the viral load is more than 500–1,000 copies/mL, it is necessary to perform drug resistance genotype testing. Therapy should also be changed in the case of immunologic failure, which is defined as failure to achieve and maintain an adequate CD4 T-cell response despite virologic suppression, especially when the CD4 T-cells remain firmly below 200 cells/mm^3. No consensus exists, however, on how best to change the antiretroviral regimen in the event of immunologic failure.

Change Due to Toxicity

Change in the ARV regimen is sometimes necessary due to adverse reactions, both those appearing shortly after initiation of treatment (commonly hypersensitivity, gastrointestinal disorders, myelotoxicity, hepatotoxicity, and CNS disorders) and those that occur with long-term use (commonly renal dysfunction with tenofovir use, depression related to efavirenz use, nephrolithiasis, lipodystrophy, hyperlipidaemia, etc.).

Change to Simplify or Modernize Therapy

Regimen simplification usually aims at reducing pill burden and dose frequency in order to improve adherence to therapy. New less-toxic or co-formulated drugs and single-tablet regimens offer options for modernizing and simplifying more complex, older combinations. Occasionally such an update will be compelled when an older drug becomes unavailable (as occurred with nelfinavir) or becomes only available in a new formulation (as occurred when Viramune (a brand of NVP) changed its formulation to Viramune XR).

Special Issues

Adherence/Drug Resistance

The effectiveness of ART is determined by the treatment duration and the efficacy of each of the drugs. Both of these factors depend on the drugs' genetic barriers (i.e. the number of mutations of HIV required for the development of drug resistance) and the ease of selection of the mutations. When such drug resistance develops, treatment response decreases, and viral replication increases. Resistance mutations are detected by genotypic resistance tests that must be performed before the start of therapy and in the event of virologic failure. Based on the results of these resistance tests, any failed drugs are replaced with active agents.

Such drug failures are most commonly caused by a lack of patient adherence to treatment; frequently missed doses, arbitrary dose reduction, and discontinuation of therapy lead to increased viral replication in the presence of the drugs' genetic information, which encourages the selection of resistance mutations. When virologic failures are repeated and new mutations constantly appear, treatment options decrease and subsequent regimens are usually more complex and may include more drugs with more side effects and limited efficacy. Thus, patient adherence to treatment is particularly important for its success. Factors commonly associated with poor adherence include depression, use of alcohol or recreational drugs, and patients' personal perceptions of medications, all of which should be investigated before therapy is initiated.

Genotypic resistance tests, at the time of initial diagnosis, detect mutations that are there due to transmission of resistant strains during the initial infection or during reinfection, and the likelihood that a patient will acquire a drug-resistant virus is not rare; in Europe, 8–10 % of patients have transmitted resistance.

Ageing

The prolongation of survival has led to increased patient age and the emergence of comorbidities associated with ageing. It is likely that after 2015, 50 % of HIV patients will be over 50 years old. Thus, patients who are treated with antiretrovirals have increased risk for several non-AIDS complications, many of which are commonly associated with ageing. The most common complications in treated subjects are related not directly to AIDS but to hypertension, diabetes mellitus, cardiovascular disease, osteopenia-osteoporosis, liver or kidney failure, neurocognitive disorders, and increased incidence of cancers. The emergence of these disorders occurs in patients younger than expected and contributes to a phenotype of frailty.

Due to the changing spectrum of HIV-associated diseases, the medical management of HIV infection is evolving; a lower proportion of time is now spent managing drug resistance and short-term toxicities and a higher proportion is spent managing these premature age-associated complications.

These disorders are related to the incomplete correction of immunological function, the persistent defects, and the presence of low-level inflammation which acts on the endothelium of blood vessels and at cellular level.

The occurrence of events which are not directly related to HIV infection creates the need for further treatment. The multi-morbidity leads to polypharmacy and requires increased attention

to the selection of these drugs and antiretroviral therapy, in order to avoid drug interactions.

HIV Co-infection with Hepatitis B (HBV) or Hepatitis C (HCV)

HIV co-infection with HBV or HCV is common. In Western Europe, the incidence of HBV in HIV patients has been found to be 6–14 % overall. Its prevalence is estimated at 9–17 % in men who have sex with men (MSM), 7–10 % in injectable drug users (IDU), and 6.4 % in heterosexuals. HCV-HIV co-infection has been found to be 25–30 % overall: 72–95 % in IDUs, 1–12 % in MSM, and 9–27 % in heterosexuals. HIV infection has been associated with a more rapid progression of viral hepatitis. HIV patients with HBV or HCV have greater levels of HBV or HCV viraemia, faster progression to cirrhosis, and severe hepatic impairment and suffer more frequently from hepatocellular carcinoma. Furthermore, HIV patients with viral hepatitis exhibit rapid progression to AIDS. The increase of CD4 T-cells and the improvement of the immune response associated with ART also improve the course of viral hepatitis. Moreover, NRTIs such as emtricitabine, lamivudine, and tenofovir are potent drugs against HBV. Accordingly, the 2012 EACS guidelines for the treatment of HIV infection recommend the rapid onset of ART in co-infected patients, particularly those who need or are receiving treatment for hepatitis (see Table 41.1).

HAART Optimism

Excessive optimism from the effectiveness of HAART, deemed 'HAART optimism', involves inaccurate beliefs about susceptibility to HIV transmission, a reduction in the use of condoms, frequent unprotected sexual contacts, an increase in the number of sexual partners, and a general resurgence of high-risk behaviour. HAART optimism has been associated with an increased incidence of sexually transmitted diseases such as syphilis, particularly among MSM. HAART optimism remains a controversial topic, though many studies conclude that risky behaviour is a factor in the growth of HAART optimism and not the reverse. However, it is clear that the causal relationship can act in both directions, each perhaps due to differences in individuals or populations.

Lipodystrophy

HIV-associated lipodystrophy is a syndrome that represents a group of disorders observed in HIV patients under treatment. It includes morphological changes, such as the loss or redistribution of subcutaneous fat (in the form of lipoatrophy and/or adiposity [lipohypertrophy]), and other physical and metabolic disorders. The metabolic disorders are diverse and are primarily associated with hyperlipidaemia and insulin resistance. HIV-related changes in the distribution of subcutaneous fat often coexist with metabolic abnormalities, but these may exist independently of one another.

Lipoatrophy is characterized by loss of subcutaneous fat through the face (cheeks, temples, nasolabial regions), the upper and lower extremities, and the buttocks. These changes appear as sunken cheeks, prominent temporal veins, and increased wrinkling in the face. Lipoatrophy has been associated more with long-term use of NRTIs, particularly derivatives of thymidine (e.g. d4T and zidovudine). Lipohypertrophy, on the other hand, is mainly associated with the use of PIs and is characterized by increased fat deposition in the abdomen, breasts, and, more rarely, shoulders and neck (sometimes referred to as 'buffalo hump'). Lipohypertrophy may occur as multiple subcutaneous lipomas, but this is a rare presentation. The two forms of lipodystrophy can coexist in the same patient. Lipoatrophy, particularly of the face, and/or the development of buffalo hump, can be cosmetically disfiguring, significantly reducing the patient's quality of life. Facial lipoatrophy carries a social stigma and is undoubtedly one of the most distressing side effects for HIV patients.

The HIV-related metabolic disorders, meanwhile, include hyperglycaemia, reduced glucose

tolerance, and elevated triglycerides and total cholesterol. Other metabolic symptoms include increased levels of low-density lipoprotein, very low-density lipoprotein, and apolipoprotein B (which is considered an independent risk factor for atherosclerosis) and slightly decreased levels of high-density lipoprotein. Other metabolic abnormalities that are associated or may coexist with lipodystrophy are a disturbance in calcium metabolism, osteoporosis and osteopenia, and aseptic bone necrosis.

The pathogenesis of lipodystrophy is not yet adequately understood. Some evidence suggests that NRTIs may cause mitochondrial toxicity, leading to reduced energy production, increasing insulin resistance, and dyslipidaemia. PIs are also implicated, as they compete with enzymes involved in the metabolism of retinoic acid and lipoproteins or directly affect adipocytes' life cycles. In addition, HIV infection itself causes dyslipidaemia and lipodystrophy, especially in its advanced stages.

Overall, risk factors for developing lipodystrophy involve the course of HIV/AIDS, the duration of treatment, the types of medication used, the CD4 nadir, and the patient's race and gender (white patients and female patients experience higher risk). As long as the offending drug is being administered, a patient's lipodystrophy will continue to evolve. Switching from thymidine analogues to other NRTIs or from PIs (particularly older ones such as IDV and lopinavir/ritonavir) to other drugs (NNRTIs, integrase inhibitors, newer PIs such as darunavir), if feasible, may help. However, such have been shown to result in only limited and slow improvements in appearance.

Managing the metabolic disorders (e.g. diabetes, hyperlipidaemia) is essential for the treatment of lipodystrophy. Many drugs, such as anabolic steroids, human growth hormones, and naltrexone, have been tested in clinical trials for treating lipodystrophy. However, at present, only tesamorelin has been approved by the USA's Food and Drug Administration (FDA) for the treatment of lipodystrophy.

Approaches using plastic surgery, such as liposuction or lipectomy, have achieved moderate success in treating lipohypertrophy, as have commercial fillers or implants (e.g. poly-L-lactic acid, hyaluronic acid, calcium hydroxyapatite, and injectable collagens). Autologous fat grafting from lipohypertrophy areas to areas of lipoatrophy has also been used.

Drug Eruptions

Adverse cutaneous drug eruptions are very common in HIV-infected patients and occur 10–100 times more frequently than in the general population. Such drug eruptions can range from extremely mild to very serious and life threatening, and they usually occur within 6–14 days of therapy initiation. The typical form in the vast majority of cases is maculopapular morbilliform rash, with or without pruritus. Systemic symptoms (e.g. fever or headache) may occur with the rash. Other forms of eruption include urticaria, erythema multiform, fixed drug eruption, drug reaction with eosinophilia, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

The pathogenesis of this phenomenon is unknown. Suggested related factors include advanced immunosuppression or immune activation, differences in the expression of cytokines, complex medication interactions, disturbances in the metabolism of compounds such as glutathione deficiency, liver dysfunction, and individual factors. The drugs that are most commonly responsible for rash are trimethoprim-sulphamethoxazole, NNRTIs, and semi-synthetic penicillins. Trimethoprim-sulphamethoxazole is administered to all patients who have CD4 T-cell counts <200 cells/mm^3 as chemoprophylaxis against *Pneumocystis jirovecii* pneumonia and toxoplasmosis, but its use and resulting eruptions were more frequent before the HAART era. NNRTIs are often responsible for hypersensitivity reactions, and 12.5–20 % of NVP-treated patients experience an exanthematous eruption. The NRTI abacavir (ABC) may also cause a hypersensitivity reaction, which manifests within the first 6 weeks of treatment as rash, fever, fatigue, nausea, abdominal pain, and respiratory symptoms such as pharyngitis, dyspnoea, or

coughing. If ABC is discontinued due to hypersensitivity, it must not be used again because of the risk of recurrence of immediate hypersensitivity in a much more intense, life-threatening form. Because ABC hypersensitivity is strongly associated with the HLA-B*5701 allele, all treatment guidelines recommend HLA-B*5701 testing before initiating ABC treatment. PIs, meanwhile, particularly older agents such as IDV, may cause retinoid-like effects, including xerosis, desquamative cheilitis, paronychia, and onychodystrophy. In some cases of mild rash, the responsible drug may be continued under close monitoring, and the eruption may resolve, but drug discontinuation is usually required. A re-challenge test may be performed for mild NVP, but not ABC, hypersensitivity.

Drug Interactions

HIV/AIDS patients receive a combination of three or four drugs (including boosters) for the treatment of their disease. They often have to take other medications for comorbid disorders (co-infection with hepatitis, depression, etc.) or to address the effects of ageing (hypertension, hyperlipidaemia, etc.), and many patients also take methadone, alternative medications, and recreational drugs. Such a proliferation of substances significantly increases patients' risks for drug interactions.

Most drug interactions in HIV/AIDS patients are associated with PIs or NNRTIs, both of which are metabolized by cytochrome p450. The most common isoenzyme is CYP3A4, followed by CYP2C19 and CYP2D6. Drugs that inhibit, induce, or act as a substrate for p450 alter the metabolism of other drugs, resulting in higher drug levels and an increased potential for toxicity or lower drug concentrations and decreased efficacy. Drugs such as rifampicin, azoles, methadone, anticonvulsants, hypolipidemics, and many others that are also metabolized by the same enzyme system should be used with caution. A thorough medication history must be taken for every patient before initiating ART or other drug treatments, and each visit should include a review of all currently used drugs. Extensive appendices of interactions between ARVs and other drugs are listed in international and national guidelines, and they are widely available and frequently updated on the websites of international organizations.

Pregnancy

The administration of ART in pregnant HIV-infected women has two aims: treating the patient and preventing perinatal transmission of HIV. This is achieved:

- By reducing the viral load in the mother's blood
- By reducing the viral load in genital secretions
- By achieving high protective drug levels in the foetus due to the passage of the drugs across the placenta

Thus, the objective of HAART in pregnancy is the maximum suppression of the viral load, at least in the last trimester and especially during the labour. However, ART during the whole pregnancy is better than therapy only in the third trimester. Given that HIV is transmitted through breastfeeding, the mother is not allowed to breastfeed.

The probability of transmitting HIV to the foetus when the mother receives full ART throughout pregnancy is less than 2 %. According to the 2012 EACS guidelines, a pregnant HIV-positive woman must:

- Continue therapy, if she is already receiving treatment
- Start therapy after the completion of the first trimester, if she has not started treatment because she had not yet had indication for receiving ART
- Start therapy immediately, if the diagnosis is made after the first trimester, especially after the 28th week

Generally, the choice of antiretroviral drugs for treating HIV-infected pregnant women should be made with the same criteria as in non-pregnant patients. Most antiretroviral drugs have not been associated with teratogenicity in humans, and their administration is associated with a much

stronger potential benefit than potential risk. Neither EFV nor NVP should be initiated as a component of a pregnant woman's regimen, each for different reasons. If the pregnant woman is already taking these drugs, however, it is acceptable to continue them. Combinations that are contraindicated in pregnancy, such as d4T and ddI, or regimens with three NRTIs are to be avoided in all pregnant women. Preferred PIs for pregnant women are those for which there is more recorded data. In addition, administration of additional intravenous zidovudine during labour is recommended, although its necessity when the viral load is undetectable (<50 copies/ml) is in dispute. The performance of a caesarean section is no longer considered necessary when the viral load is undetectable at the end of pregnancy. In any other case, however, a caesarean section is imperative. According to the 2012 DHHS–USA guidelines, a child born to an HIV-infected mother should receive postexposure prophylaxis with zidovudine immediately after birth, for a duration of 6 weeks.

Outlook

The treatment of HIV infection has developed faster than treatment for any other disease in history. This progress has been the result of intensive research, which has yielded side benefits for the treatment of other infections, such as reverse transcriptase inhibitors for HBV, protease and DNA-polymerase inhibitors for HCV, and drugs for *Cytomegalovirus*.

As a result of all of these advancements, HIV/AIDS is no longer the same undefeatable spectre the world faced with a sense of hopelessness and terror in the 1980s. However, a large number of old and new issues remain. Time and research will reveal the potential long-term toxicities of newer drugs, strategies for treating comorbidities, the possibility of reducing HIV incidence by the immediate initiation of treatment ('test and treat'), and the effects of economic crises on the epidemiology and treatment of the disease. The definitive eradication of the virus from an infected individual, moreover, does not appear to be feasible in the near future. A high priority remains, then, on limiting the spread of HIV, largely through the concerted prevention efforts of international and local organizations and governments.

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Hidradenitis Suppurativa

42

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Key Points

- Hidradenitis suppurativa/acne inversa (HS) is a chronic, multifactorial, debilitating, inflammatory skin appendage condition of the hair follicle.
- HS is a common disorder with a point prevalence of 1.0 % and a female preponderance.
- Management of HS should encompass the education of the patient regarding the nature of the disease, general measures, pharmacological topical or systemic treatment and surgical therapy.
- Antibiotic, immunosuppressive, anti-inflammatory, antiandrogenic and surgical treatments, as well as laser and light sources, have been used for the management of HS, although few randomised, controlled trials exist to provide evidence-based data on their efficacy for this condition.
- Topical clindamycin 1 % is the only studied topical antibiotic for HS.
- Systemic treatments that have been used for HS include antibiotics, retinoids (acitretin), biologic agents, antiandrogens, zinc gluconate, dapsone, colchicine, corticosteroids, ciclosporin and metformin.
- The combination of clindamycin and rifampicin is indicated for active inflammatory HS.
- The treatment choice will depend on the severity and extent (localised or widespread disease) of HS.
- The combination of different treatment modalities may be required to achieve improvement.

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Definition and Epidemiology

The definition of hidradenitis suppurativa (HS) relies on clinical criteria. According to the 'Dessau definition' of HS, it is a chronic, inflammatory, recurrent, debilitating skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal and anogenital regions (First International Conference on Hidradenitis suppurativa, March 30–April 1, 2006, Dessau, Germany).

Although HS was considered a rare disease in the past, its prevalence has been estimated to be 1–4 %. It presents as a sporadic or familial form.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_42, © Springer-Verlag Berlin Heidelberg 2015

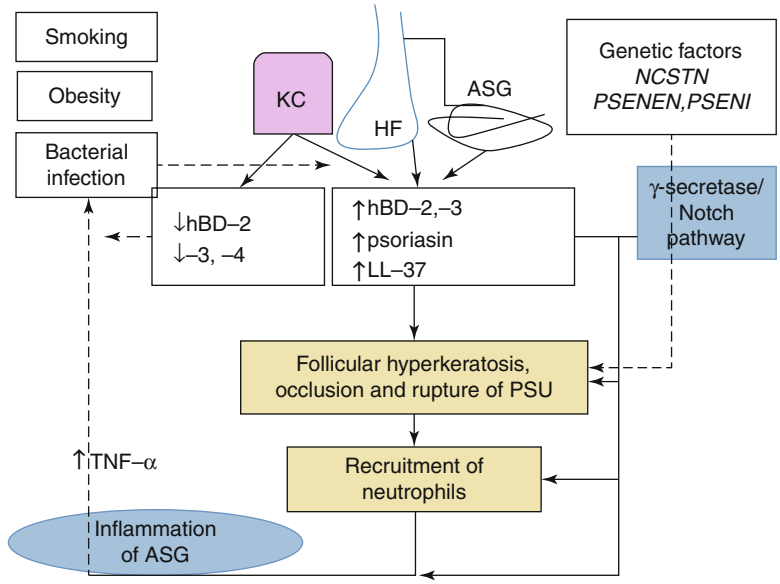

Fig. 42.1 Schematic pathophysiology of HS (Dessinioti et al. 2013)

HS affects more women than men, with a female-to-male predominance as high as 4:1. The disease occurs almost always after puberty and before the age of 40 years.

The chronicity, relapses and sequelae of the disease, including dermal contraction, scarring, restricted limb mobility, lymphoedema and fistula formation, contribute to the long-term burden of the disease and have a considerable negative impact on the patients' psychology, sex health and quality of life.

Basic Concepts of Pathogenesis

The pathogenesis of HS has not yet been elucidated, but it is considered to be a multifactorial disease. Current theories implicate the hyperkeratosis of the follicular epithelium as the morphological hallmark of HS pathogenesis, leading to occlusion of the apocrine glands with subsequent follicular rupture, inflammation and possible secondary infection. Genetic factors, hormones, smoking, obesity, bacterial infection and alteration of antimicrobial peptides (AMPs) that regulate cutaneous innate immunity have been implicated in the multifactorial pathogenesis of HS (Fig. 42.1).

It is clear that bacterial infection is not the primary cause of HS. However, bacteria, their products and immune responses raised against bacterial antigens may influence the clinical phenotype of HS lesions as well as the course of HS in any given patient (Zouboulis et al. 2012). In terms of natural immunity, patients with HS may respond abnormally to these bacteria (e.g. *Propionibacterium acnes*), whose products stimulate Toll-like receptors, producing pro-inflammatory cytokines such as IL-1α and giving rise to abnormal keratinisation (Zouboulis et al. 2012).

Current smoking has been associated with HS, with a highly significant association in multivariate analysis (OR = 12.55) (Hana et al. 2007). It has been suggested that smoking affects polymorphonuclear cell chemotaxis. Obesity and being overweight are frequent in HS and could represent a risk factor. Two case-control studies by Revuz et al. showed an association of HS with body mass index in medically assessed patients ($n = 302$) (odds ratio = 1.12 [1.08–1.15]) for each increase of 1 U of BMI. However, HS may also develop in low or normal body mass index.

Clinical Presentation

The clinical lesions of HS consist of primary lesions including painful nodules and abscesses and secondary lesions including sinus tracts,

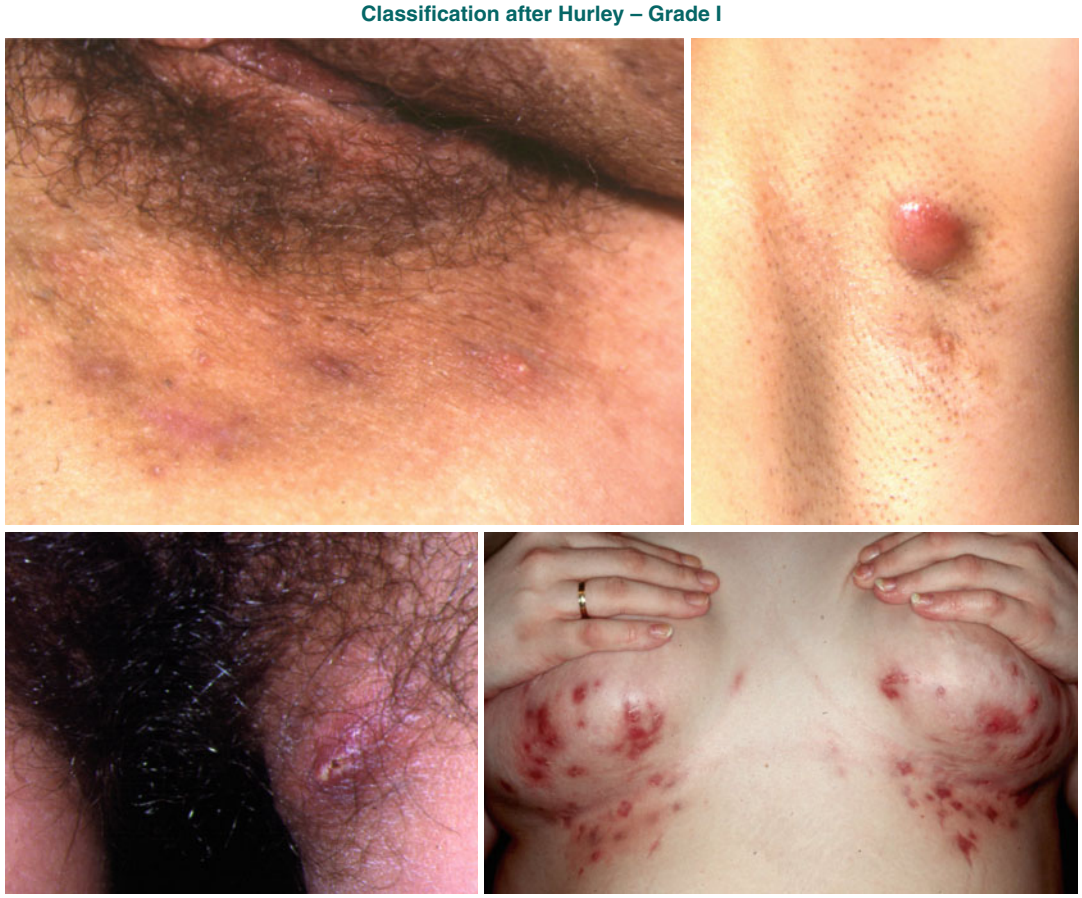

Fig. 42.2 Hidradenitis suppurativa Hurley grade I

hypertrophic scars and multiparous or uniporous 'tombstone' open pseudo-comedones. In contrast to acne, there is no hyperseborrhoea or closed comedones in HS.

The topography of involvement may be explained by the distribution of apocrine glands and shearing forces, which originate in large skin folds, especially of overweight patients. The location of HS lesions is along the 'milk line' of apocrine and mammary tissues that have the same embryonic origin.

For each affected body site, the severity of the disease can be classified in three grades according to the Hurley classification (Figs. 42.2, 42.3 and 42.4) that provides a simple but static assessment (Table 42.1). The Sartorius score is also used as a more complex, dynamic score to assess severity of HS, mainly in the context of clinical studies, grading the number, size and extent of individual lesions.

Recently, Canoui-Pointrine et al. reported three distinct HS phenotypes in 618 patients, including the 'axillary-mammary' class (48 %) that had a high probability of breast and armpit lesions and hypertrophic scars; the 'follicular' class (26 %) that were more often male, current smokers and with more severe disease and had a high probability of breast, armpit, ear, chest, back or leg lesions and follicular lesions and a family history of HS; and the 'gluteal class' that were less often obese and had less severe, with gluteal involvement, papules and folliculitis.

Complications of HS include lymphatic obstruction and lymphoedema of the anogenital area; the development of squamous cell carcinoma in 2–4 % of patients, especially in men and in the buttock area; and serious infections, anaemia or hypoproteinaemia.

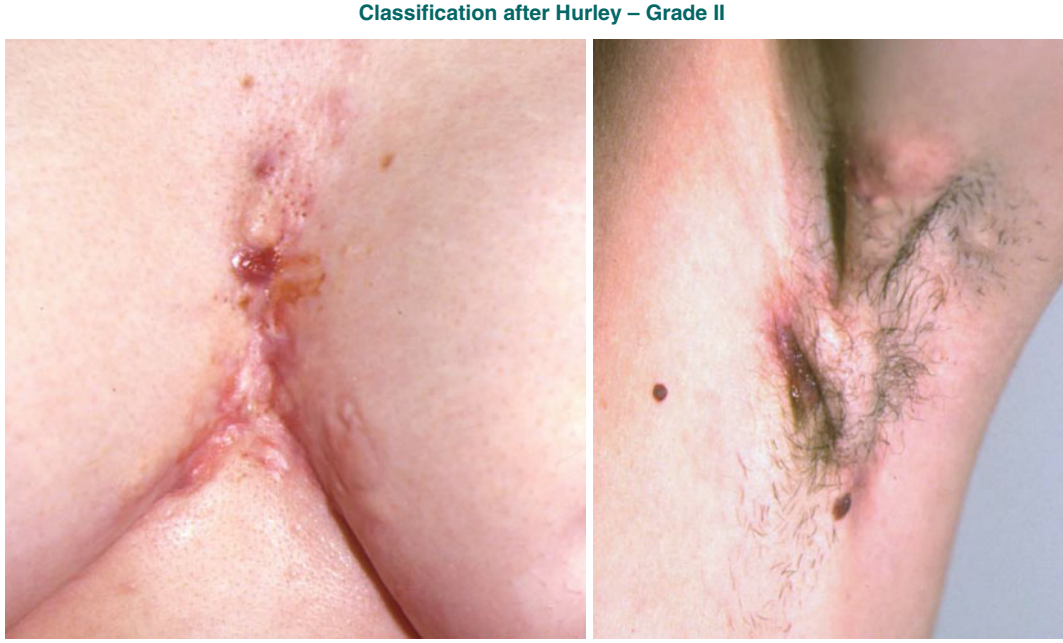

Fig. 42.3 Hidradenitis suppurativa Hurley grade II

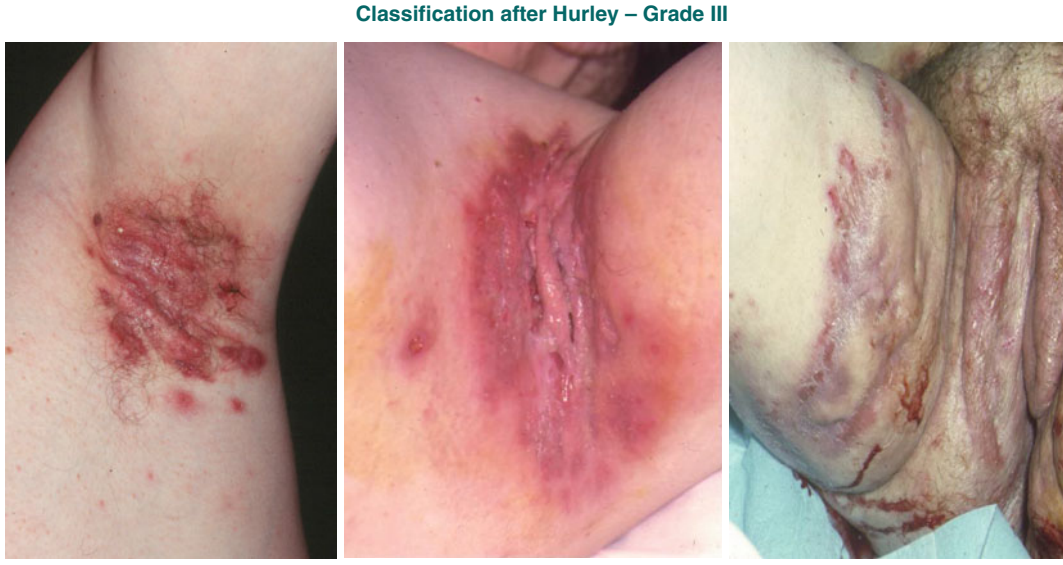

Fig. 42.4 Hidradenitis suppurativa Hurley grade III

Several diseases have been reported in association with HS, including Crohn's disease, the synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome, pyoderma gangrenosum, acne and suppurative hidradenitis (PASH) syndrome, pyoderma gangrenosum, Adamantiades-Behçet's disease, spondyloarthritis without or with follicular occlusion triad signs, genetic keratin disorders associated with follicular occlusion (pachyonychia congenita, steatocystoma multiplex, Dowling-Degos disease without and with arthritis), keratitis-ichthyosis-deafness (KID) syndrome and Down syndrome.

The follicular occlusion tetrad includes HS, acne conglobata, pilonidal sinus and dissecting cellulitis of the scalp; these conditions are characterised by follicular occlusion as the initial event.

Table 42.1 Severity classification of hidradenitis suppurativa according to Hurley staging

Stage I	Abscess formation, single or multiple, without sinus tracts and cicatrisation
Stage II	Recurrent abscesses with tract formation and cicatrisation, single or multiple, widely separated lesions
Stage III	Diffuse or near-diffuse involvement or multiple interconnected tracts and abscesses across the entire area

Diagnosis and Differential Diagnosis

The diagnosis of HS is clinical and a biopsy is not necessary for diagnosis. The following three diagnostic criteria must all be met:

1. Chronicity and recurrences
2. Typical lesions, i.e. deep-seated painful nodules: 'blind boils' in early lesions; abscesses, draining sinus, bridged scars and 'tombstone' double-ended pseudo-comedones in secondary lesions
3. Typical topography, i.e. axillae, groins, perineal and perianal region, buttocks and infra- and inter-mammary folds.

Closed comedones in HS are never present. The apparently open comedones are never closed; they are double-ended 'pseudo-comedones', i.e. literally scars.

Histologically, HS is a disease of the hair follicle, with follicular occlusion leading to the occlusion of the apocrine gland and subsequent follicular rupture, associated with lymphohistiocytic inflammation, inflammation, granulomatous reactions, sinus tracts and scarring. The early lesions of HS demonstrate follicular hyperkeratosis. The deep part of the follicle appears to be involved. Dermal features include perifolliculitis, active folliculitis or abscess, sinus tract formation, fibrosis and granuloma formation.

HS should be differentiated from:

- Folliculitis: it presents with follicular pustules. Comedones are absent.
- Furuncles (boils): may be confused with the early solitary, painful nodules of HS. In HS, nodules are more deeply seated, they are located on the characteristic anatomic sites affected by HS and there are recurrences and progression to abscesses and scars over time.
- Crohn's disease: cutaneous CD mimicking HS has to be taken into consideration in case of sole perianal lesions. Metastatic CD cannot be easily differentiated from HS. There is associated intestinal Crohn's disease.
- Acne vulgaris: there are always closed comedones and different topography of the lesions.

General Principles of Treatment

Management of HS includes the education of the patient regarding the nature of the disease, general measures, pharmacological topical or systemic treatment and surgical therapy.

The education of the patient by the treating dermatologist is pivotal, so that he/she understands that HS is usually a chronic disease, with exacerbations and remissions, and that it may necessitate long-term therapies. Also, the patient should be reassured that HS is not contagious and that it is not caused by an infection of the skin or by the lack of hygiene.

General measures and lifestyle changes may contribute to the better management of HS. Friction should be avoided by wearing loose-fitting clothes. Although no data exist for the improvement of HS lesions after reduction of weight and cessation of tobacco smoking, the general expert opinion (EDF) is that cigarette smoking and overweight have to be avoided.

Antibiotic, immunosuppressive, anti-inflammatory, antiandrogenic and surgical treatments, as well as laser and light sources, have been used for the management of HS, although few randomised, controlled trials exist to provide evidence-based data on their efficacy for this condition. A systematic review on the use of immunosuppressive treatments and systemic retinoids for HS evaluated 87 papers including 518 HS patients treated with biologics, colchicine, ciclosporin, methotrexate, dapsone, acitretin or isotretinoin and graded the level of evidence. The authors reported that infliximab, adalimumab and acitretin were the most effective systemic agents, with 89, 79 and 95 % of patients, respectively, responding to treatment (however, the quality of

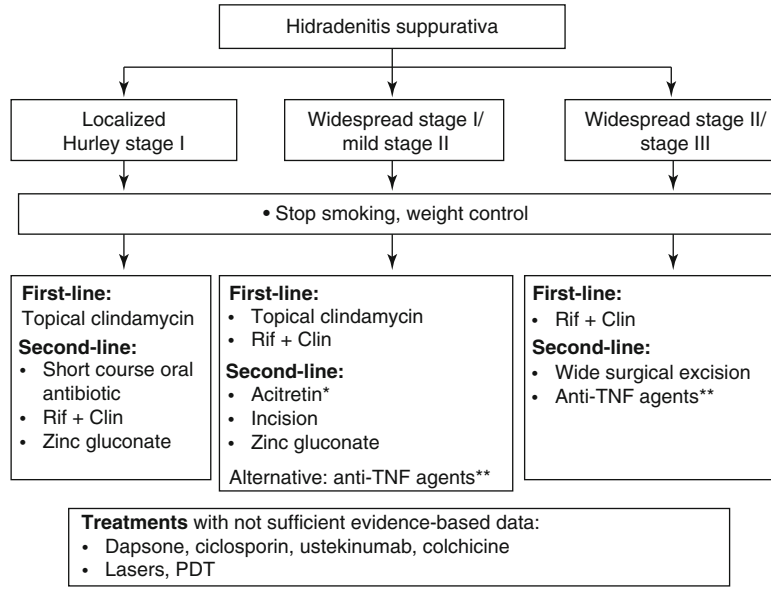

Fig. 42.5 Algorithm of treatment for hidradenitis suppurativa. *Rif+Clin* rifampicin plus clindamycin, * strictly contraindicated for women of childbearing potential, ** off-label therapies

evidence was lower for acitretin) (Matusiak et al. 2009). Nonsteroidal anti-inflammatory drugs (NSAIDs) may be proposed as analgesics for the symptomatic therapy of pain.

Based on the severity of HS, for Hurley stage I, topical or systemic drugs are proposed; stage II may benefit from medical treatment and from limited excisions of locally recurring lesions; and stage III requires radical surgery (Zouboulis et al.). The severity of HS, and whether it is localised or more widespread, should be taken into account before determining optimal treatment. The combination of different treatment modalities may be required to achieve improvement (Matusiak et al. 2009). A proposed algorithm of treatments is presented in Fig. 42.5.

Topical Treatments

Topical Antibiotics: Clindamycin

Topical clindamycin is the only antibiotic that has been studied in HS. A randomised, placebo-controlled study by Clemmensen et al. in 27 HS patients showed that topical clindamycin 0.1 % was superior according to patients' assessments and improved lesion counts. Another randomised trial by Jemec et al. compared topical clindamycin 1 % solution twice daily with oral tetracycline 500 mg twice daily, for 3 months, with response and no significant difference in efficacy between topical and oral treatment (Brocard et al. 2007). Topical clindamycin may be applied twice daily for 3 months or longer if clinically indicated.

Resorcinol 15 %

Resorcinol 15 % cream twice daily has been described for flares of lesions in patients with Hurley stage I or II HS.

Intralesional Steroids

Intralesional injection of triamcinolone acetonide may be used for individual early HS lesions.

Topical Treatments at a Glance

- Topical antibiotic treatment with clindamycin is indicated for localised Hurley stage I or mild stage II disease.

Systemic Treatments

The use of systemic treatments is indicated for more severe or widely spread lesions. Systemic treatments that have been used for HS include antibiotics, retinoids, biologic agents, antiandrogens, zinc gluconate, dapsone, colchicine, corticosteroids, ciclosporin and metformin.

Antibiotics

Antibiotics may be used as a short-term treatment to provide a rapid control of an exacerbation of the disease or as a long-term therapy with the aim to provide improvement as well as sustained remission.

For an acute flare of HS, a short course of an oral antibiotic such as amoxicillin/clavulanic acid, cephalosporin or clindamycin may be proposed.

For long-term continuous therapy, the combination of clindamycin and rifampicin is useful.

Clindamycin and Rifampicin

Although HS is not primarily an infectious disease, the combination of two antibiotics, rifampicin and clindamycin, is one of the most useful regimens in cases of inflammatory lesions. The combination of clindamycin and rifampicin for the treatment of HS has been evaluated in three retrospective studies, including a total of 118 patients. A response was reported in 96 patients (81.36 %), with 32 (27.11 %) achieving complete remission (Van der Zee et al. 2009, 2010; Mendonca and Griffiths 2006). Most reported side effects were gastrointestinal and affected 23 of 104 (22.11 %) patients (Gener et al. 2009).

Another prospective study of Bettoli et al. in 23 patients with HS treated with oral clindamycin (600 mg daily) and rifampicin (600 mg daily) for 10 weeks reported improvement (a Sartorius score improvement higher than 25 %) in 85 % of patients. Side effects were reported in three patients (13 %) and included nausea and vomiting.

Oral clindamycin should not be used in patients with intestinal inflammatory disease. The development of marked diarrhoea should prompt its immediate discontinuation, as it may progress to pseudomembranous colitis caused by *Clostridium difficile*. Liver function evaluation and complete blood count should be carried out during prolonged treatment.

Oral rifampicin at very high doses has been shown to have teratogenic effects in animals. There are no well-controlled studies with rifampicin in pregnant women (FDA pregnancy category C). Rifampicin causes an orange coloration of urine, swat, sputum and tears. Monitoring of hepatic function is necessary during treatment with oral rifampicin, and liver function evaluation, bilirubin, serum creatinine and complete blood count should be carried out.

The EDF guidelines recommend this combination for any stage active inflammatory HS.

Retinoids

Isotretinoin

Systemic isotretinoin (13-*cis* retinoic acid), a vitamin A derivative, has been used as an off-label treatment for HS, but it is ineffective in the treatment of HS, as this agent primarily works on sebaceous glands, which are not involved in the pathogenesis of HS (Zouboulis et al.; Matusiak et al. 2009).

The systematic review of Blok et al. reported seven papers evaluating the use of isotretinoin for HS in a total of 174 patients. Daily dosages were 0.5–1.2 mg/kg and treatment duration was 4–12 months. There was no response in the majority of patients (112 patients, 64 %), while 30 patients (17 %) had moderate improvement and 32 patients (18 %) had significant improvement.

Oral isotretinoin is a known teratogen for women (FDA pregnancy category X). Before treatment initiation, women of childbearing age should be informed about teratogenicity of isotretinoin and the absolute need of avoidance of pregnancy and effective contraceptive measures throughout treatment and for 1 month after treatment completion.

Acitretin and Etretinate

Retinoids have antiproliferative and immunomodulatory properties. Etretinate is a prodrug of acitretin. Acitretin is converted in vivo to etretinate

by re-esterification. Acitretin also has anti-inflammatory actions and may target the process of hyperkeratosis of the infundibular follicular epithelium, normalising epithelial cell proliferation and differentiation (Matusiak et al. 2009).

In the study of Boer et al., 12 patients with HS Hurley stage II/III were treated with acitretin (mean dose 0.59 mg kg once daily) as monotherapy for 9–12 months (mean 10.8). Overall, an improvement was noted in all 12 patients. Nine patients achieved marked or complete remission after one course of acitretin therapy, and the other three patients showed mild or moderate improvement. Follow-up showed that nine patients had a long-lasting improvement, with remissions ranging from 6 to 45 months (mean 24.9). A systematic review evaluated six available studies on the use of acitretin and etretinate for HS that included 22 patients. Used doses were 0.35–1.1 mg/kg for etretinate and 0.25–0.88 mg/kg for acitretin for a period of 2–29 months. Significant improvement was reported in 16 of 22 patients (73 %), moderate improvement in 5 (13 %) and no response in 1 (5 %). Within a follow-up of 6 months, there was recurrence in 6 of 17 patients (35 %), while 8 patients (47 %) relapsed later than 1 year after discontinuation of treatment.

The EDF guidelines recommend acitretin for early HS stages (Hurley I or mild II) and for the chronic stages of HS with recurrent abscesses with sinus tracts and/or scarring.

Retinoids, including etretinate and acitretin, are potent teratogens, leading to strict requirements for pregnancy prevention during their use and after their discontinuation. In the case of acitretin (FDA pregnancy category X), women of childbearing potential have to use adequate contraception measures during therapy and for 24–36 months after discontinuation, depending on local regulations.

Biologic Agents

Anti-TNF-α Agents: Adalimumab, Etanercept, Infliximab

Tumour necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine produced by many cell typesı, including macrophages, monocytes and T cells. It is expressed in the basal layer of the epidermis, sweat glands and hair follicles. The rationale for the use of anti-TNF agents for the treatment of hidradenitis was based on the clinical observation of improvement of HS in patients with concomitant Crohn's disease, as well as on experimental evidence that TNF-α may play a key role in HS. TNF-α serum concentration in 54 HS patients was significantly higher than healthy controls ($p = 0.006$), although it was not associated with the severity of the disease. Van der Zee et al. showed elevated TNF-α production after culture of biopsies of lesional and perilesional skin of 20 HS patients compared to skin of six healthy controls and similar TNF-α levels with that of the skin of seven psoriasis patients. Also, the −238 G⁄A SNP at the promoter region of the TNF gene was significantly more frequent in HS patients than in healthy controls ($p = 0.027$), and a certain haplotype of the TNF gene seems to be associated with a greater reduction of disease severity after treatment with TNF agents.

Adalimumab is a fully anti-TNF monoclonal antibody that binds with high affinity and specificity to soluble and membrane-bound TNF-α. It is administered subcutaneously. In the systematic review of Blok et al., adalimumab was evaluated in 15 papers in 68 HS patients, with only one being a randomised, double-blind, placebo-controlled design (evidence level A). Dosing regimens varied from 40 to 80 mg, in a frequency ranging from weekly to every other week. In total, 30⁄68 patients (44 %) showed a significant response to adalimumab, 24 patients (35 %) had a moderate response and 14 patients (21 %) did not respond. Relapse of HS was reported in 23 out of 35 responders (66 %) within 3–10 months after discontinuation of treatment, while 7 patients (20 %) relapsed during treatment but improved with an increase in the dose of adalimumab.

Etanercept is a soluble fusion protein comprising a TNF-α receptor and the Fc component of human immunoglobulin G1. It is administered subcutaneously. Etanercept was evaluated in nine papers in 54 patients, with only one being a randomised, double-blind, placebo-controlled design (evidence level A). Dosing schedules varied from

25 to 50 mg once or twice weekly to 100 mg weekly. In total, 21⁄54 patients (39 %) showed a significant response to etanercept, nine patients (17 %) had moderate improvement and 24 patients (44 %) did not respond. Relapse of HS was reported in 18 out of 30 responders (60 %) within immediately up to 8 months after discontinuation of treatment.

Infliximab is a chimeric (mouse/human) anti-TNF monoclonal antibody that binds both soluble and transmembrane TNF-α. It is administered intravenously. Infliximab was evaluated in 42 papers in 147 patients, with only one being a randomised, double-blind, placebo-controlled design (evidence level A). Dosing schedule was 5 mg kg^{-1} at weeks 0, 2 and 6 and every 6–8 weeks thereafter. In total, 74⁄147 patients (50 %) showed a significant response to infliximab, 57 patients (39 %) had moderate improvement and 16 patients (11 %) did not respond. Relapse of HS was reported in 26 out of 131 responders (20 %) 2 weeks to 3 years after discontinuation of treatment.

Anti-IL12/23 Agents: Ustekinumab

Ustekinumab is a human monoclonal antibody against interleukin 12/23 (IL 12/23). It is administered subcutaneously. The systematic review of Blok et al. reported two papers in four patients evaluating ustekinumab for HS (both evidence level C). Dosing schedule was 45 mg at weeks 0, 4 and 12 and every 3 months thereafter. In total, two out of four patients showed a significant response to ustekinumab, one patient had a moderate response and one patient did not respond. Relapse of HS was reported in two out of three responders.

Antiandrogens

The rationale for the use of antiandrogens for HS was based on the female preponderance of HS, its development after puberty and its association with PCOS.

On the other hand, the usual absence of clinical signs of hyperandrogenism and the normal levels of serum androgens do not support a role for androgens. This may explain the limited effect of anti-androgen treatments for HS.

Zinc Gluconate

Zinc acts via inhibition of polymorphonuclear cell chemotaxis. Its anti-inflammatory activity could be related to a decrease in TNF-α production and the modulation of the expression of integrins and the inhibition of Toll-like receptor 2 (TLR2) surface expression by keratinocytes.

In a pilot study of Brocard et al., 22 patients with Hurley grades I and II were treated with 90 mg/day zinc gluconate. Complete remission was noted in eight patients and partial remission in 14 patients. Four out of 22 patients experienced side effects of gastrointestinal upset.

The EDF guidelines recommend zinc gluconate as maintenance therapy for HS Hurley stages I and II.

Dapsone

A systemic review of Blok et al. reported three studies in 34 patients treated with dapsone at dosages of 25–100 mg daily during 0.5–48 months. There was a significant improvement seen in 12 of 34 patients (35 %), moderate improvement in 7 patients (21 %) and no response in 15 patients (44 %). It was reported that there was a rapid recurrence after treatment discontinuation in all patients.

The EDF guidelines recommend dapsone as third-line treatment for mild to moderate HS (Hurley stage I or II).

Colchicine

Colchicine is a natural product that can be extracted from plants of the lily family. It inhibits neutrophil expression of cell adhesion molecules and decreases neutrophil degranulation, chemotaxis and phagocytosis.

There is a report by van der Zee et al. of eight patients with refractory HS treated with

colchicine 0.5 mg twice daily for up to 4 months that reported that six patients (75 %) did not respond, while there was a moderate response in the remaining two patients. Adverse events were nausea and diarrhoea. The authors suggested that higher doses may be needed for clinical efficacy and that colchicine treatment should start with 1 mg followed by 0.5 mg every 2 h with a cumulative maximum of 5 mg, followed by 1 mg daily (Boer et al. 2011).

The EDF guidelines recommend that colchicine should not be used for the treatment of HS.

Corticosteroids

Systemic steroids may provide relief from pain and inflammation and be used as an alternative or in combination with oral antibiotics. Steroids may be used for a short period of time and tapered rapidly.

Ciclosporin

Ciclosporin is a calcineurin inhibitor with potent immunosuppressive activity. It targets T lymphocytes and it inhibits the production of TNF-α and IL-2.

Ciclosporin at a dose ranging from 2 to 6 mg/kg/day has been studied in four patients for 4–16 months, with a significant response in three patients and a moderate response in the remaining two patients.

Metformin

Metformin improves insulin insensitivity and has antiandrogenic properties. Verdolini et al. studied metformin in 25 patients with HS, at a starting dose of 500 mg once daily for the first week, increased to 500 mg twice daily for the second week, with a maximum dose of 500 mg three times daily for a total of 24 weeks. There was improvement in 18 patients, while seven patients (28 %) showed no response. Only minor gastrointestinal side effects were reported.

Systemic Treatments at a Glance

- The combination of clindamycin and rifampicin is indicated for any stage active inflammatory HS.
- A systematic review evaluating immunosuppressive treatments and oral retinoids for hidradenitis suppurativa reported that infliximab, adalimumab and acitretin were the most effective systemic agents, with 89, 79 and 95 % of patients, respectively, responding to treatment (however, the quality of evidence was lower for acitretin).
- Oral acitretin should be reserved for male patients and sterilised or postmenopausal women due to its long-term teratogenic side effects.
- Oral isotretinoin was shown to be ineffective for hidradenitis suppurativa.
- There are a limited number of studies in a small number of patients on the efficacy of ustekinumab, colchicine, dapsone, ciclosporin and zinc gluconate.
- There is limited data on long-term results and relapse rates with systemic treatments for HS.

Surgical Therapy

The surgical approach for HS Hurley stage I is incision and drainage; for stage II, deroofing and secondary healing; and for HS stage II/III, wide surgical incision and healing with secondary intention or skin graft.

Surgical incision and drainage is indicated as means of symptomatic relief of pain, e.g. as an analgesic for a fluctuating abscess. Incision does not affect the course of the disease nor does it provide clearance of the incised lesion.

A simple technique consists of unroofing under local anaesthesia and debridement of the scars, abscesses, cysts and sinuses. In the study of van der Zee et al., 44 patients with mild to moderate HS were treated with the surgical deroofing technique, with no recurrence in 83 % of treated lesions after a median follow-up of 34 months.

Traditional surgery for hidradenitis suppurativa (HS) consists of en bloc wide excision followed by primary closure or healing by secondary

intent. Mapping of sinus tracts with methyl blue intra-operatively is crucial. In one series of 106 patients, there was a 70 % recurrence rate requiring subsequent operation in the primary closure cohort and no recurrence in the split-thickness graft and flap groups. In general, the recurrence rate with wide excision has been reported to be less than 30 %. However, poor surgical outcomes (scarring) have been associated with surgery (van der Zee and Prens 2011).

Other Treatment Options

Lasers and Light Sources

There is scarce data on the use of laser and light sources for the treatment of HS.

Long-pulsed neodymium:yttrium-aluminium-garnet (Nd:YAG) laser is a laser hair reduction device. The rational for treating HS was based on the role of follicular occlusion as the initiating event in the pathogenesis of HS. The proposed mechanism of action included the release of obstruction of the hair follicle and photothermolysis.

A prospective, randomised study of Mahmoud et al. in 22 patients with HS evaluated the efficacy of Nd:YAG laser, clinically and histopathologically. Topical benzoyl peroxide wash 10 % and clindamycin 1 % lotion were used on both sides of the face. Laser treatment consisted of four monthly sessions. The reported fluence was 40–50 J/cm^2, pulse duration was 20 ms and spot size was10 mm, whereas for skin types IV–VI, the fluence used was 25–35 J/cm^2, pulse duration was 35 ms and spot size was 10 mm. The percent improvement was 72.7 % on the laser treated side and 22.9 % on the control side ($p<0.05$). Similar results were reported by Xu et al. in 19 patients with HS Hurley stage II, treated with two monthly sessions of long-pulsed 1,064-nm Nd:YAG laser. The percentage change in HS severity after two sessions of laser treatment was −31.6 over all anatomic sites ($p<0.005$).

Photodynamic therapy (PDT) as treatment for HS has been recently described in three small case series, but it is neither established nor has it been standardised.

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Primary Hyperhidrosis

43

Benedetta Brazzini and Sana Sultan

Key Points

- Hyperhidrosis is excessive sweating which goes beyond the normal physiological reaction that occurs in response to fluctuations in temperature.
- It affects 3 % of the population and can be a severely disabling condition with a significant negative impact on quality of life.
- Several treatment modalities are available and are broadly divided into medical and surgical.
- Medical treatments include topical medication, iontophoresis, systemic anticholinergic medications and botulinum toxin injections.
- Surgical treatments include retro-dermal curettag, liposuction and thoracoscopic sympathectomy.

Definition and Epidemiology

Sweating is a normal physiological reaction that occurs in response to fluctuations in temperature. It mainly occurs from cutaneous eccrine glands that are widely distributed throughout the whole body at an average of 100–200 per cm^2 but more concentrated on the palms, axillae, soles and forehead.

Hyperhidrosis is excessive sweating in certain parts of the body and is thought to have a prevalence of 3 % in the population. It can be severely distressing for patients due to the negative perception of sweating and body odours by the majority of cultures throughout the world. For this reason hyperhidrosis can have a debilitating psychosocial element and can have a significant negative impact on quality of life.

Hyperhidrosis can be classified as primary or secondary. Primary hyperhidrosis is an emotional stress response that causes excess sweating particularly affecting the palms, axillae, soles and forehead and, in a small proportion of patients, the whole body surface. Excess sweating is a result of overstimulation of the eccrine glands. However, the exact mechanism of this overstimulation remains unclear but is thought to be due to a dysfunction in the neuro-exocrine interplay between the sympathetic nervous system and the eccrine sweat glands. The sweating tends to be bilateral and symmetrical, and in the absence of a secondary cause, the history will be sufficient for making a diagnosis.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_43, © Springer-Verlag Berlin Heidelberg 2015

Secondary hyperhidrosis implies an underlying cause and encompasses a range of conditions that precipitate excess sweating such as fevers, neurological diseases (Parkinson's, syringomyelia and Riley-Day syndrome), endocrinopathies (diabetes mellitus, hypoglycaemia, thyrotoxicosis and hyperpituitarism), trauma (medullary accidents and Frey's syndrome) and various other disorders (drug and alcohol withdrawal, dumping syndrome, carcinoid, Hodgkin's disease, menopausal state, anxiety, congestive heart disease and obesity).

General Principles of Treatment

Several treatment modalities exist for hyperhidrosis and will be explored in this chapter. Figure 43.1 clearly demonstrates that there are differences in the treatment of palmar-plantar and axillary hyperhidrosis. These will all be explored within the text.

Topical Treatments

Perfumes, Deodorants and Antimicrobials

Perfumes have been used for centuries to hide unpleasant body odours. However, the successors of perfumes, deodorant soaps and cosmetic deodorants are not strong enough to hide bad odour for a long period of time. Antimicrobial fragrances have been used to suppress the microorganism responsible for bromhidrosis. However, products such as antiseptic benzalkonium chlorides and quaternary ammonium compounds, are inactivated very rapidly and therefore rendered useless. Other antiseptics like triclosan and triclocarban are effective over longer periods of time but are very irritating and therefore poorly tolerated by patients.

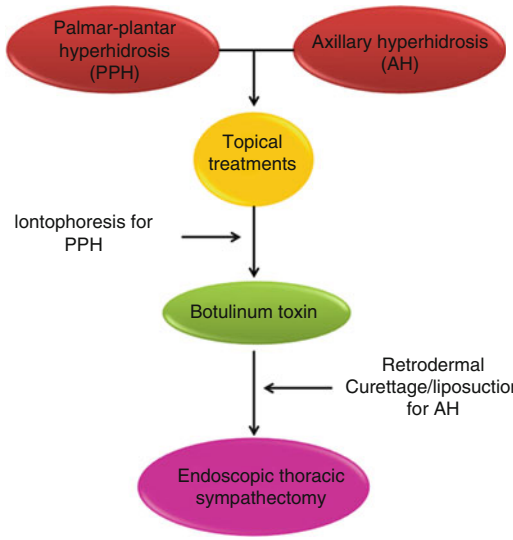

Fig. 43.1 Treatment options available for different types of hyperhidrosis

Antiperspirants

Satisfying results have been obtained with topical antiperspirant salts. In particular, aluminium chloride hexahydrate is reported to be the most effective topical treatment and acts by diffusion into the ducts of the eccrine glands. It will then complex with metal ions and mucopolysaccharides, thus causing reversible damage to the surface of the non-cornified cell causing temporary occlusion to the sweat gland ducts, which becomes reversed during normal regeneration of the skin.

The best results are obtained with topical applications of aluminium salts at night when the eccrine sweat glands are largely inactive. The side effects of treatment include irritation, soreness and pruritus. Traditionally, it has been thought that optimum concentration of aluminium chloride is dependent upon body area affected. Therefore, higher concentrations of aluminium chloride were recommended for palmar-plantar (up to 30 %) than for axillary (10–15 %) hyperhidrosis. However, Streker et al. (2012) recently conducted a study on 20 patients comparing the efficacy and safety of two different concentrations (12.5 and 30 %) of aluminium chloride hexahydrate for the treatment of plantar hyperhidrosis and found that both concentrations were equal in efficacy and safety. The effect of aluminium chloride treatment is optimal and lasts for several days in patients with moderate hyperhidrosis, but in severe cases it remains ineffective.

Aqueous solutions of glutaraldehyde (glutaraldehyde 10 % in a buffered solution pH 7.5) are effective in controlling palmar-plantar hyperhidrosis. The mechanism of action is not entirely

clear; however, it is thought to act by partial occlusion of the sweat ducts. At the beginning it must be applied on alternate days until control is achieved. Thereafter, it can be decreased to a once-weekly application or used only when needed. However, commonly reported side effects include a yellow coloration of the skin and clothes, irritation and allergic reactions. Also 10 % methenamine, which is hydrolysed to ammonia and formaldehyde when applied to the skin, is effective in mild hyperhidrosis and rarely produces allergic reactions. Finally, topical glycopyrrolate (glycopyrronium bromide) has been shown to be an appropriate treatment for hyperhidrosis with particular benefits seen in head and neck hyperhidrosis.

Anticholinergic Topical Drugs

Topical anticholinergic drugs are absorbed sufficiently to produce a beneficial local effect without producing systemic side effects, but none of those available at present can be relied upon.

Iontophoresis

Tap water iontophoresis is a simple and effective treatment for mild to moderate palmar-plantar hyperhidrosis. Its use extends back to 1952 where the principle of tap-water iontophoresis was first introduced for the treatment of hyperhidrosis. Since then it has become an established method of treatment for hyperhidrosis, and its efficacy has been proved by several studies with a significant reduction in sweating in about 90 % of patients.

The procedure consists of applying moisturised paddles to the affected areas and passing a 15–20 mA electrical current. The current is conducted through tap water to cause reversible disruption of ion channels that leads to blockage of sweat glands. Better results are obtained if a diluted solution of an anticholinergic drug is used as it causes blockage at the neuro-glandular junction, thus reducing sweat production.

The duration of each session varies between 10 and 40 min, with an accepted average of 20 min. Usually a euhydrotic state can be achieved with an intensive treatment regimen that consists of two to six sessions a week until euhydrosis has been achieved. The euhydrotic state is then maintained with treatments repeated every 3–6 weeks. The interval between the two sessions should be constant because there is no structural alteration in the sweat glands. In theory the treatment should be carried out indefinitely, although the pathology generally decreases with age.

Iontophoresis is a non-invasive well-tolerated treatment, which can be carried out in the comfort of one's home using the Drionic or Idrostar units. A recent study by McAleer and Collins (2013) showed that patients perceive an 85 % improvement with home therapy. Nonetheless, hospital iontophoresis is thought to be better because patients tend to apply lower currents in the home than those used in the hospital environment.

The conventional iontophoresis treatment is through the use of a direct current, which is associated with side effects such as pain and discomfort. In recent years it was shown that the use of alternating current iontophoresis is just as effective with fewer reported side effects. This approach is still being developed, and clear treatment guidelines are yet to be agreed upon.

There has been no report of adverse side effects following long-term iontophoresis therapy; however, some of the short-term side effects include discomfort (burning and tingling sensations), skin irritation, erythema and vesicles and deep burning (defective devices and badly protected electrodes). Contradictions to treatment include pregnancy, cardiac pacemaker and metal orthopaedic implants. Iontophoresis is an effective treatment, but the fact remains that it only offers symptomatic relief and therapy has to be continued on a maintenance schedule over many years. This has a negative impact on the patient, as it affects lifestyle due to multiple follow-up appointments, and is economically draining and time consuming for clinical staff.

Systemic Treatments

Anticholinergic Drugs

In theory anticholinergic drugs are effective against hyperhidrosis; however, in reality they carry a large number of side effects that are

poorly tolerated by patients. In Germany two anticholinergic drugs have been licensed for the treatment of hyperhidrosis: methantheline bromide (Vagantin®) and bornaprine hydrochloride (Sormodren®). In a multicentre randomised clinical trial carried out by Müller et al. (2012), it was shown that methantheline bromide is an effective and safe treatment for axillary hyperhidrosis when given at a dose of 50 mg three times daily.

Oxybutynin is an anticholinergic drug that is commonly used to treat urological disorders; however, an observed side effect of the drug includes significant reduction in sweating. Wolosker et al. (2013) carried out a study on 30 patients suffering from plantar hyperhidrosis who were treated with oxybutynin (starting from 2.5 mg daily up to 5 mg twice a day, for 12 weeks). More than 70 % of patients reported improvements in symptoms with significant positive impact on their quality of life in general.

Bornaprine hydrochloride is an antiparkinsonian drug with some anticholinergic properties, which led to its use in the treatment of hyperhidrosis. In 80 % of patients treated, there was a marked sweat reduction within 2 weeks of treatment; however, there were several adverse side effects such as dry mouth, tachycardia, disturbance in accommodation, disturbed micturition and inability to concentrate. This, unsurprisingly, leads to cessation of treatment (Togel et al. 2002).

Others

Psychoactive drugs, tranquillisers, sedatives and β-blockers have all been used to treat hyperhidrosis; however, no controlled clinical trials exist to prove the efficacy and safety of these treatments. Often they are administered on an individual case basis to treat a pronounced emotional factor suggesting secondary rather than primary hyperhidrosis.

Botulinum A Toxin Subcutaneous Injection

Clostridium botulinum is a gram-positive rod-shaped anaerobic bacteria, which is best known for producing the botulinum toxin. There are currently seven serotypes of the botulinum toxin labelled A–G which act by inhibiting the presynaptic release of acetylcholine by disrupting the Ca^{2+}-dependent K^{+}-evoked release mechanism that ultimately causes a flaccid paralysis to ensue. Both neuromuscular junction and eccrine sweat glands utilise acetylcholine as the primary neurotransmitter; therefore, disruption of transmission leads to reduction in sweat volume. Of the seven serotypes mentioned, only types A, B, E and F are poisonous to humans, and only types A and B are used therapeutically for the treatment of hyperhidrosis.

Botulinum toxin is approved in many countries to treat spasticity, including blepharospasm, focal dystonia, achalasia and chronic anal fissures. Botulinum toxin A is available in Europe and in the United States. In terms of clinical efficacy in humans, 1 U of Botox® is estimated to be equal to 3–4 U of Dysport®. Botulinum toxin B is available in Europe as NeuroBloc® and is used in those patients who are unresponsive to the botulinum toxin A injections.

To this day administration of botulinum toxin injections for the treatment of hyperhidrosis is slightly variable and practitioner dependent. Some practitioners will administer Minor's iodine-starch test which helps to visualise the area for treatment, whilst others will prefer to inject around the hair distribution in the axilla or following a grid in the palm and feet without Minor's test. In addition the botulinum toxin injections can be painful, particularly for the palms and the soles, and thus a deterrent for seeking treatment. However, there are a number of anaesthetic options available such as oral or IV sedation, Dermojet®, topical anaesthetic creams, nerve block (radial and ulnar), Bier's block and cryoanalgesia.

A reasonably effective dose of the botulinum toxin A (Botox) is 50, 100 and 150 U for each axilla, palm and sole, respectively. The difference in units of the botulinum toxin used is related to the differences in surface area of the regions affected. Before the injections are administered, they must be diluted using 1 ml of normal saline for each 25 U of botulinum toxin (Botox). Twenty-six or thirty gauge needles are then used to administer the botulinum toxin in subdermal injections.

Studies for the efficacy of botulinum toxin have demonstrated a high patient satisfaction rate

with treatments lasting 4–11 months. Treatments are not permanent, and there is a high recurrence rate of hyperhidrosis possibly because symptom-free patients become intolerant of sweating or, according to some authors, due to antibody formation against the toxin leading to reduced efficacy of treatment. Contraindications of the treatment are disorders of neuromuscular function including myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis. Also pregnant or lactating women or those with a severe blood clotting disorders are isolated from treatment.

Surgical Treatments

In some patients with moderate to severe hyperhidrosis, surgery may be indicated where all medical treatments have been unsuccessful. Currently, there are two surgical interventions available: retro-dermal curettage and liposuction, which is used for axillary hyperhidrosis and thoracoscopic sympathectomy for the treatment of axillary, palmar-plantar and facial hyperhidrosis.

Retro-dermal Curettage and Liposuction

Retro-dermal curettage involves a small incision at the posterior, inferior and caudal aspects of the axillary hair distribution area of the skin. Blunt dissection of the area is then carried out, and the curette is used to scrape against the skin, thus removing the sweat glands from the dermal layers. Before skin closure, a washout is performed and a suction drain is placed, which can only be removed when sweat output is less than 10 ml. Liposuction follows the same principle, and instead of using a curette, a liposuction syringe is used to scrape of the underside of the dermis with 15–20 strokes of the cannula.

Despite the lack of long-term follow-up data, both retro-dermal curettage and liposuction appear to be a safe and effective method of treatment. They show a significant reduction in sweat production that lasts for up to 6 months in 80–90 % of patients; however, relapse does occur in 7–8 % of patients (Proebstle et al. 2002; Rompel and Scholz 2001). There are some post-operative complications that have been noted, and these include wound infection, skin necrosis, bleeding, haematoma formation and induration. Some of the longer-term potential complications include partial alopecia, skin discoloration, scar formation, wound contracture, paraesthesia and pain with arm movements.

Thoracoscopic Sympathectomy

The nerves innervating the sweat glands are the sympathetic postganglionic fibres, which consist of unmyelinated C fibres. The sympathetic nerves to the arm arise from spinal cord segments T_2–T_6 and leave the spinal canal in the corresponding ventral rami to synapse or pass through the second to sixth thoracic sympathetic ganglia. All postganglionic sympathetic fibres to the hand, forearm and arm except the axilla run with the somatic nerves of the brachial plexus. Consequently, division of the sympathetic trunk between the first and second thoracic ganglia will interrupt all the sympathetic innervation to the arm, comprising preganglionic and postganglionic fibres.

The procedure is performed under general anaesthesia and the patient placed in a semi-sitting position with the arm at 90° abduction. To begin with, patients will be intubated using a single- or double-lumen endotracheal tube, which will then be clamped. Access to the thorax is achieved through 5 or 10 mm ports, and once a pneumothorax has been established, the sympathetic chain will then be visualised. The mediastinal pleura will be opened allowing dissection of the sympathetic chain from T2 to T4.

This operation is not without risk and indeed some of the minor complications include wound infections, hematoma and pain on movement of the arms. However, rare but more serious complications include pneumothorax, haemothorax, atelectasis, radial nerve paralysis and Horner's syndrome (T1 nerve root damage). The commonest post-operative complication reported (86–100 % of patients) is compensatory hyperhidrosis, which is excess sweating in a previously

unaffected area such as the face, foot, trunk, buttocks and popliteal fossa. Currently, there is no medical treatment for compensatory hyperhidrosis, and the only available treatment is surgical reconstruction of the sympathetic chain, which is a risky operation with limited efficacy. For plantar hyperhidrosis, sympathectomy of L_2 and those nerves of the lower lumbar extremities are thought to relieve symptoms efficaciously. However, lumbar sympathectomy has no place in the treatment of pedal hyperhidrosis since ejaculatory impotence and anorgasmia are almost certain consequences.

In view of the post-operative complication, thoracoscopic sympathectomy should be considered for moderate to severe palmar or axillary hyperhidrosis once all other therapies have been explored. In a retrospective study conducted by Dumont et al. (2004) on long-term follow-up for thoracoscopic sympathectomy, 90 % were reportedly satisfied with the outcome. Currently, this procedure is considered the surgical gold standard for treatment of palmar and axillary hyperhidrosis.

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Ichthyoses

44

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Abbreviations

ARCI	Autosomal Recessive Congenital Ichthyosis
TGM1	Transglutaminase 1 gene
ABCA12	gene ATP-binding cassette, sub-family A (ABC), member 12
ALOXE3	gene arachidonatelipoxygenase 3
ALOX12B	gene arachidonate 12-lipoxygenase, 12R type
FLJ39501	gene

Key Points

- The ichthyoses represent a large heterogeneous group of Mendelian disorders of keratinization (cornification), clinically characterized by the presence of scales on the skin.
- They may manifest at birth or later on, and they could be isolated or associated with extracutaneous anomalies.
- The classification of ichthyoses has been recently revised in (a) non-syndromic ichthyoses and (b) syndromic ichthyoses and in congenital and later onset.
- The choice of treatment depends on the type of ichthyoses, age of the patient, the involved areas, and the extent of the disease.

Definition and Epidemiology

The ichthyoses represent a large heterogeneous group of Mendelian disorders of keratinization (cornification), clinically characterized by the presence of scales on the skin. They may manifest at birth or later on, and they could be isolated or associated with extracutaneous anomalies.

The classification of ichthyoses has been recently revised during a consensus conference of experts based on clinical aspects (Oji et al. 2010; Fleckman et al. 2013) in (a) non-syndromic ichthyoses and (b) syndromic ichthyoses (Fig. 44.1) and in congenital and later onset (Fig. 44.2). This classification represents an intermediate step toward a new classification based on the molecular diagnosis, whenever they will be all identified.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_44,

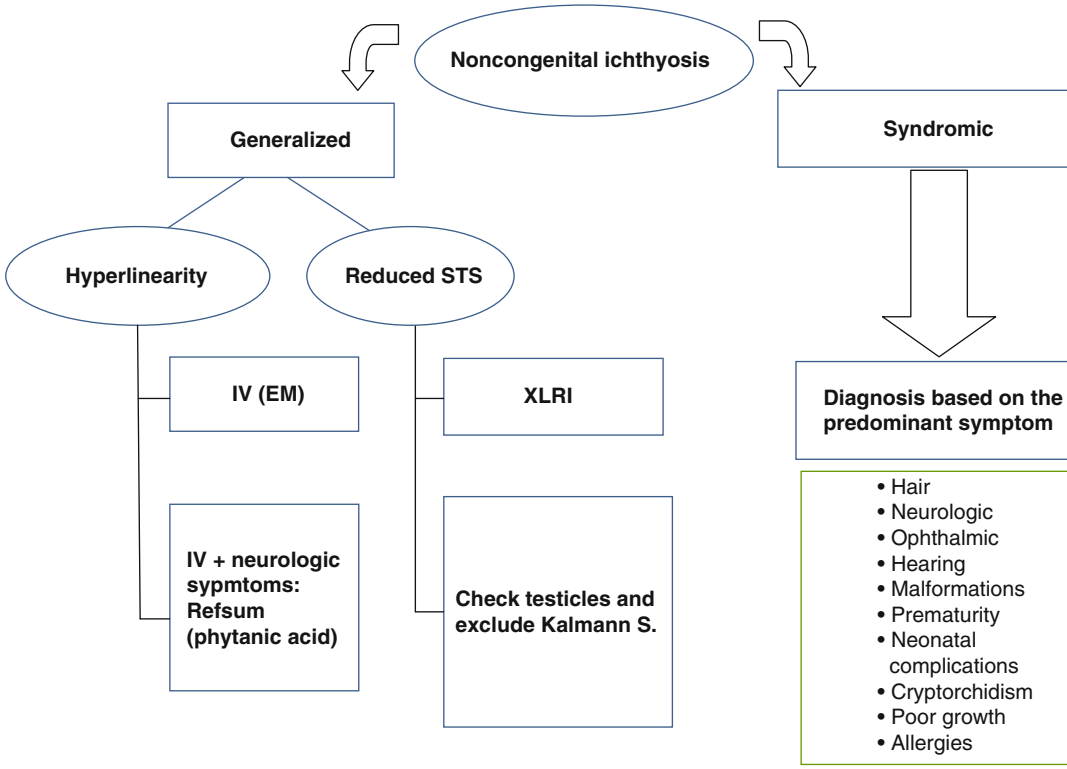

Fig. 44.1 Classification of non-congenital ichthyoses. *IV* Ichthyosis vulgaris, *EM* Electron Microscopy, *STS* steroid sulfatase enzyme, *XLRI* Recessive X-linked Ichthyosis

The epidemiology varies upon the type of ichthyosis, from a common form such as ichthyosis vulgaris (1:300) and recessive X-linked ichthyosis (1:6,000) to the rare autosomal recessive congenital ichthyosis, ARCI, (1:300,000) and other extremely rare forms such Harlequin fetus, Dorfman-Chanarin Syndrome, etc.

Traditionally, the keratinopathic ichthyoses, once called epidermolytic ichthyosis, are also included between the ichthyoses (Fig. 44.3). The incidence varies from 1:200/300,000 for the generalized epidermolytic ichthyosis to extremely rare for other forms such as ichthyosis hystrix, Curth-Macklin type. They are transmitted in an autosomal dominant trait.

Basic Concepts of Pathogenesis

Ichthyoses are due to mutations of many genes (identified until now six, Fig. 44.4), codifying for proteins and lipids involved in the different stage of the cornification. The pathophysiology may be related to a disorder in keratinocyte proteins, proteases, lipid metabolism (assembly or transport), or connexins.

Clinical Presentation

I. Ichthyosis vulgaris (Fig. 44.5a, b), the most common type of genetic ichthyoses, is characterized by small, gray-white scales mainly on the extensor surfaces without fold involvement. There is a strong association with atopy, keratosis pilaris, and palmar hyperlinearity. It improves with age.

II. Recessive X-linked ichthyosis affects males, and the clinical feature is characterized by large brown scales, fold involvement, and asymptomatic corneal opacity.

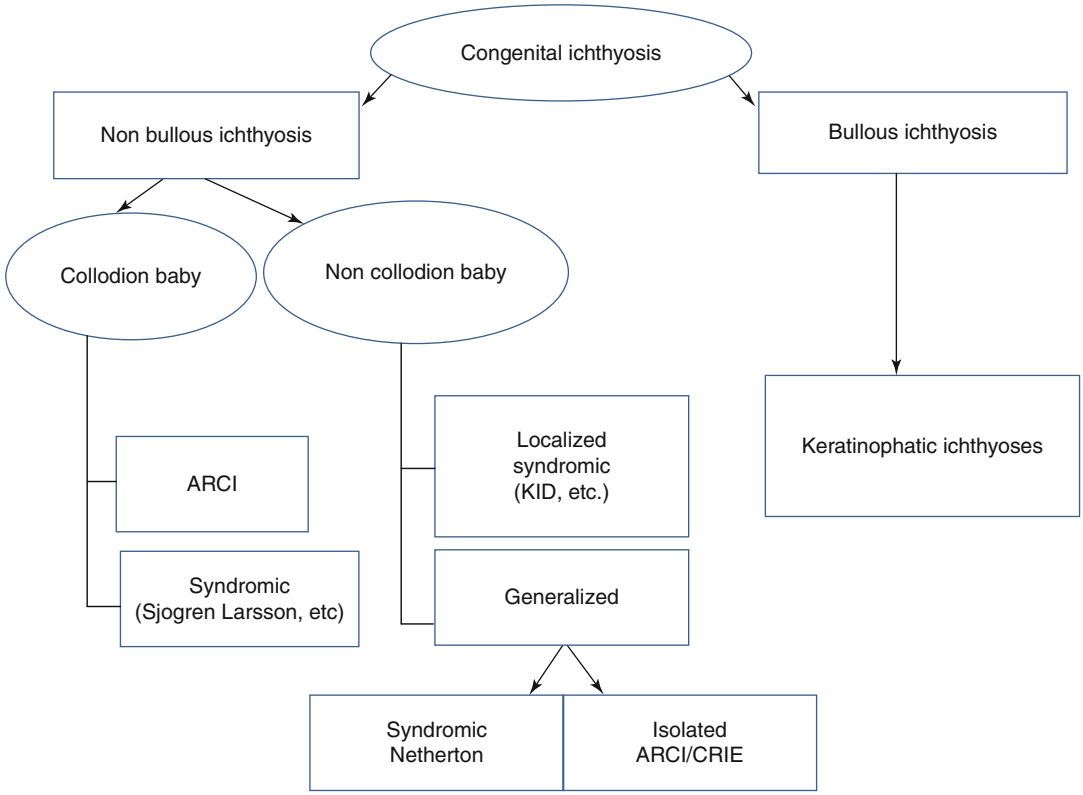

Fig. 44.2 Classification of congenital ichthyoses. *ARCI* Autosomal Recessive Congenital Ichthyosis, *KID* Keratitis, Ichthyosis, Deafness syndrome, *CRIE* Congenital Reticular Ichthyosiform Erythroderma

III. ARCI represents a wide heterogeneous group. Until now, some genes (TGM1, ABCA12, ALOXE3, ALOX12B, Ichthyin, FLJ39501) were identified as the cause of ARCI, but others have yet to be discovered. The most common form manifests initially as collodion baby and evolves successively in ichthyosis with or without erythroderma congenital ichthyosiform erythroderma (CIE) and lamellar ichthyosis (LI). The scales are generally flat, thick, large, and brown. Ectropion and electrolytes imbalances are also frequently associated. The most severe and lethal form is Harlequin fetus.

IV. Keratinopathic ichthyoses (Fig. 44.6a, b) are characterized by erythroderma, blistering, erosions, and desquamation since birth. The skin is easily macerated with consequent bad smelling and itching. We distinguish generalized or localized forms.

Syndromic Ichthyosis

The first group is represented by:

I. Recessive X-linked ichthyosis syndromes with hypogonadism:

IFAP: ichthyosis follicularis, atrichia, photophobia

Conradi-Hunermann-Happle syndrome: severe ichthyosiform erythroderma clearing after a few months, lifelong linear hyperkeratosis, follicular atrophoderma, chondrodysplasia punctata, skeletal and eye anomalies, and unilateral hypoplasia of the face.

II. Autosomal ichthyoses with prominent hair abnormalities:

Netherton syndrome (Fig. 44.7) is the most severe form of this group and is characterized by erythroderma, severe atopic manifestations, trichorrhexis invaginata which may not be present during the first months of life, and hypernatremia.

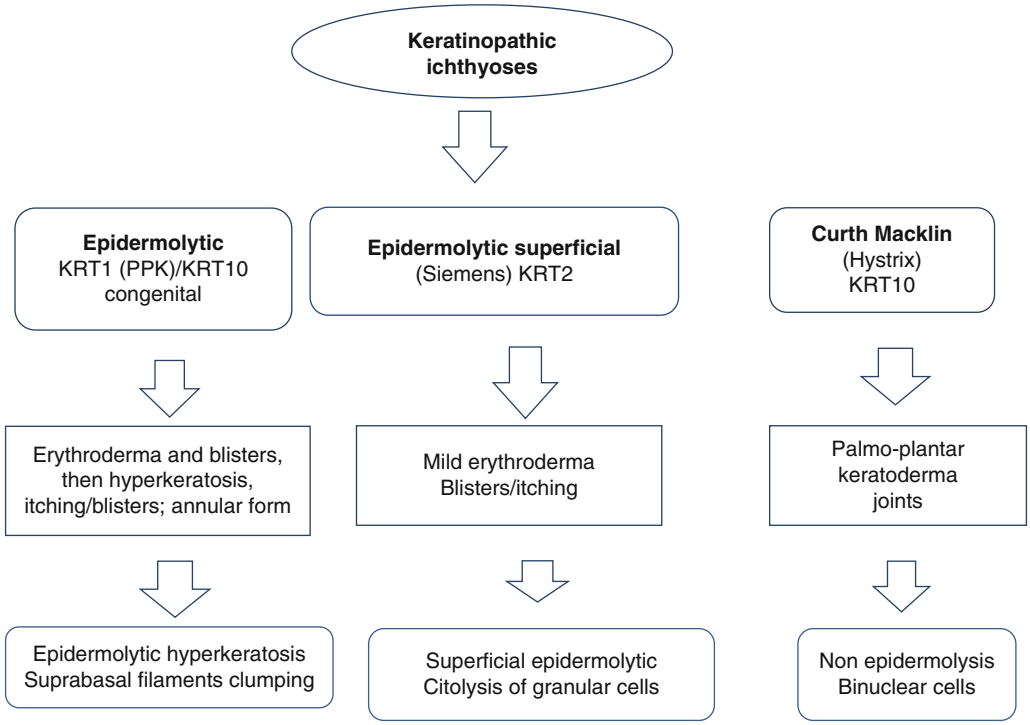

Fig. 44.3 Classification of keratinopathic ichthyoses. *KRT1* gene coding for cytokeratins type 1, *KTR2e* gene coding for cytokeratins type 2e, *KRT10* gene encoding cytokeratin type 10, *PPK* palmoplantar keratoderma

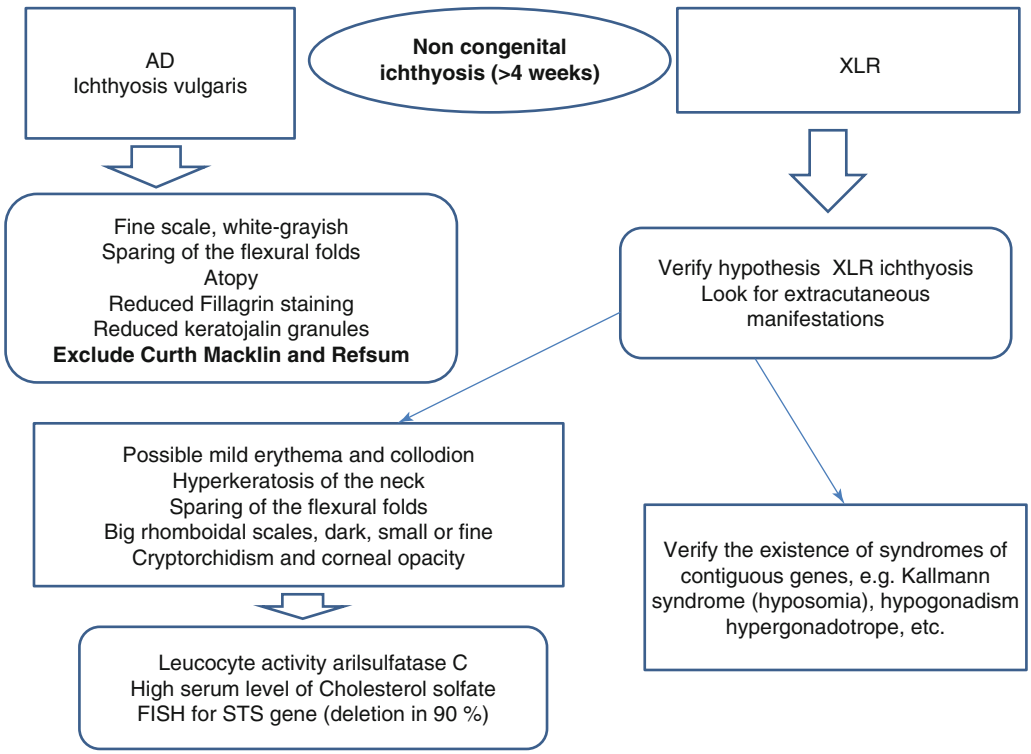

Fig. 44.4 Non-congenital ichthyoses and identified genes. *FISH* Fluorescent in situ hybridization, *STS* steroid sulfatase

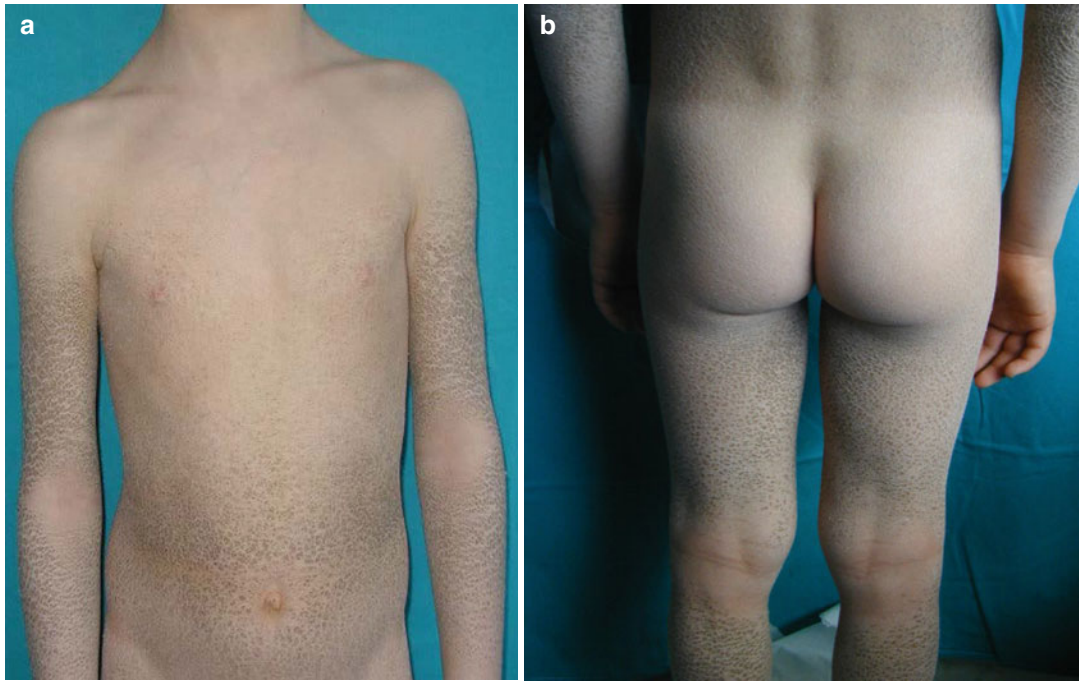

Fig. 44.5 (**a**, **b**) Ichthyosis vulgaris

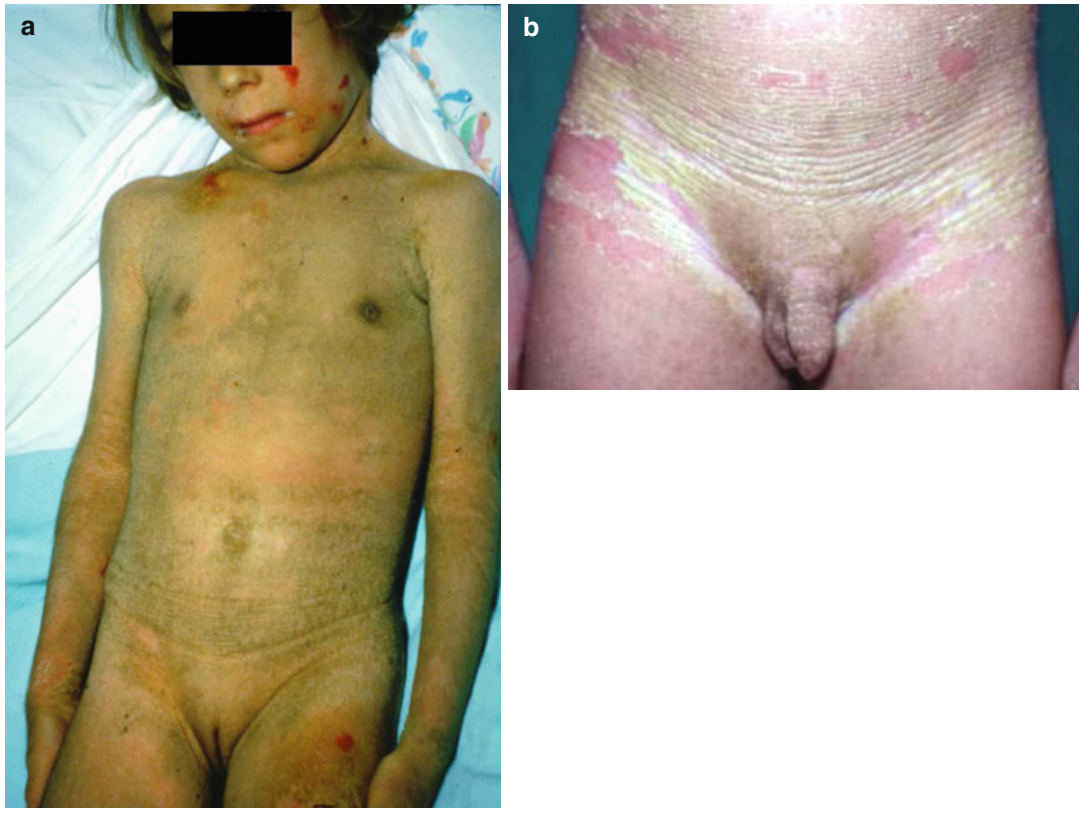

Fig. 44.6 (**a**, **b**) Keratinopathic ichthyoses

Trichothiodystrophy (TTD) (collodion baby (Fig. 44.8) or not, with or without photosensitivity, cataracts, hair fragility with low content of sulfur, tiger tail).

III. Autosomal ichthyosis with prominent neurologic signs such as Sjogren-Larsson (congenital ichthyosis, palmoplantar keratoderma, spastic paraplegia, reduced aldehyde dehydrogenase) and MEDNIK (mental retardation, entheropathy, deafness, neuropathy, ichthyosis, keratoderma)

IV. Autosomal recessive ichthyosis with fatal course, such as

ARC (arthrogryposis, renal dysfunction, and cholestasis) and CEDNIK (cerebral dysgenesis, neuropathy, ichthyosis palmoplantar keratoderma)

V. Autosomal ichthyosis with other associated signs such as KID (keratitis, ichthyosis, and deafness), neutral lipid storage disease with ichthyosis, and ichthyosis prematurity syndrome

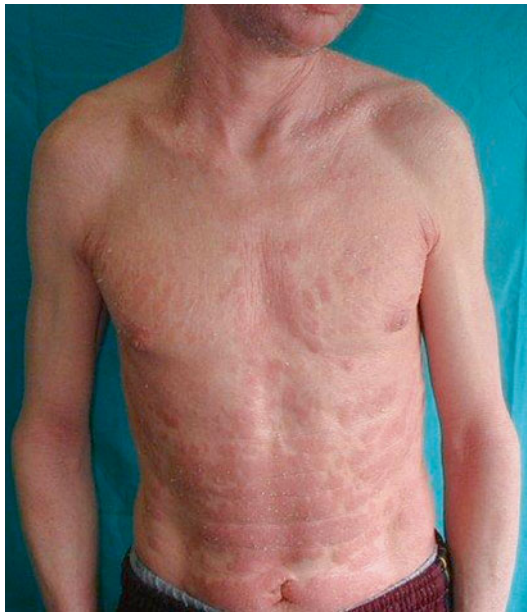

Fig. 44.7 Netherton syndrome

Diagnosis

See flow chart (Fig. 44.9).

General Principles of Treatment

The choice of treatment depends on the type of ichthyoses, age of the patient, and severity of the clinical picture. In fact in the mild forms of ichthyoses, such as ichthyosis vulgaris or X-linked ichthyosis, a local treatment is sufficient; in the severe forms, i.e., ARCI, complex syndromic ichthyoses, or generalized epidermolytic ichthyosis, an associated systemic therapy is necessary.

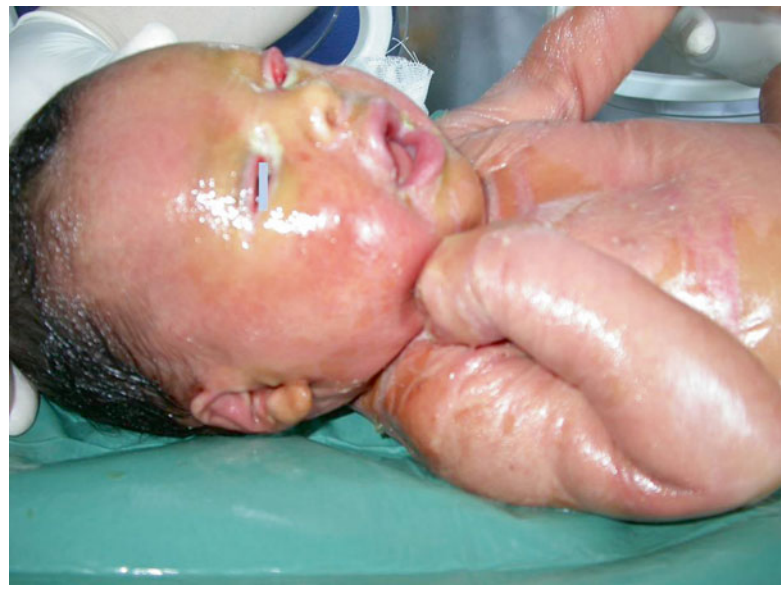

Fig. 44.8 Collodion baby

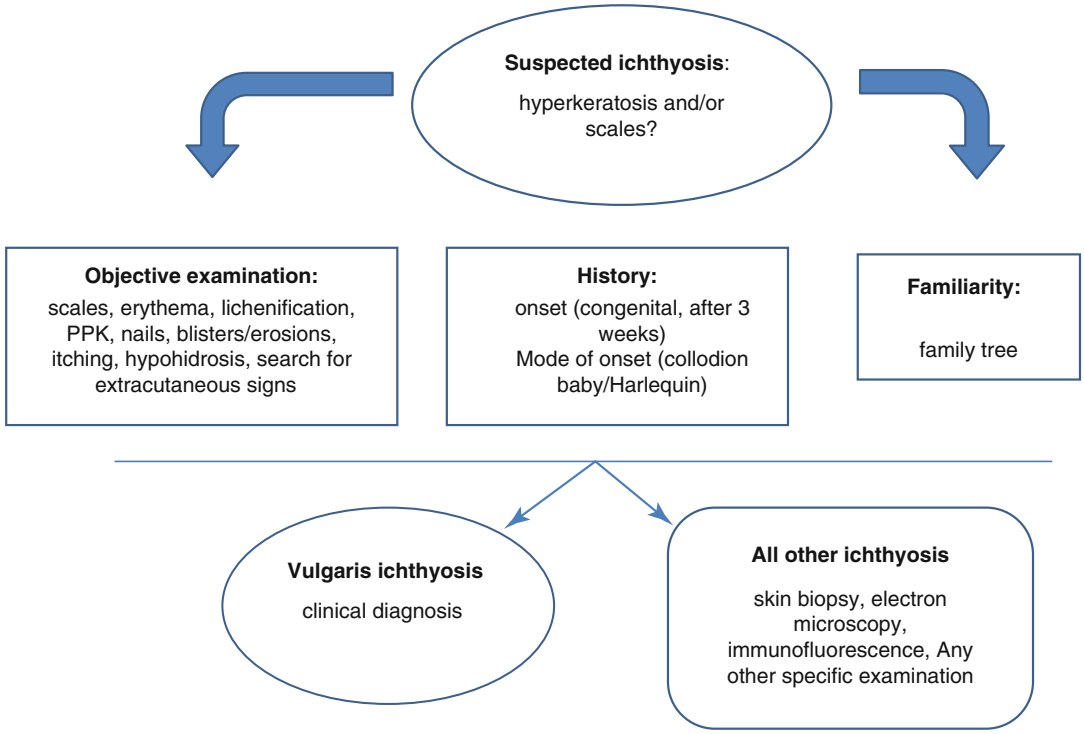

Fig. 44.9 Ichthyoses diagnosis algorithm

The treatment must clearly be linked to the patient's age, the involved areas, and the extent of the disease. The total dosage of the drug absorbed through the skin depends on the relationship between the cutaneous layer and the weight of the patient; this relationship is higher in newborns and infants than in adults; therefore, it is better to avoid, particularly in childhood, the use of potentially toxic drugs. For example, the use of salicylic acid as a keratolytic at concentrations varying between 5 % and 10 % previously in vogue has recently been excluded because of the risk of toxicity both in adults and children. In children acute toxicity (tinnitus, hyperthermic convulsions, respiratory depressions) can be lethal. Topical products based on urea may cause skin sensitivity in children, mostly on the folds; in newborns and collodion babies, there is the risk of nephropathy due to systemic absorption. *Collodion baby* (Fig. 44.8) is used to define a particular phenotype in which the neonate is encompassed in a cellophane-like membrane stretched over the skin at birth. This transient condition spontaneously heals with desquamation within 2 weeks to 3 months, revealing the true underlying disease, ARCI most frequently and rare ichthyosis such as Netherton syndrome or seldom Gaucher disease in some cases. A complete recovery can be observed (self-healing collodion baby) in 10 % of patients. A more severe and usually lethal form due to mutations in gene ABCA12 involved in lipid transport in epidermal keratinocytes is called *Harlequin ichthyosis*. In both conditions, ectropion, eclabion, and contractures of joints and fingers are common. The very compromised skin barrier enhances the risk of dehydration, electrolytic imbalances, and sepsis. The use of simple emollient, such as vehicle cream or Vaseline, can contribute to lubricate the skin, restore the cutaneous barrier, and minimize the risks. The use of emollient as glycerol or paraffin has been proven effective and safe in neonate and children with ichthyosis, especially the vulgaris type.

Particular attention must always be paid to extracutaneous problems in severe forms of congenital ichthyoses (Fig. 44.10) (collodion baby and erythroderma) such as the risk of sepsis, hydroelectrolytic imbalances, sunstroke, and alter-

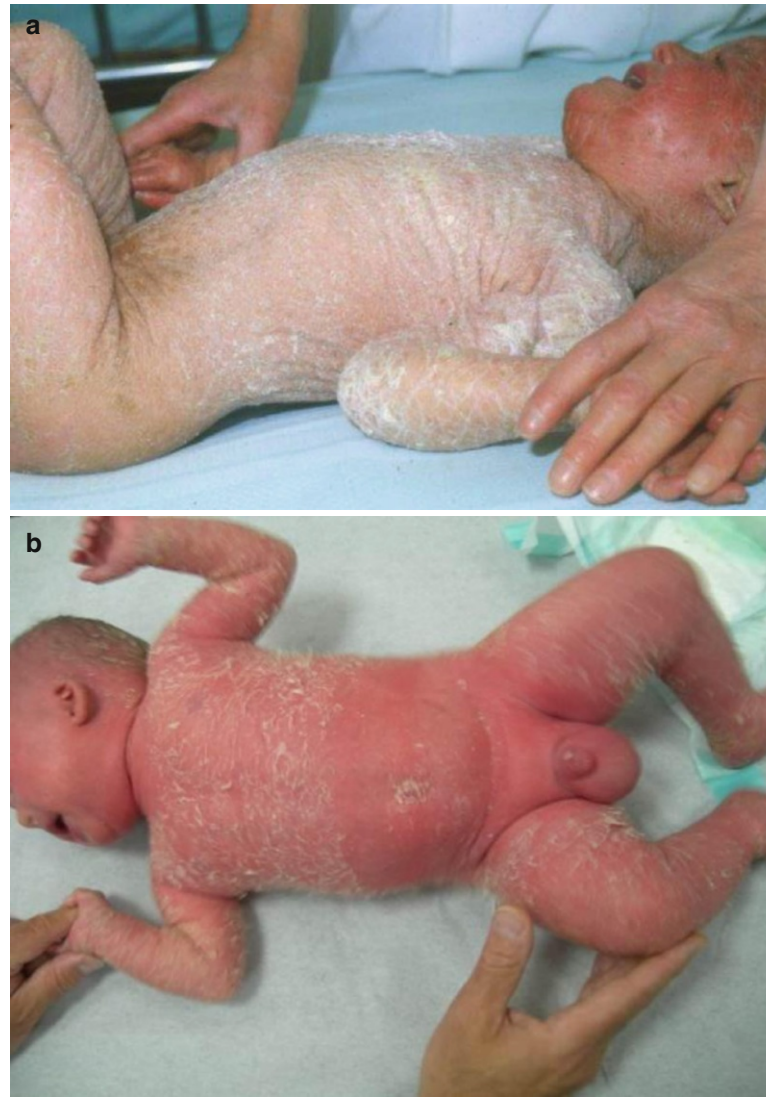

Fig. 44.10 (**a**, **b**) Congenital ichthyoses

ation of the thermoregulation; therefore, the newborn should be placed in incubator in an adequate temperature and humidity in order to reduce the trans-epidermal water loss (TEWL), generally high in ichthyosis patients. In keratinopathic ichthyoses the treatment of infected bullous lesions with antiseptics and antibiotics is mandatory.

An adequate treatment has the aim to improve hydration, obtain keratolysis, modulate keratinization, and prevent systemic complication.

Recommended Therapies

(a) Therapies that normalize keratinization
(b) Keratolytic substances that improve hydration

Therapies That Normalize Keratinization

Systemic Retinoids

The systemic retinoids like etretinate and its active metabolite acitretin produce good results in the treatment of ichthyoses because of their capacity to operate selectively on the keratinization disorders. Etretinate was the retinoid first used for serious cases of ichthyosis with the dosage of 0.5–1 mg/kg per day at the initial stage, for 1–3 months, with a successive reduction. Acitretin is more effective, manageable, and better tolerated than other retinoids. The therapeutic index of retinoids restricts their use to the most serious forms of ichthyosis. Above all they are found

most useful in the treatment of lamellar and erythrodermic ichthyosis and less in epidermolytic hyperkeratosis in which retinoids can increase the cutaneous fragility acting on the interkeratinocyte adhesion causing more bullous lesions. It is therefore advisable to begin with lower dosages (0.1–0.5 mg/kg per day) always associated with topical treatment. They have also shown very little evidence of success in Netherton syndrome. The side effects are dose dependent; part of them appears regularly: cheilitis, xeroderma and cutaneous desquamation, photosensitivity, cutaneous fragility, and sometimes paronychia. Other possible side effects include migraine; reversible alopecia; transient increase in transaminases, bilirubin, cholesterol, and triglycerides; modification of night vision; epistaxis; arthromyalgia; and occasionally intracranial hypertension and skeletal anomalies. The latter (e.g., hyperostosis, osseous condensation, extra-skeletal calcification of the soft tissues and the ligaments) are always present after 4–6 years of therapy, whereas the total bone growth and development is normal even if an early closure of the epiphysis has been registered. The potential bone damage caused by retinoids has however been reviewed in the last few years. To diminish the incidence of such a risk, it is advisable, when possible, to alternate cycles of therapy with periods of abstention from the treatment, above all during the summer in which there is a greater cutaneous photosensitivity caused by the retinoids. Radiographic monitoring of children doesn't seem to offer significant advantages in comparison to clinical observation. Bone X-ray is advisable only in symptomatic cases. However, before beginning the treatment with systemic retinoids, laboratory analyses should be performed to investigate eventual dyslipidemia, liver diseases, and pregnancy; in these cases the therapy cannot be indicated. A lipidic balance and hepatic function will be repeated monthly in the initial phase of the treatment and, after that, at greater intervals.

The main side effect of systemic retinoids is teratogenicity. An informed agreement should be signed by the women of fertile age, and measures of contraception are necessary during the treatment until 2 years after its end.

Topical Retinoids

Topical retinoids are suggested to avoid side systemic effects, and they are useful in mild forms of ichthyosis. Some recent studies show the effectiveness of the retinoic acid 13-cis (isotretinoin) cream 0.1 % because of its capacity to reduce desquamation and to improve cutaneous smoothness.

Although the use of the trans-retinoic acid (tretinoin) can produce less irritation, it is not recommended in the erythrodermic form and in the presence of atopic dermatitis.

The topical receptor-selective retinoid (tazarotene 0.05 or 0.1 % gel) has been proved effective in multiple recent studies in congenital ichthyosis in children and adults and in some cases of ectropion ichthyosis related. The most common side effect is a local sensitivity; thus a dilution with a simple moisturizing cream can be suggested mostly in children. An international multicentric trial is ongoing to test the tolerability of tazarotene cream 0.05 %.

Topical calcipotriol, the biologically active form of vitamin D3 (1.25-dihydroxy vitamin D3), is effective in the treatment of lamellar and epidermolytic ichthyoses because of its capacity to stimulate the terminal differentiation of the epidermal keratinocytes and to inhibit their proliferation. Topical application of calcipotriol cream 0.05 % twice a day for at least 12 weeks is found to be moderately effective and well tolerated. It is also possible to treat 15–20 % of the cutaneous surface, not exceeding the weekly dose of 120 g in order to prevent the risk of hypercalcemia.

Keratolytic Products

I. Urea Cream or Ointment

Urea cream ointment at 5–20 % is effective in the treatment of ichthyoses and psoriasis. The mechanism of the action is partially known; it seems linked to proteolytic and keratolytic activity (at 6–30 %) and keratolytic; furthermore it increases links between water and the stratum corneum, induces epidermal differentiation, and reduces epidermal hyperproliferation. Urea is also available in many concentrations till 40 % which is useful in adults in areas with

thick scales. Urea should be used carefully in young children and infants for the risk of increased blood urea nitrogen level, and it may cause burning and irritation. In adults it is generally well tolerated.

II. The α-Hydroxy Acids (AHA)

These simple organic hydroscopic acids present an oxydrile in their chemical structure that links to the carbon atom in the alpha position. Among the numerous AHA, for example, lactic, pyruvic, malic, and glycolic acids, the first is the most effective in ichthyoses. They act in a different way from the normal keratolytic; they reduce the cohesion of the corneocytes at the deep stratum corneum level without exercising any effect on the more superficial cells. They stimulate the turnover of the epidermis and also favor the penetration of other associated substances. This action explains the greater effectiveness of the lactic acid in the treatment of recessive X-linked ichthyosis.

Creams with lactic acid (8 %) are effective in reducing the hyperkeratosis associated with ichthyoses and in increasing the hydration of the stratum corneum.

The following formula with lactic acid base is simple and effective:

- Lactic acid 5 g
- Water 40 ml
- Ethanol 35 ml
- Propylene glycol 20 g

This preparation should be applied four times a day for 1–3 weeks. Afterwards the medication is reduced to once or twice a day, depending on the clinical situation.

III. Propylene Glycol

Propylene glycol at the concentration of 40–70 % in water is effective in removing the scales with occlusive medication at bedtime (covering the treated parts with a layer of impermeable film). It is however necessary to avoid the use on extensive skin surface, particularly in children. It can be used in lesser concentration associated with other substances. It has also a moistening effect which increases the content of water in the stratum corneum, which can however cause cutaneous irritation and contact dermatitis even at low concentrations.

Alternative Therapies

(a) PUVA

This therapy seems useful in the treatment of Netherton syndrome. Some studies have reported an association between etretinate and PUVA which has resulted in patients responding positively to this combination but only poorly to etretinate when given alone.

(b) Liarozole

This is a new hymidazolic derivative recently used as topic in the treatment of various forms of ichthyoses. It acts by inhibiting the hydroxylation in position 4 of the retinoic acid that depends on cytochrome P-450, responsible for its physiological degradation. Oral administration is also convenient (150 mg twice a day for 12 weeks), with undesired subjective effects similar to those of the retinoids.

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Impetigo

45

Stefano Veraldi and Ermira Çuka

Key Points

- Impetigo is a superficial infection of the skin caused by staphylococci and/or streptococci.
- It is the most frequent bacterial dermatitis in infancy: it occurs mainly in preschool-aged children, particularly during the summer.
- Impetigo actually consists of two distinct entities from the aetiopathogenetic and clinical point of view: non-bullous impetigo and bullous impetigo.
- Non-bullous impetigo may be caused by staphylococci or streptococci or both. It is at first characterized by vesicles surrounded by an erythematous halo. These vesicles can rupture, resulting in erosions, or they may remain intact; however, the fluid becomes purulent, with formation of a pustule. Subsequently, both erosions and pustules dry up and become crusts. Uncovered areas are characteristically affected, particularly the nose, cheeks, lips and chin; covered areas can be involved by self-inoculation.
- Bullous impetigo is always caused by *Staphylococcus aureus*. It is characterized clinically by vesicles and/or blisters which may be widespread on the face, trunk and skinfolds.
- Diagnosis of impetigo is basically clinical.
- The treatment is based on the use of topical antibiotics (fusidic acid and mupirocin).

Definition and Epidemiology

Impetigo is a superficial infection of the skin caused by staphylococci and/or streptococci. It is the most frequent bacterial dermatitis in infancy: it occurs mainly in preschool-aged children, particularly during the summer. The disease is contagious: it is not rare to observe minor epidemics in kindergartens.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_45,

The transmission is prevalent by direct person-to-person contact and is favoured by:

- Environmental factors:
  - High temperatures
  - High humidity
  - Overcrowding
  - Poor hygiene
- Personal factors:
  - Malnutrition
  - Poor hygiene
  - Abnormalities in humoral or cellular immunity
  - Presence of debilitating diseases
  - Previous or concomitant systemic therapies with antibiotics, corticosteroids, immunosuppressives or antitumourals

Impetigo often develops on a pre-existing skin disease characterized by more or less severe pruritus: atopic dermatitis, other allergic diseases, chickenpox, pediculosis, scabies, arthropod stings and bites. In these cases it is more appropriately referred to as secondary impetigo or impetiginization.

Basic Concepts of Pathogenesis

The term "impetigo" actually consists of two distinct entities from the aetiopathogenetic and clinical point of view: non-bullous impetigo (or contagiosa or vulgaris or pustular impetigo) and bullous impetigo.

Non-bullous impetigo may be caused by staphylococci or streptococci or both. In the past, streptococcal aetiology was most common. Group A β-haemolytic streptococci (*Streptococcus pyogenes*) are usually isolated. The infections caused by groups B, C, D and G are very rare. In Western countries, staphylococcal infections are currently more frequent (approximately 65 % of cases).

Bullous impetigo is always caused by *Staphylococcus aureus* (phagic II group in approximately 80 % of cases); furthermore, about 60 % of staphylococci are of types 55 and 71. These staphylococci synthesize some exotoxins with lytic and exfoliative properties both in vitro and in vivo. These toxins induce a detachment of keratinocytes of the granular layer of the epidermis, with consequent development of vesicles and blisters.

Clinical Presentation

Non-bullous impetigo is at first characterized by the appearance of one or more round vesicles, small in size, containing a clear fluid, and surrounded by an erythematous halo (Fig. 45.1). These vesicles can rupture, resulting in erosions, or they may remain intact; however, the fluid becomes purulent, with formation of a pustule (Fig. 45.2). Subsequently, both erosions and pustules dry up and become crusts: these are rather thick, poorly adherent, yellowish in colour, similar to honey, and surrounded by an erythematous halo. Their removal shows an underlying surface which is erythemato-erosive, moist and bright red in colour (Fig. 45.3). Uncovered areas are characteristically affected, particularly the nose, cheeks, lips and chin; covered areas can be involved by self-inoculation.

Bullous impetigo presents with isolated vesicles and/or blisters which may be widespread on the face, trunk and skinfolds. These lesions are round, sometimes large (some centimetres in diameter) and flaccid, containing initially a clear fluid which becomes frankly purulent, surrounded by very mild or no erythema. The removal of the roof reveals moist erosions which eventually become yellow-brown crusts.

Both varieties of impetigo are asymptomatic or accompanied by mild pruritus.

General health is good: only in chronic and/or diffuse infections fever may be sometimes observed. Regional lymphadenitis is also rare.

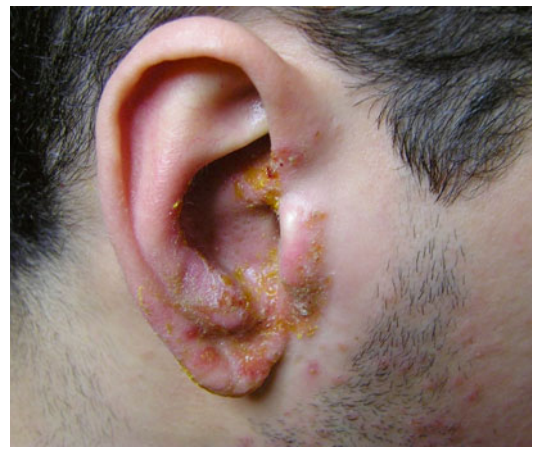

Fig. 45.1 Impetigo of the ear. Notice the yellow crust

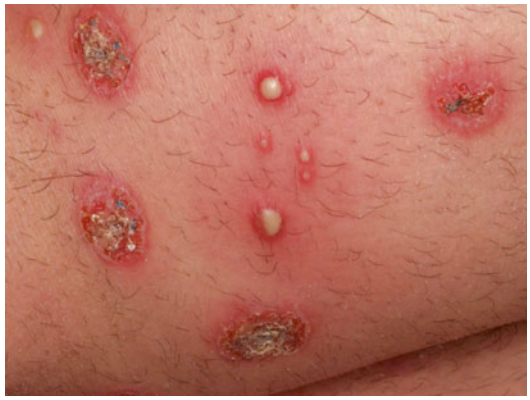

Fig. 45.2 Pustular and crusted lesions of impetigo

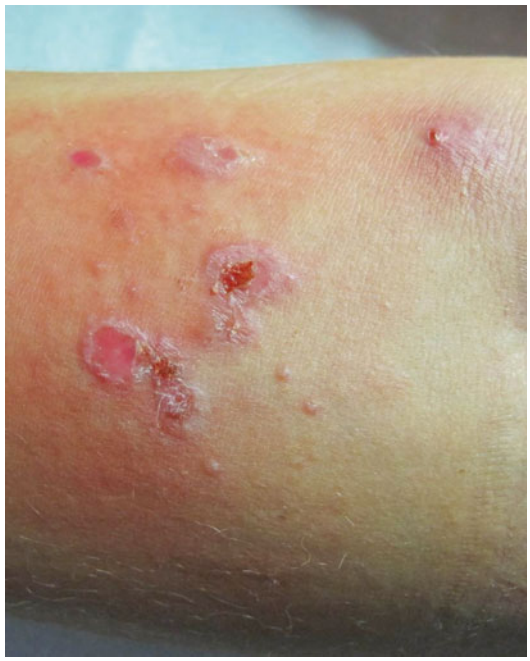

Fig. 45.3 Vesicular and erosive lesions of impetigo

Both varieties of impetigo can resolve spontaneously within some weeks; with adequate therapy, the duration usually is 5–7 days. The disease heals without leaving scars; transitory hyper- or hypopigmentation may persist for some weeks.

Complications (lymphangitis, lymphadenitis) are extremely rare. Glomerulonephritis is rare today compared to the past. It is caused by strains of nephritogenic streptococci, mainly M49 and less frequently 55 and 57. Glomerulonephritis usually occurs 3–4 weeks (up to 7 weeks) after the appearance of the skin lesions and is at first characterized by proteinuria and microhaematuria.

Recurrences of impetigo are possible if bacterial foci are not adequately eradicated in the patient, in his/her family and in the community.

Diagnosis

Diagnosis of impetigo is clinical.

Bacteriological examination of the fluid or the pus removed from a vesicle, blister or pustule and then Gram stained allows the observation of both extracellular and intracellular (particularly in the cytoplasm of neutrophils) Gram-positive cocci, which are arranged in bunches or chains.

The same modality of collection may be followed for bacterial culture and antibiogram.

Antistreptolysin and antistaphylolysin titres increase in an inconstant and delayed fashion. Anti-DNAse B antibodies are slightly more specific.

Laboratory abnormalities are rare and aspecific: mild leucocytosis with neutrophilia and increase in inflammatory tests (erythrosedimentation rate, C-reactive protein, alpha1-acid glycoprotein).

Three to 4 weeks after cure, it is helpful to perform urinalysis to exclude a post-streptococcal glomerulonephritis.

Differential Diagnosis

- Herpes simplex: small grouped vesicles on an erythematous base, which always recur at the same sites
- Irritant/allergic contact dermatitis: tiny vesicles on an erythematous base, accompanied by more or less severe pruritus
- Herpetiform dermatitis: papular-vesicular lesions at typical sites (shoulders, elbows, lumbosacral region, buttocks, knees) accompanied by intense pruritus
- Tinea corporis: erythematous-vesicular borders and scaling in the centre of the lesion

General Principles of Treatment

An early diagnosis and an adequate therapy limit the extension of the infection and its diffusion within the family and the community.

The therapy must be preceded or accompanied by a careful search in the patient, in his/her family and in his/her contacts for any possible infective reservoir:

1. For staphylococci:
   - Nostrils
   - External auditory canal
   - Major skinfolds (axillae, inguinal, intergluteal and perineal folds)
2. For streptococci:
   - Pharynx
   - Tonsils
   - External auditory canal
   - Major skinfolds

During the course of the disease, the patient must use personal underwear, towels and bed sheets.

It is necessary to open vesicles, blisters and pustules with the tip of a scalpel or a needle.

It is then helpful to wash and disinfect the erosive lesions. This can be achieved with several cleansers/antiseptics:

- 5 % benzoyl peroxide.
- 0.4 % chlorhexidine digluconate.
- 1–5.16 % hydrogen peroxide.
- Potassium permanganate [250 mg in 2–3 l of water (dilution, 1:10,000, approximately)]. Since potassium permanganate is toxic, maximum caution must be taken by the patient: its use on the face must be avoided.
- 3 % urea peroxide.

All these antiseptics may be used two to three times/day for 7–10 days. However, the last Cochrane review on impetigo, published in 2012, stated that there is a lack of evidence for the benefit of antiseptics (Koning et al. 2012). Therefore, they should be considered as a complementary treatment in impetigo.

In the same Cochrane review, a total number of 68 trials, based on 5,578 evaluable patients, reporting on 50 different treatments, including placebo, were considered as clinically and statistically evaluable. Topical antibiotics showed better cure rates than placebo in six studies on 575 patients. There is good evidence that topical fusidic acid and mupirocin are equally, or more, effective than oral antibiotics. In four studies on 440 patients, fusidic acid and mupirocin showed to be of similar efficacy. In ten studies on 581 patients, topical mupirocin was shown to be slightly superior to oral erythromycin. Furthermore, penicillin was inferior to erythromycin in two studies on 79 patients and cloxacillin in two studies on 166 patients. The reported number of side effects was low, and most of these were mild. Side effects (in particular gastrointestinal side effects) were more common for oral antibiotics compared to topical antibiotics. Worldwide, bacteria causing impetigo show increasing resistance rates for commonly used antibiotics. However, no cases of resistance have yet been reported for retapamulin. In our personal clinical experience, also gentamicin sulfate is effective in bullous impetigo; furthermore, it is very well tolerated and resistance is rare, in spite of the fact that this drug was marketed many years ago. Topical antibiotics should not be used for more than 14 days, with the aim of minimizing the possibility of development of resistant strains (particularly staphylococci). Other topical antibiotics (amikacin, bacitracin, chlortetracycline, clindamycin, meclocycline, neomycin, polymyxin B) are considered ineffective for the treatment of impetigo. Five per cent benzoyl peroxide gel may be used as a cleanser for the prevention of recurrences (two to three cleanings or baths/week).

Therapeutic Algorithm

- Localized impetigo – A topical antibiotic (fusidic acid or mupirocin or retapamulin or gentamicin) and a topical antiseptic (benzoyl peroxide or chlorhexidine or hydrogen peroxide or potassium permanganate or urea peroxide)
- Widespread impetigo or impetigo resistant to topical antibiotics – An oral antibiotic (erythromycin or clarithromycin or amoxicillin or amoxicillin/clavulanic acid)

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Kaposi's Sarcoma

46

Erwin Tschachler and George-Sorin Tiplica

Key Points

- Kaposi's sarcoma (KS) is a multifocal tumor of endothelial cell origin which occurs in four clinical variants: (1) classic KS, (2) endemic African KS, (3) KS in therapeutically immunosuppressed patients, and (4) AIDS-associated KS.
- The diagnosis is established by the clinical aspect, histopathology, and demonstration of HHV-8 in tumor lesions.
- The therapeutic approach is dependent on the clinical variant and on the extent of the lesions and comprises local destructive measures or systemic chemotherapies.
- Localized cutaneous KS treatment includes surgical excision or lesion destruction with radiotherapy, liquid nitrogen, laser, photodynamic therapy, and topical therapy with 9-cis-retinoic acid.
- AIDS-associated KS responds to liposomal anthracyclines: liposomal doxorubicin or liposomal daunorubicin. KS in organ transplant patients benefits from replacement of calcineurin inhibitors with rapamycin in their immunosuppressive regimen.
- Classic KS with widespread skin lesions responds to chemotherapeutic drugs (doxorubicin, bleomycin, vincristine, etoposide, dacarbazine) as well as to liposomal anthracyclines.
- In AIDS patients, it is pivotal to combine KS therapy with antiretroviral therapies.

Definition and Epidemiology

In 1872, the Austro-Hungarian dermatologist Moritz Kaposi described five patients with multicentric cutaneous and extracutaneous neoplasms that primarily affected older individuals. Kaposi's sarcoma (KS) was originally described as "idiopathic multiple pigmented sarcoma" and was later named after its first describer. Based on distinct epidemiological features and clinical evolution, there are four clinical variants of KS. All of those variants have comparable histopathology, and in all of them the human herpesvirus type 8 (HHV-8), also known as Kaposi's sarcoma–associated herpesvirus, plays a causative role.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_46, © Springer-Verlag Berlin Heidelberg 2015

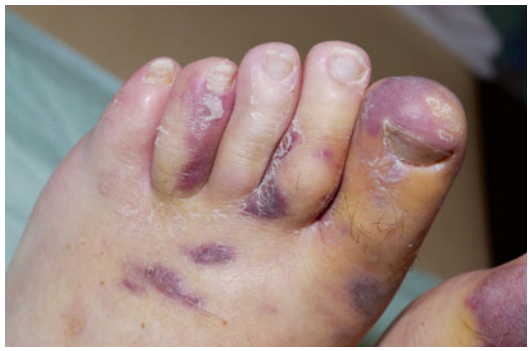


Fig. 46.1 Classic Kaposi's sarcoma lesions in typical locations on the distal extremities

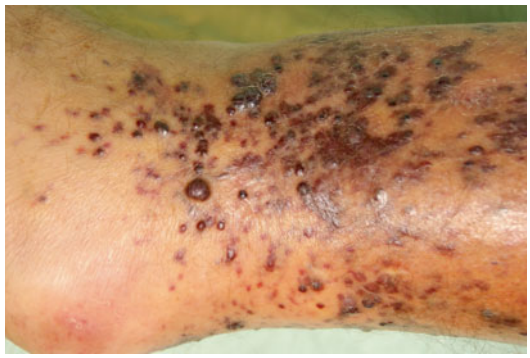


Fig. 46.2 Advanced Kaposi's sarcoma, nodular lesions surrounded by pitting edema

Clinical Presentation

Classic KS

Classic KS preferentially occurs in Caucasians over 60 years of age with a Mediterranean or Jewish background. The male to female ratio is 3:1–5:1. Classic KS lesions manifest on the skin as unilateral or bilateral violaceous (hematoma-like) macules and plaques with acral disposition, frequently on the distal portions of the lower extremities (Fig. 46.1). These lesions progress slowly into coalescent firm plaques and nodules surrounded by pitting edema (Fig. 46.2) and, subsequently, into nodules, while additional lesions start to arise in the surroundings or at distant sites. This clinical variant is usually slowly progressive, and patients may live with slowly progressive disease for many years. However, also in classic KS, ultimately dissemination to other body sites such as lymph nodes, mucous membranes, and inner organs, in particular the gastrointestinal tract, may occur. Since classic KS mostly affects elderly patients, death from other causes may precede its full spread.

The higher incidence of KS in countries surrounding the Mediterranean Sea has led some authors to speak of a Mediterranean KS variant as a separate entity. Since the clinical course and the epidemiology are comparable to the classic KS, the authors prefer to not separate classic and Mediterranean KS.

African Endemic Kaposi's Sarcoma

An increased frequency of Kaposi's sarcoma in black Africans in Central Africa was reported already in the 1950s. This clinical form is more prevalent in male patients, with ratios ranging from 3:1 in children up to 18:1 in adults. In some Equatorial African countries, endemic KS comprises up to 10 % of all malignancies in men. The age at onset is lower than in classic KS, with a peak at 25–39 years in women and 35–39 years in men. There are four clinical variants of the African endemic KS: nodular, florid, infiltrative, and lymphadenopathic. The florid and infiltrative variants are showing an aggressive behavior, and the lesions may extend deeply into the muscle and bone. The lymphadenopathic variant is mainly seen in children and young adults and may rapidly progress.

Kaposi's Sarcoma in Patients Receiving Immunosuppressive Therapies

After organ transplantation had become a routine procedure in the 1970s, a high incidence of KS was reported for organ-transplant recipients undergoing immunosuppressive therapy. The occurrence of KS has been reported, less frequently, in patients who receive therapeutic immunosuppression for other reasons such as the treatment

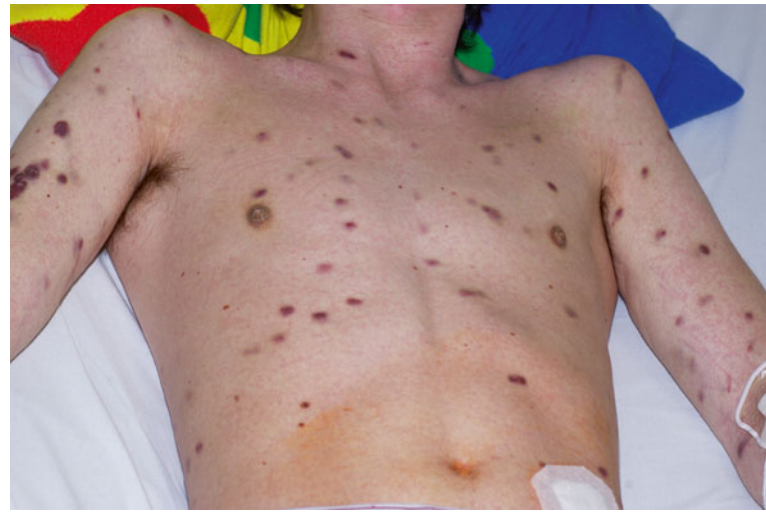


Fig. 46.3 HIV-associated Kaposi's sarcoma, multiple lesions on the trunk

of autoimmune diseases. Transplantation-associated KS is observed predominantly in kidney allograft recipients, while in recipients of other solid organs and bone marrow allografts, it is rarely seen. An important risk factor for KS development is the dose and type of the immunosuppressive drug. The risk in association with cyclosporin A is higher than with glucocorticoids and azathioprine, and the disease onset is earlier. Discontinuation of immunosuppressive therapy was followed in some cases by the regression of KS lesions.

The clinical course of KS in therapeutically immunosuppressed patients may be slowly progressing like in the classic variant or rapidly disseminating like in AIDS-associated KS. Skin lesions are present in more than 85 % of the patients with transplantation-associated KS, while the remaining 15 % of patients have visceral disease without skin involvement.

AIDS-Associated KS

Rapidly progressing, multifocal KS occurring in young homosexual men was one of the diseases which alerted health authorities in the USA on the advent of a new disease, i.e., the acquired immunodeficiency syndrome (AIDS). KS is considered an AIDS-defining illness. At the beginning of the AIDS pandemic, KS was seen in more than 20 % of HIV-1–infected patients. In recent years, it is in a strong decline due to efficient anti-HIV drugs. AIDS-associated KS is more frequent in homosexual or bisexual men and less common in injection drug users or transfusion recipients. In Europe and the USA, the AIDS-associated KS is seen mostly in males, whereas in Africa, it is encountered in high numbers in HIV-1–infected women and children.

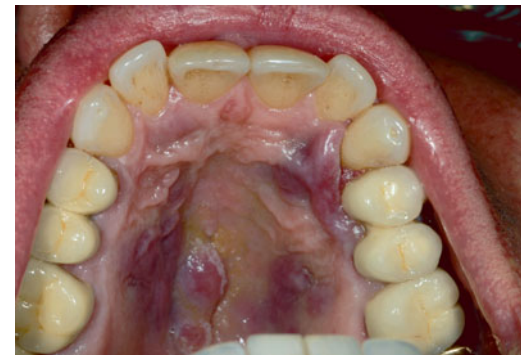


Fig. 46.4 Involvement of the oral mucosa. Nodular Kaposi's sarcoma lesions on the hard palate

AIDS-associated KS evolves with multifocal dissemination and undergoes a more rapid course than classic KS. The KS lesions in AIDS are asymptomatic, are elliptical, and occur along the skin tension lines, frequently on the face (nose, eyelids, ears) and on the trunk (Fig. 46.3). Over time, KS lesions may unite to form large plaques that can interfere with the normal movements of the limbs. Mucosal lesions occur early in the disease. Hard palate (Fig. 46.4), gingival,

and pharyngeal lesions may easily ulcerate and result in difficulties of eating, speaking, and breathing.

AIDS-associated KS involves rapidly all visceral sites. Tumors are frequently found in lymph nodes, gastrointestinal tract, lungs, liver, pancreas, heart, bone marrow, etc. Involvement of the gastrointestinal tract may cause severe clinical symptoms including extensive bleeding, ileus, malabsorption, nausea, vomiting, and abdominal pain. Pulmonary involvement can be manifest with coughing, chest pain, hemoptysis, bronchospasm, and progressive respiratory insufficiency.

Diagnosis of KS

The diagnosis of KS is based on the clinical aspect and confirmed by the histological examination. To assess the dissemination of KS and the coexistence of other diseases, laboratory and imaging studies are needed.

Histopathology is similar for the different clinical forms and depends on the stage of KS lesions. Early patch lesions show a discrete increase in dermal vessels, which may appear slightly irregular and may form slits and clefts in the papillary dermis. The dermis also shows hemosiderin deposits and extravasated erythrocytes. In the plaque stage, extensive vascular proliferation can be seen at all levels of the dermis with dilated and angulated vascular spaces dissecting the collagen and leaving a spongy network. At this stage, solid cords and fascicles of spindle cells arranged between the vascular channels may be already present. On further progression to the nodular stage, bundles of spindle cells delineating irregular slit-like vascular spaces without endothelial linings become predominant. In these advanced lesions, pronounced pleomorphism, nuclear atypia, and mitotic figures are frequently present. In all stages of the KS lesions, a moderate inflammatory infiltrate consisting of lymphocytes, histiocytes, plasma cells, and, sporadically, neutrophils is regularly present. On immunophenotyping KS tumor cells are $vWF^{+/-}$, $PAL\text{-}E^{-}$, $CD31^{+}$, $CD34^{+}$, and$VEGFR3^{+}$ which characterizes them as part of the lymphatic endothelial differentiation lineage.

Laboratory studies include a complete blood count (CBC) and blood chemistry tests together with screening for sexually transmitted infections including HIV tests. In HIV-positive patients, CD4 T-lymphocyte count and plasma HIV viral-load studies should be performed.

Imaging Studies

- Conventional radiology of the chest is nonspecific in case of pulmonary KS showing diffuse reticulonodular infiltrates, lymphadenopathy, pulmonary nodules, and pleural effusion.
- Computerized tomography (CT) of the thorax can also identify nonspecific lesions in pulmonary KS: nodules (poorly defined), bronchovascular infiltrates, lymphadenopathy, or pleural effusions. Contrast CT scan can detect liver KS nodules.
- Magnetic resonance imaging (MRI) can identify KS lesions with better contrast resolution than CT. MRI findings can be suggestive for pulmonary KS and for cardiac or bone involvement.
- ^{99}Tc scintigraphy (planer or single photon emission computerized tomography (SPECT)) can detect KS lesions and can be used in combination with ultrasound to indentify KS lymph node involvement or with ^{67}Ga scintigraphy to differentiate lung infection.

Medical procedures can be used to identify KS lesions in internal organs and take tissue samples for histopathologic examination: bronchoscopy, upper endoscopy, or colonoscopy.

KS and Human Herpesvirus Type 8 (HHV-8)

Epidemiological data and electron microscopic studies had suggested the involvement of an infectious agent in the etiology of KS for a long time. Finally, in 1994 Chang and colleague set the stage for a viral cause of KS when they discovered and characterized a novel human herpesvirus: HHV-8. This virus is present in all KS variants. HHV-8 is a member of the γ-Herpesviridae subfamily, genus *Rhadinovirus*. Several of the HHV-8 regulatory genes are homologous to human genes

involved in regulation of apoptosis, cell proliferation, and angiogenesis, and some of them have been shown to transform cells. It is therefore generally accepted that HHV-8 is a transforming herpesvirus and plays a direct role in the development of KS. In addition to KS, HHV-8 has been implicated in the pathogenesis of pleural effusion lymphoma, a rare B cell neoplasm seen primarily in AIDS patients, and in multicentric Castleman's disease. The routes of HHV-8 transmission are not yet entirely known. Epidemiological studies have confirmed that sexual transmission occurs during oral-genital and oral-anal contacts. In areas where the virus is highly prevalent, such as in Mediterranean countries and Africa, nonsexual transmission is possible as the HHV-8 can be shed in saliva.

The prevalence of HHV-8 is largely overlapping with that of KS. In regions of low KS incidence such as the USA and Northern Europe, HHV-8 prevalence is below 0.1 %, whereas in regions with high KS incidence such as in Southern Italy and Central Africa, HHV-8 prevalence reaches 20 and 70 %, respectively. In HIV-1–infected patients in the USA and Northern Europe, HHV-8 prevalence is highest in homosexual and bisexual men and reflects the incidence of KS in this risk group.

Differential Diagnosis

The violaceous lesions of KS can be sometimes misdiagnosed, mainly in patients with few skin or mucosal lesions:

- Bacillary angiomatosis
- Pseudo-Kaposi's sarcoma (acral angiodermatitis)
- Blue rubber bleb nevus syndrome
- Pyogenic granuloma
- Hematoma
- Tufted angioma
- Melanocytic nevi
- Melanoma
- Angiokeratoma
- Stewart-Treves syndrome
- Nodal angiomatosis
- Glomus tumor
- Lymphangioma
- Arteriovenous malformations (pseudo-KS)
- Severe stasis dermatitis (pseudo-KS)
- Skin metastasis of other tumors (e.g., renal cell carcinoma)
- Erythema elevatum et diutinum
- Insect bites

General Principles of Treatment

The treatment of KS depends on the clinical variant, on the extent of the skin lesions, and on the internal organ involvement (Table 46.1). Despite the presence of the oncogenic herpesvirus HHV-8, the treatment with modern anti-herpetic drugs did not prove to be effective.

Localized Cutaneous Disease

Regardless of the clinical variant, if a patient presents with limited disease confined to the skin, local therapies aimed for the destruction of individual

Table 46.1 Treatment options for Kaposi's sarcoma

Localized disease
Surgical excision
Cryotherapy
Topical 9-cis-retinoic acid
Photodynamic therapy
Radiation therapy (on regions not easily accessible for surgery)
For patients with AIDS: initiate HAART
Disseminated disease/internal organ involvement
For AIDS patients not responding to HAART alone – systemic cytotoxic chemotherapy (and continuation of HAART)
Liposomal anthracyclines (e.g., liposomal doxorubicin 20–40 mg/m^2
every 2–4 weeks)
Paclitaxel (100 mg/m^2 every 2 weeks)
For patients with classic KS
Liposomal anthracyclines (e.g., liposomal doxorubicin 20–40 mg/m^2 every 2–4 weeks) (preferred treatment of the authors)
Vinblastine (6 mg IV once a week)
Doxorubicin/bleomycin/vincristine (20–30 mg/m^2, 10 mg/m^2, 1–2 mg, respectively, every 2–4 weeks)
Interferon alpha (3–30 million units daily to 3 times a week)
For patients on immunosuppressive therapy – reevaluate drug regimen and further treatment depending on the immunosuppressive regimen and the degree of organ involvement

lesions are recommended as first-line treatment. These include surgical excision or local destruction with liquid nitrogen, laser or photodynamic therapy, and topical therapy with 9-cis-retinoic acid. Radiotherapy can be used at body sites difficult to reach by other local therapies such as on the nose and in the oral mucosa. Radiation therapy may be given as low-voltage (100 kV) photons or electron-beam radiotherapy. For localized skin lesions, electron beam therapy can be used once weekly in 4 Gy fractions. In patients with widespread skin involvement, extended-field electron beam radiation therapy was reported to be effective. The treatment is maintained for 6–8 weeks/cure.

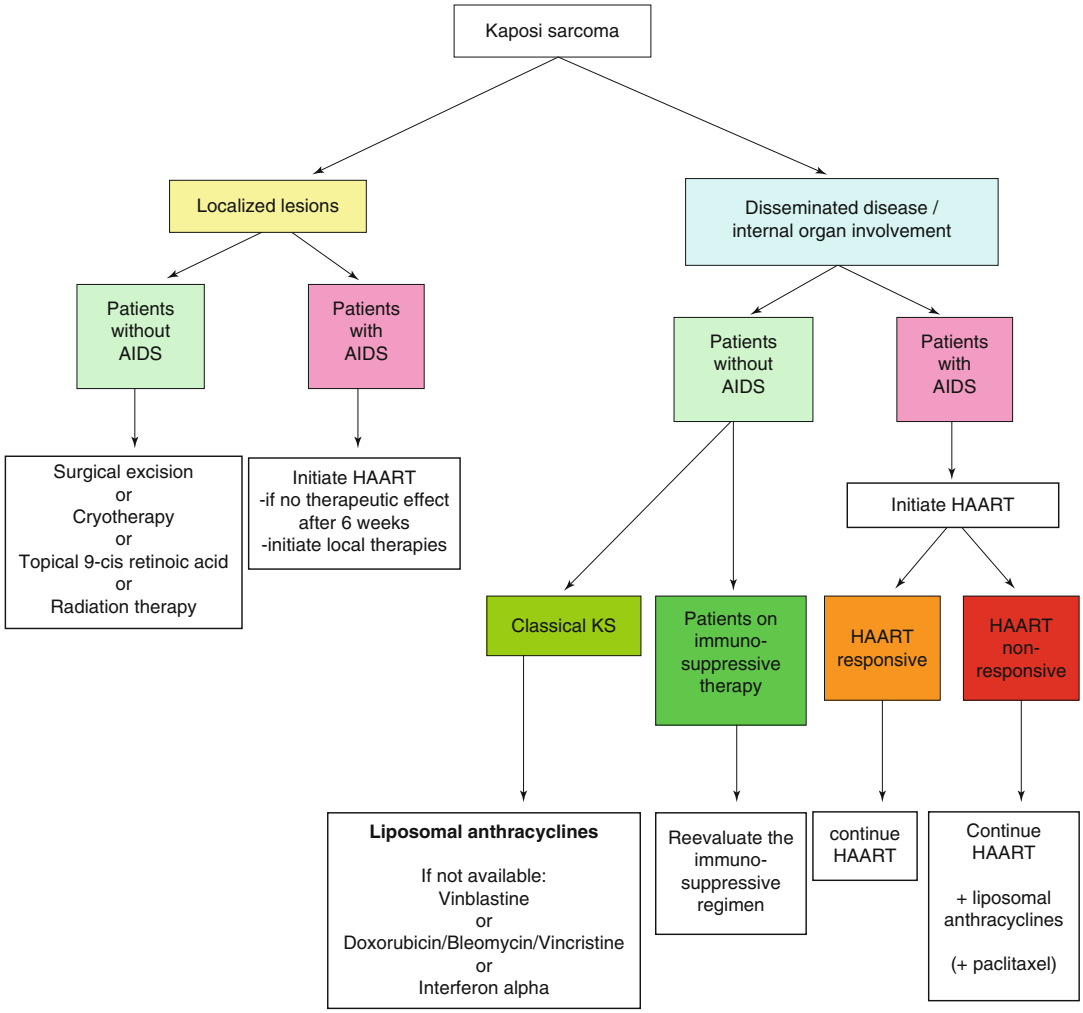
Although recurrence rates are high, local therapies might be satisfactory for years in slowly progressing classic KS. By contrast, in the other clinical variants, it is necessary that additional measures such as change of the immunosuppressive therapy in transplantation-associated KS and initiation of HAART in patients with AIDS-associated KS.

Progressive Cutaneous Diseases and Involvement of Other Organs

AIDS-Associated KS. The advent of highly active antiretroviral therapies (HAART) had led to a decrease of AIDS-associated KS incidence, and remission of early KS lesions occurred after initiating HAART. However, advanced KS cannot be controlled or reversed by HAART but requires chemotherapy. Among several chemotherapeutic regimens used in the past decades, liposomal anthracyclines emerged as more efficient and better tolerated than the combination therapies of bleomycin with vincristine or both combined with doxorubicin. *Liposomal doxorubicin* is an anthracycline antibiotic liposome encapsulated with polyethylene glycol coating that has a preferential concentration in the skin. Doxorubicin inhibits DNA and RNA synthesis by intercalating between DNA base pairs. Liposomal doxorubicin is recommended for the treatment of AIDS-related KS in IV administration: *20 mg/m^2 once every 2–3 weeks*. The treatment continues as long as the patient is responding and tolerating it. The doses need adjustments in case of hepatic impairment. Bone marrow suppression may occur during the treatment, and CBC monitoring is recommended before each drug administration. Leukopenia is usually transient. Neutropenia may result in superinfection and hemorrhage may occur due to thrombocytopenia. Doxorubicin may cause cumulative, dose-related myocardial toxicity that may lead to congestive heart failure as the cumulative dose of liposomal doxorubicin approaches 550 mg/m^2. Left ventricular ejection fraction is used to evaluate the cardiac function prior to treatment and periodically during treatment. Other adverse reactions include peripheral edema, fever, palmar-plantar erythrodysesthesia (hand-foot syndrome), transient alopecia, nausea, and stomatitis. Doxorubicin may potentiate the toxicity of cyclophosphamide and mercaptopurine, may diminish the therapeutic effect of inactivated vaccines, and may enhance the adverse effect of live vaccines. Liposomal doxorubicin may diminish the therapeutic effect and enhance the adverse effect of zidovudine. The adverse effects of liposomal doxorubicin may be enhanced by taxane derivatives or tacrolimus.

Daunorubicin is another anthracycline antibiotic with antineoplastic activity, first obtained from *Streptomyces peucetius*. Cell structure studies have demonstrated the drug rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations. Encapsulating daunorubicin in liposomes maximizes the drug selectivity for solid tumors. *Liposomal daunorubicin* is indicated as a first-line cytotoxic therapy for advanced HIV-associated KS at a dose of *40 mg/m^2 administered* IV *at 2 weeks' interval*. Treatment is maintained as long as KS lesions are not progressing (over 25 % new or evolving lesions) or HIV disease complications do not impose the discontinuation. Due to the liposomal daunorubicin myelosuppressive effect, CBC monitoring is performed before each administration, and therapy is postponed when the total neutrophil count is less than 750 cells/mm^3. Other side effects include cardiac toxicity (cardiomyopathy), back pain, flushing, chest tightness, and temporary hair loss. Echocardiographic monitoring is performed at a total cumulative dose of liposomal daunorubicin of 320 mg/m^2 and afterward at every 160 mg/m^2.

Table 46.2 Flow diagram for KS treatment



For patients with anthracycline-refractory AIDS-associated KS, paclitaxel has been recently advocated as potential rescue therapy. It is important to keep in mind that HAART needs to be continued during chemotherapy of KS in HIV-infected patients. Interferon alpha which was the most frequently used drug for AIDS-associated KS treatment during the 1980s and early 1990s still holds some promise for AIDS patients with early disseminated KS who simultaneously receive highly active antiretroviral therapy.

KS in organ transplant patients may respond well to a reduction or change of the immunosuppressive therapy. Replacement of calcineurin inhibitors by rapamycin may lead to dramatic therapeutic effects with complete remission of advanced KS lesions. This effect seems to be not only due to the modulation of the immune response by the change of therapy but also to direct antitumor effects of rapamycin.

Classic KS. Chemotherapeutic drugs including doxorubicin, bleomycin, vincristine, etoposide, and dacarbazine alone or in combination had been administered also to patients with progressive or widespread classic KS in particular in those with involvement of inner organs. However, large prospective studies are not available. Data from the literature (Martin-Carbonero, 2004) as well as the authors' experience shows that liposomal anthracyclines are efficient as in the AIDS-associated KS.

Flow Diagram for KS treatment (Table 46.2).

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Keloids and Hypertrophic Scars

47

Ivana Binic

Key Points

- Keloids and hypertrophic scars are benign, localized proliferations of connective tissue of the skin and are the result of abnormal wound healing.
- Hypertrophic scarring usually occurs within 4–8 weeks after some traumatic skin injury, has a rapid growth phase for up to 6 months, and then gradually regresses over a period of a few years. Keloids appear as firm, mildly tender tumors, pink or purple, with shiny surface and sometimes telangiectasia.
- The most important factor in hypertrophic scar and keloid formation is prevention. Before any surgical procedure, patients should be asked if they have had previous problems with scarring.
- Multiple studies on hypertrophic scar and keloid formation have led to a plethora of therapeutic strategies to prevent or attenuate keloid and hypertrophic scar formation. The current arsenal of treatment methods includes surgical, medical, physical, and radiologic therapies, often used in combination. In the present, no existing single method is superior to others as an effective solution for all hypertrophic scars and keloids.

Definition

Keloids and hypertrophic scars are benign, localized proliferations of connective tissue of the skin and are the result of abnormal wound healing. Excessive scars may develop following any injury of a deep dermis, including burns, surgery, abrasion, piercings, vaccinations, and lacerations.

Hypertrophic scars are raised, but they stay within the boundaries of the original wound, and there is a possibility of spontaneous regression. Keloids are also raised, but spread beyond the original wound boundaries, invading the surrounding skin. They may continue to grow over time and often recur following excision. Hypertrophic scars usually are more responsive to different treatment modalities than keloids.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_47, © Springer-Verlag Berlin Heidelberg 2015

Basic Concepts of Pathogenesis

Despite advancements in knowledge of the mechanisms of wound healing and scar formation, the etiology and pathophysiology of hypertrophic scarring are not fully understood. Keloids and hypertrophic scars represent an exaggerated fibroproliferative response of the dermis. There is imbalance of matrix degradation and collagen synthesis, resulting in excess accumulation of dermal collagen, fibronectin, and glycosaminoglycan content and increased collagen turnover. It is shown that the dermal fibroblasts under the influence of persistently high levels of fibrogenic cytokines play a major role in stimulating matrix production. Also, it is found that keloid-derived fibroblasts show a rate of fibronectin biosynthesis that is four times higher than that of fibroblasts from normal scars and normal skin. Experiments on cells isolated from keloid tissue demonstrate numerous alterations on their function such as in proliferation, apoptosis, and/or expression of growth factors and matrix molecules.

In the normal maturation phase of wound healing, the connective tissue elements regress after the third week. In keloids, the collagen synthesis is approximately 20 times as great as that in normal skin and 3 times as great as in hypertrophic scar. Also, it is shown that not only high collagen production matters, but the ratio of type I to type III collagen is also high.

Histologically, hypertrophic scars display a nonspecific dermal fibroblastic proliferation, thickened dermis, and atrophy of the epidermis. Hypertrophic scars are more cellular than keloids, which in contrast display characteristic hypocellular, glassy, hyalinized, eosinophilic collagen fibers.

Clinical Presentation

Hypertrophic scarring usually occurs within 4–8 weeks after some traumatic skin injury (infection, wound closure with excess tension, burn), has a rapid growth phase for up to 6 months, and then gradually regresses over a period of a few years. Eventually, hypertrophic scars may finish like flat scars with no further symptoms. Keloids, in contrast, may develop up to several years after minor injuries. They persist, usually for long periods of time, and do not regress spontaneously.

Keloids appear as firm, mildly tender tumors, pink or purple, with shiny surface and sometimes telangiectasia. The borders of the tumor are well demarcated, but irregular in outline. A hypertrophic scar has a similar appearance but is usually linear if following a surgical scar or papular or nodular if following inflammatory lesions. Both types of scars are very often pruritic, but keloids may be the source of significant pain and hyperesthesia.

In most cases, hypertrophic scars develop in anatomic locations with high tension, as the shoulders, sternum, knees, neck, and ankles. Keloids are more often found on the skin of the anterior chest, earlobes, cheeks, upper arms, and shoulders. Less affected locations are the eyelids, cornea, mucous membranes, genitalia, palms, and soles, but both can occur at any anatomic location. Risk factors for the development of hypertrophic scars or keloids include trauma, mechanical forces (namely, increased wound tension or stretching), infection, inflammation, and foreign body reaction.

The incidence of keloids and hypertrophic scars is highest in the second to third decade of life, and their occurrence has equal sex distribution. Incidence rates of hypertrophic scarring vary from 40 to 70 % following surgery to up to 91 % following burn injury, depending on the depth of the wound. Patients with keloids often report a positive family history, unlike patients suffering from hypertrophic scarring, and the concept of a genetic predisposition to keloids has long been suggested. Keloid formation is seen in individuals of all races, except albinos, but dark-skinned individuals have been found to be more susceptible to keloid formation, with an incidence of 6–16 % in African populations.

Diagnosis and Differential Diagnosis

A clinical finding of flesh-colored to erythematous fibrotic plaque, together with history of recent surgery or trauma, is sufficient to make

diagnosis. Biopsy is unnecessary. In the absence of supportive findings, malignant tumors, including dermatofibrosarcoma protuberans, and giant cell fibroblastoma, along with infections and sarcoidosis, should be considered in the differential diagnosis.

In some cases clinical differentiation between hypertrophic and keloid scars is of central importance before the initiation of any treatment, because of a different course and prognosis.

Prevention

The most important factor in hypertrophic scar and keloid formation is prevention. Before any surgical procedure, patients should be asked if they have had previous problems with scarring. Avoiding all unnecessary wounds, elective surgical operations, especially in keloid-prone patients, remains an obvious but incomplete solution. Risk factors that promote the development of hypertrophic scars and keloids and that can be limited by physicians are attention to the early care of wounds, mechanical force (stretching tension) on the wound, wound infections, and foreign body reactions.

Anything that accelerates wound healing and reduces skin tension (e.g., postsurgical taping for 12 weeks) will diminish the risk of abnormal scar formation. Surgical closure of an open wound should take into account the tension on the wound, incisions should not cross joint spaces, midchest incisions should be avoided, and incisions should follow skin creases whenever possible.

General Principles of Therapy

Multiple studies on hypertrophic scar and keloid formation have led to a plethora of therapeutic strategies to prevent or attenuate keloid and hypertrophic scar formation. The current arsenal of treatment methods includes surgical, medical, physical, and radiologic therapies, often used in combination. In the present, no existing single method is superior to others as an effective solution for all hypertrophic scars and keloids. Patients usually are treated with several treatment modalities combined depending on the patient's special circumstances and the clinician's experience with each specific treatment method.

Hypertrophic scars and keloids are benign skin lesions, but very often they are associated with pain and/or pruritus with different degrees of discomfort; sometimes they cause functional problems (e.g., contraction/mechanical irritation due to elevation) and also cause cosmetic-aesthetic concerns which may lead to psychological stress and functional disabilities that ultimately affect the patient's daily life.

The ultimate goal of hypertrophic scar and keloid management is to prevent function impairment and maintain a cosmetically acceptable appearance; therefore, thorough treatment should include different therapeutic options that are appropriate for the patient.

The therapy goals must be set on an individual basis and be oriented to the complaints of the patient. Depending on the treatment option, marked improvement should be achieved after three to six treatments or after 3–6 months (e.g., volume reduction by 30–50 %, symptom reduction >50 %, and/or sufficient satisfaction of the patient).

Treatment modalities for keloids and hypertrophic scars include pressure therapy, radiation, intralesional injections, cryotherapy, silicone-based products, surgical excision, lasers, and different combinations of two or more treatments.

Pressure Therapy

Pressure therapy has been the preferred conservative management for both the prophylaxis and treatment of hypertrophic scars and keloids since the 1970s, when physicians noted that pressure stockings used on lower extremity burns resulted in scars that matured more rapidly, with less erythema and thickness. Currently, pressure garments are predominantly used for the prophylaxis of hypertrophic burn scar formation, despite controversial data regarding their value in reducing excessive scarring and little scientific evidence supporting their use.

The compression phenomenon is not well understood, but theories include the following: decrease in blood flow with a resultant decrease in a2-macroglobulin and a subsequent increase in collagenase-mediated collagen breakdown, normally inhibited by a2-macroglobulin; hypoxia leading to fibroblast degeneration and collagen degradation; lower levels of chondroitin 4-sulfate, with a subsequent increase in collagen degradation; and decreased scar hydration, resulting in mast cell stabilization and a subsequent decrease in neovascularization.

Histologic examination showed that pressure therapy in hypertrophic scars partly restores the extracellular matrix organization, like that observed in normal scar tissue, and induces the disappearance of a-SMA-expressing myofibroblasts, probably by apoptosis.

Recommendations for the amount of pressure and the duration of the therapy are based merely on empirical observations, and continuous pressure of 15–40 mmHg for at least 8–24 h a day is recommended for the first 6 months while the scar is still active. Pressure therapy should be started immediately after reepithelialization of the wound. The success rate depends largely on patient compliance.

Radiation Therapy

The first use of x-rays in the treatment of scars was at the beginning of the last century. Later evidence showed that radiation therapy used as monotherapy is inadequate for the treatment of keloids, and therefore the use of radiation therapy was started as an adjunct to surgical excision.

Ionizing radiation has two effects on pathological scars: (1) an antiproliferative effect due to inhibition of new cell formation by delay of mitosis or the mitosis-induced cell death and (2) an antiinflammatory effect due to lymphocyte apoptosis and induction of differentiation of fibroblasts/fibrocytes. The result is a hypocellular, poorly vascularized, and hypoxic tissue, less new fibroblasts formation, decreased amount of collagen production, and finally inhibition of keloid development. An adequate radiation dose establishes the balance between scar formation and excessive cell growth without influence on wound healing.

Surgical excision in combination with radiotherapy is considered the most effective treatment available in severe keloids. Surgical excision as a sole treatment of keloids has a very high recurrence rate, between 45 % and 100 %. Surgical excision followed by radiation therapy for the treatment of keloids provides the highest reported regression rates.

Electron beam irradiation is usually started 24–48 h after keloid excision, and the total dose is limited to 15–20 Gy over the course of several treatments. Response rates ranged from 65 to 99 %, and recurrence rates ranged from 21 to 72 %, with most occurring within 13 months of radiation treatment. Risk factors for increased recurrence after adjuvant radiation therapy include a keloid with a diameter greater than 2 cm, prior treatment of the keloid, and male gender. Also, one of the advantages of radiation therapy is the amelioration of pruritus and tenderness often associated with keloid lesions.

Adverse effects include hypo- and hyperpigmentation, erythema, telangiectasia, ulcerations, and atrophy. Radiation-induced malignancies from scar treatments are rare. The total-body radiation dose from a superficial low-voltage radiotherapy technique is low, and it is difficult to definitively implicate this kind of treatment as the cause of neoplasm. There is concern regarding the use of radiation in pregnant women and children as well as in regions of the body with high carcinogenic potential (i.e., breast, thyroid).

The selection of radiation type, i.e., a conventional radiotherapy (RT), brachytherapy or electron therapy, or fractionating, should be made individually by the treating radiation therapist. The current use of radiotherapy for keloids in routine practice is limited both because of the nonavailability of the modality in most centers and also a general understanding about its use. Treatment should preferentially be performed in specialized clinics with interdisciplinary consultation (dermatology, surgery, nuclear medicine). It may be an effective option for recalcitrant and large keloids not responding to other treatments.

Intralesional Therapy

Corticosteroids

Intralesional corticosteroid injections are one of the most common approaches in therapy of hypertrophic scars and keloids. Most of the known effects of corticosteroids are thought to result primarily from its suppressive effects on the inflammatory process in the wound. In addition corticosteroids reduce the excessive growth of the scar by diminishing collagen synthesis as well as glycosaminoglycan synthesis and inhibiting fibroblast proliferation.

The most used corticosteroid is triamcinolone acetonide (TAC, 10–40 mg/mL, maximally 5 mg/cm^2), pure or diluted with 0.9 % NaCl or lidocaine 1:2–1:4, injected strictly intralesional. The concentration of triamcinolone acetonide depends upon the size and site of the lesion and age of the individual. It is important to inject the steroid at a correct depth in the mid-dermis; otherwise, it may lead to irreversible atrophy. A blanching effect signals the endpoint of the infiltration. Further injections are performed as needed at 3–4-week intervals, and usually two or three sessions are sufficient. Occasionally, injections are continued for 6 months or more. The total number of injections depends on the response and possible side effects. Response rates have been highly variable, ranging from 50 to 100 %, and a recurrence rate is reported to be 9–50 %.

When used alone, intralesional corticosteroid injections have the best effect on younger keloids, which can become completely flattened. In older hypertrophic scars and keloids, corticosteroids can soften and flatten the scars only to some degree and can provide symptomatic relief. Injections may be used alone or combined with other therapies, of which the combination with cryotherapy or surgery is the most widely used modality in clinical practice.

Side effects include dermal atrophy, telangiectasia, and pain at the site of injection. The latter can be averted by topical anesthesia and/or regional injections of local anesthetic around the scars. With available evidences, intralesional steroids should be considered as the first-line treatment for early keloids and a second-line treatment for early hypertrophic scars if other easier treatments have not been efficacious.

5-Fluorouracil (5-FU)

Recent data suggest that intralesional 5-FU injection is a safe new efficient tool in the ongoing battle against keloid scars. This treatment is increasingly becoming popular, because of good results. As a nucleotide analog (pyrimidine analog) that incorporates into DNA in place of uracil, 5-fluorouracil (5-FU) inhibits DNA synthesis, especially in rapidly proliferating cells, and has been shown to inhibit fibroblast proliferation in vitro and in vivo. It also has an inhibitory effect on type I collagen gene expression in human fibroblasts through inhibition of TGF signaling.

5-FU alone is effective in the treatment of keloids, but there are recommendations that for better results, it can be combined with surgical excision, as it prevents recurrence after excision in a majority of patients. Also, there is evidence that a combination of triamcinolone and 5-FU results in less skin atrophy and telangiectasia than triamcinolone alone. Recommended doses vary from different authors, from 50 mg per session (total exposure 50 mg) to 150 mg per session (total exposure 1,200–2,400 mg). Further work to determine appropriate doses should be initiated. Adverse effects of 5-FU include skin ulceration, burning, pain, and hyperpigmentation.

Bleomycin

Bleomycin is a polypeptide antibiotic isolated from a strain of *Streptomyces verticillus* with antitumor, antibacterial, and antiviral properties. In addition to blocking the cell cycle, bleomycin also directly inhibits collagen synthesis via decreased stimulation transforming growth factor β1 and induces fibroblast apoptosis. It was first investigated in the mid-1990s as a scar-reducing agent.

Only few relevant studies have investigated the efficacy of bleomycin in the treatment of hypertrophic scars and keloids. It can be administered

either by intralesional injections or by multiple punctures. A recent technique for delivering bleomycin to these lesions is called bleomycin tattooing in which multiple punctures are made on the keloid or hypertrophic scar with a 25-gauge needle and bleomycin (2 mL/cm^2) is dripped onto the lesion. In one randomized controlled trial, the relative mean resolution score in the bleomycin tattoo group was approximately 88 %, with a complete response observed in 47 % of patients.

Locally applied bleomycin results in minimal side effects, with transient hyperpigmentation and mild to moderate local pain among the most common. Systemic toxic effects of intralesionally administered bleomycin seem to be uncommon. Bleomycin may thus be a promising agent for the therapy of keloids and hypertrophic scars; however, further investigation and efficacy trials are needed before this agent is included in future treatment protocols.

Interferons (INF)

Interferons are cytokines secreted by T-helper cells that, apart from other properties, interferes with collagen synthesis and fibroblast proliferation, increases collagenase activity, and inhibits overproduction of collagen and glycosaminoglycans by fibroblasts. All interferon isoforms (a, b, g) have been shown to have these effects, but most of them have been applied only experimentally and in small numbers of patients.

Specifically, IFN-alfa-2b has been proposed to have antiproliferative properties, and it may improve the pathologic features of dermal fibrosis directly or by antagonizing the effects of TGF-β. It can be used as monotherapy or as adjunctive therapy. Conclusions from trials of interferon as monotherapy have shown inconsistent results, but as postoperative therapy or in combination with other treatment methods, interferon seems to be more promising, with lower recurrence rates and better outcomes. However, contradictory results have also been reported, so current evidence is therefore not sufficient to recommend the routine use of interferons. It may be used in selected cases, particularly when the other treatment modalities have failed. Adverse effects are common with the use of interferons and include flu-like symptoms (fever, chills, night sweats, fatigue, myalgia, and headache) and pain on the site of injection.

Cryotherapy

Cryotherapy has been used as monotherapy and in conjunction with other forms of treatment for both hypertrophic scars and keloids. The low temperature induced by cryogens causes vascular damage leading to anoxia, thrombosis, and consecutive ischemic cell death.

Cryotherapy delivery methods include contact, sprays, and intralesional needles. Response to cryosurgery has been reported as high as 80 %, but newer keloids that are more vascular are more susceptible to this kind of therapy than chronic, older keloids. Also, there is a better response in smaller keloids. Success rates in studies in which contact or spray cryosurgery with liquid nitrogen was used varied between 32 and 74 % after two or more sessions, with higher response rates of hypertrophic scars compared with keloids. Treatment recommendations include two 15- to 20-s thaw cycles performed on each visit every 3/4 weeks for a total of eight to ten visits. Recently, the intralesional-needle cryoprobe method has been assessed in the treatment of hypertrophic scars and keloids and has been demonstrated to have successful results. Compared with that obtained with contact/spray probes, there is shorter reepithelialization time, and it requires fewer treatments to achieve results.

Cryotherapy is often used in combination with intralesional corticosteroids, and this combination is superior to either treatment alone. Cryotherapy is used directly before the administration of intralesional corticosteroid injections, because success rates seem to be increased with this sequence. One study found that this combination therapy produced an 84 % positive response rate. Lesions treated with combination therapy require fewer procedures and have lower recurrence rates.

Immediate local complications associated with cryotherapy include pain, stinging sensation, edema, and bulla formation. Other adverse effects include atrophy, necrosis, and hypopigmentation and hyperpigmentation. The risk for pigment abnormalities is related to the duration of freezing as well as the number of sessions. A freeze/thaw time that exceeds 25 s may lead to destruction of the cold-sensitive melanocytes, thereby causing hypopigmentation, and should be avoided to achieve cosmetically successful results.

Silicone-Based Products

Silicone therapy was first reported in the early 1980s, and since than an effective and well-established therapy has become the noninvasive standard of care for scar management. The mechanism of action remains not completely determined. Presumed effects include hydration of the stratum corneum, increased skin surface temperature, development of a static electric field, reduction of evaporation, and oxygen transmission. Also, it is likely that silicone products act on the epidermis to initiate signaling cascades that affect dermal fibroblasts.

Silicone is available as cream, gel sheet, strip, spray, and foam. To be effective, silicone sheet must be used over the scar for 12–24 h per day for 2–3 months, with removal for routine hygiene. The sheets can be reused until they start to disintegrate. Silicone gel is better for areas of consistent movement, where sheeting will not conform, and should be applied twice daily. Positive effects from silicone products that have been reported include reduction of erythema, pigmentation, and induration and an improved overall appearance. Silicone products may be especially useful in patients who cannot tolerate the pain associated with other treatment procedures.

Results from numerous randomized controlled trials demonstrate that silicone is safe and effective for the treatment of hypertrophic scars and keloids with consistent treatment effects. In the past years, more and more studies have supported the use of silicone gels for prophylaxis of abnormal scarring. In a Cochrane Review the benefit of silicone use in scar prevention in patients with a predisposition to developing keloids after surgery was confirmed.

In patients who are known to have predisposition to form hypertrophic scars, application of topical silicone gel sheets should begin as soon as reepithelialization is finished, and daily application for at least 12 h is recommended. It is unknown what exact duration of treatment is needed for maximum benefit.

The efficacy of silicone gel dressings depends on the location of the scar, early commencement, the grade of response, and patient compliance. Side effects are minimal and very rare; however, rashes, pruritus, maceration, and dryness of the skin have been reported.

Surgical Excision

Although surgical excision is the most practical, effective, and traditional treatment for keloids and hypertrophic scars, it is very important before starting any surgical intervention to clearly differentiate the type of scar.

In case of hypertrophic scars, the timing of surgical intervention is an important consideration in the treatment protocol. This type of scar is formed during a period of at least 1 year, and in the course of that year, the scar can show decreased contractures along with flattening, softening, and repigmentation. Surgical excision thus might not be needed, even though postexcisional recurrence rates of the original hypertrophic scar are usually low.

In contrast, recurrence rates of keloids, after excision, range between 45 and 100 %, and surgical removal is not recommended as monotherapy. Excising the abnormal keloid tissue creates a new wound where new collagen begins to form; unfortunately, a larger and more aggressive keloid can recur in its place. Ideally surgical excision of keloid should be avoided as far as possible. Sometimes surgery can be used to treat keloids in order to reduce keloid mass (remove infected regions and provide symptomatic improvement).

In combination with other different treatment modalities, the recurrence rate is lower, between

8 and 50 %. Adjuvant therapy for surgical intervention for keloids can be the preoperative and/or postoperative use of intralesional corticosteroids, pressure therapy, interferon injections, and radiation therapy; these combinations all have shown promising results.

There are many methods for scar removal, including simple scar revision, resurfacing with skin grafts, local or distant flaps, intrascar excision, geometric broken line closure, and dermabrasion. Tangential shaving leads to better healing and reepithelialization, better cosmetic outcomes, and less recurrence rates, and it is a method of choice for earlobe keloids. Z-plasty, W-plasty, and V-Y and Y-V advancement flaps are some of the techniques currently used to remove keloids.

Lasers

Since the introduction of laser treatment for keloids in the mid-1980s, various lasers have been evaluated for the treatment of hypertrophic scars and keloids, with varied success. Current data is difficult to compare due to different laser systems, too small case numbers, too short follow-up periods, lack of information on the age and activity of the scars, and lack of differentiation between hypertrophic scar and keloids. Commonly used ablative lasers include the CO2 and erbium:YAG (Er:YAG) lasers, and nonablative lasers include the pulsed dye laser (PDL) and the Nd:YAG laser.

CO2 lasers emit light at a wavelength of 10,600 nm, which is strongly absorbed by water in the tissue, producing vaporization. In hypertrophic scars and keloids, the CO2 laser causes focal necrosis, which leads to collagen remodeling and lesion contraction. The CO2 laser may be used as monotherapy, but optimal treatment occurs when used in conjunction with intralesional corticosteroids. Intralesional steroids injected at regular 3- to 4-week intervals for up to 6 months demonstrated a lower recurrence rate compared to irregular-interval injections. Adverse events associated with the CO2 laser include erythema, reversible hyperpigmentation, and permanent hypopigmentation.

The Er:YAG laser emits infrared light at a wavelength of 2,940 nm and is more strongly absorbed by water than the CO2 laser. A randomized clinical trial found the Er:YAG laser to be effective in improving the elevation and vascularity of hypertrophic scars, with fewer side effects than the CO2 laser.

The use of the long pulsed 1,064-nm Nd:YAG laser, which selectively inhibits collagen production based on in vivo and in vitro studies, in the beginning demonstrated softening and flattening of keloids. Results, however, were transient and scar recurrences were common. Side effects were mild and included a prickling sensation during treatment and post-treatment erythema. Nevertheless, more studies are necessary to elucidate the effect of an Nd:YAG laser for the treatment of hypertrophic scars and keloids.

Until today, the most encouraging results have been obtained with the 585-nm pulsed dye laser (PDL), which has been recognized as an excellent therapeutic option for the treatment of younger hypertrophic scars and primarily keloids. Research studies since the mid-1990s have shown evidence of improvement in scar erythema, texture, height, pliability, and associated symptoms using the flashlamp-pumped 585-nm PDL for treating both hypertrophic scars and keloids, with low recurrence rates and a low adverse effect profile. Several theories have been proposed on the mechanisms by which this laser achieves clinical effects. By causing tissue hypoxia via destroying blood vessels, the 585-nm PDL therapy is believed to induce neocollagenesis, collagen-fiber heating with disruption of disulfide bonds, resulting in reorganization and realignment of collagen fibrils. Irradiation with the flashlamp-pumped 585-nm PDL may also affect collagen remodeling through cytokine stimulation and reduce extracellular matrix expression by reducing transforming growth factor β1. Adverse effects include transient hyper- or hypopigmentation and blistering. The most common adverse side effect of 585-nm PDL treatment is postoperative purpura, which can persist for 7–10 days.

The recommended protocol for the treatment of hypertrophic scars and keloids with the 585-nm PDL is the use of nonoverlapping laser pulses at fluences ranging from 6.0 to 7.5 J/cm^2 (spot

size 5–7 mm) or from 4.5 to 5.5 J/cm^2 (spot size 10 mm). Lower fluences should be applied at initial treatment sessions, with upward adjustments. Two to six treatments may be necessary to successfully improve scar resolution.

Onion Extract

Onion extract is found in numerous scar treatment products. It is currently believed that the flavonoids (quercetin and kaempferol) in onion extract play the main role in reducing scar formation. This "botanical" ingredient exhibited anti-inflammatory, bacteriostatic, and collagen downregulatory properties in a rabbit ear model, but in humans the results are controversial. Quercetin, a dietary bioflavonoid, has been recently shown to inhibit fibroblast proliferation, collagen production, and contraction of keloid and hypertrophic scar-derived fibroblasts. But former clinical studies are contradicting, regarding its efficacy, so the role of onion extract remains questionable.

Imiquimod

Imiquimod is a topical immune response modifier and is approved for the treatment of basal cell carcinomas, actinic keratoses, and genital warts. Imiquimod stimulates interferon alfa, a proinflammatory cytokine, which increases collagen breakdown. Therefore, imiquimod 5 % cream has been used after excision in an attempt to reduce keloid recurrence, and it was reported to have positive effects on the recurrence rate of keloids. However, there are contradictory data in other studies, so additional investigations with a larger sample size and longer follow-up are necessary to determine the role of imiquimod 5 % cream in hypertrophic scar therapy.

Combination Therapy

Numerous therapeutic strategies have been described for prevention and reduction of hypertrophic scars and keloids, but none of the treatments is effective in all patients. No universal consensus in treatment regimen has been established, and there is limited evidence-based literature to guide the correct management. There is a great need for additional clinical studies, well-designed, double-blind, placebo-controlled, and randomized with objective and standardized evaluative measures. A polytherapeutic approach to the treatment of abnormal scars has a best chance to help, and the right combination of treatments designed for each individual patient is the goal of every therapist.

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Keratoacanthoma

48

Rodrigo Roldan, Josep Malvehy, and Susana Puig

Key Points

- Keratoacanthoma probably lies within the spectrum of intraepidermal keratinocyte neoplasia and is possibly related to squamous cell carcinoma. The majority of lesions regress spontaneously. There are both surgical and chemotherapeutic treatment options.
- Keratoacanthoma is a lesion that usually undergoes three phases: rapid growth, maturation and regression.
- There are several forms of solitary keratoacanthomas as well as syndromes involving multiple lesions. Some of these syndromes are familial.
- The major risk factor for developing this lesion is sun exposure.
- The specific aetiology of keratoacanthoma formation and regression, including the potential role of infectious, environmental and genetic factors, is not yet known.
- Keratoacanthoma shares several histologic features of squamous cell carcinoma. There are various features that usually distinguish keratoacanthoma from squamous cell carcinoma; however, no one architectural or histopathological marker clearly delineates between the two.

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Definition

Keratoacanthoma (KA) is an epidermal neoplasm of the skin and mucous membranes that exhibits rapid growth, maturation and regression. It occurs most often on the sun-exposed areas of fair-skinned adults and is thought to arise from cells in the hair follicle. The exact biologic behaviour of keratoacanthoma remains controversial. In the past it had been considered a reactive condition or pseudomalignancy which could be treated expectantly. Now the favoured view is that KA is a malignant tumour with low, but not negligible, metastatic potential, which in many cases will regress. Even those that ultimately involute can cause considerable

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_48, © Springer-Verlag Berlin Heidelberg 2015

destruction before they regress. The regression may be partially mediated by immunity, but takes the form of terminal differentiation. The exact course of these tumours is unpredictable. Recently, the clinical behaviour of KA was retrospectively reviewed in 445 cases published in 113 articles. In all cases follow-up and outcomes had been reported, and none of these resulted in death or distant metastases. Yet, in the immunosuppressed patient, any lesion with histologic features of keratoacanthoma should be managed as a squamous cell carcinoma, with complete eradication.

There are four types of keratoacanthomas: solitary, multiple, eruptive and keratoacanthoma centrifugum marginatum.

Epidemiology

The incidence of solitary keratoacanthoma is highest in fair-skinned individuals, and the majority of the lesions occur on sun-exposed areas of the body. In 1963, Ghadially documented that KA occurs twice as often in men than in women and that the most frequently affected age group was 60–65, while the average age was 56. From this group, 90 % of the lesions were on sun-exposed skin with the cheeks, nose and dorsa of the hands being most commonly affected. In 1984, Kligman and Callen noted that the majority of the lesions occurred on sun-exposed skin and were accompanied by actinic damage, including a "leathered" aged appearance, actinic keratosis, other cutaneous neoplasms, solar lentigines, poikilodermas or a combination of these findings.

The incidence of Japanese Hawaiians seeking care for KA between 1983 and 1987 was 22.1/100,000, while the incidence in white Hawaiians was 104/100,000 and the incidence in Japanese residing in Japan was approximately 0.1/100,000. Dufresne et al. in Rhode Island, an area with marked seasonal variation in temperature and daylight hours, noted a statistically significant increase in the presentation of keratoacanthoma during the summer months. More recently, other authors also found differences in the seasonal appearance of KA; the tumour occurred more frequently in the winter months in Houston, Texas, versus June, November and December in Minneapolis, Minnesota.

Multiple keratoacanthomas of the Ferguson-Smith variant are an autosomal dominant disorder in which lesions may be numerous (up to hundreds) and both men and women are equally affected. Although lesions can begin as early as infancy, the mean age of onset is 25.5 years for women and 26.9 for men (Schwartz 1994).

Basic Concepts of Pathogenesis

A single cause for keratoacanthoma is unknown. The lesion occurs most often on hair-bearing, sun-exposed skin, but can occur on non-hair-bearing, sun-protected skin as well. For instance, keratoacanthoma has been reported on the hard palate, tongue, gingiva, lip (Fig. 48.1), nasal mucosa conjunctiva, anal mucosa, vulva, palms and soles.

Several proposed aetiologic mechanisms include:

Sun Exposure

The fact that most KAs occur on sun-exposed skin and occur more often in individuals who spend more time in the sun implies a connection between solar radiation and the lesion's pathogenesis. The

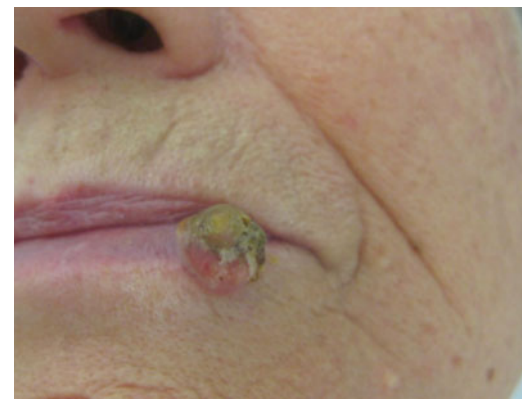

Fig. 48.1 Large keratoacanthoma of the lip

specific mechanism is unclear. Filipowicz et al. have demonstrated that the apoptotic mediator CD95 (Fas) is downregulated in two-thirds of keratoacanthoma lesions developing on sun-exposed skin. This data suggests that loss of the protective apoptotic mechanism may be one path to keratoacanthoma formation. A similar downregulation of CD95 was also seen in other lesions such as actinic keratosis, squamous cell carcinoma and basal cell carcinoma, and indeed these lesions have been described as occurring in the same patients and the same sun-exposed areas of the skin as KA.

Other Radiation-induced Forms

There have been case reports of keratoacanthoma occurring after cutaneous exposure to radiation therapy. Shaw et al. described the development of several keratoacanthomas on the face of a woman shortly after radiation therapy to her sinuses for a squamous cell carcinoma. There have also been case reports of psoralen and ultraviolet A (PUVA) therapy inducing keratoacanthoma. Brazzelli et al. reported keratoacanthoma arising in a vitiligo lesion after a prolonged course of UVB narrowband (UVB-NB) therapy.

Trauma

There have been numerous reports of keratoacanthoma developing at sites of skin trauma, even in young patients. Several specific case reports describe KA formation at the margins of excisions and skin grafts. Keratoacanthomas have also developed at the site of thermal burns and CO2 laser resurfacing. Kaptanoglu and Kutluay described a keratoacanthoma developing in previous cryotherapy sites for actinic keratosis.

Viral

There have been numerous studies suggesting a possible viral aetiology in the formation of keratoacanthoma. Specifically, HPV DNA has been demonstrated in several keratoacanthomas by various techniques including in situ hybridisation and PCR. Stockfleth et al. suggested that HPV infection does not cause KA formation in all people, but may be one predisposing factor in some patients and a cofactor for malignant transformation.

Hair Follicle Cycling

Ghadially proposed pathways by which keratoacanthomas develop from cells in the hair follicle. The cyclic nature of hair growth – anagen (growth phase), catagen (regression phase) and telogen (resting phase) – presents a similarity to the rapid growth, maturation and regression of most keratoacanthomas. The mechanism of formation of lesions on the mucosa and other non-hair-bearing skin is not known. It is also interesting to note that KA arising in the subungual area may arise from cells in the nail bed which grow constantly and do not cycle; thus, it seems logical that keratoacanthomas arising in this area would rarely show spontaneous regression. In fact keratoacanthomas of the subungual area often continue to grow, without regression, causing severe local tissue and bone destruction.

Immune Factors

Patel et al. demonstrated significant differences in the profiles of immune cells invading keratoacanthomas and squamous cell carcinomas. The infiltrates of KAs were demonstrated to be higher in CD3+ and CD4+ cells as well as cells expressing the interleukin-2 receptor and the adhesion molecule, CD36.

Keratoacanthomas tend to develop more frequently in immunosuppressed patients, and the lesions tend to be more locally aggressive in this population. These differences suggest that there is an immunologic role in KA regression, although a specific mechanism has not been elucidated.

Genetics

Several forms of keratoacanthoma express specific genetic patterns. KAs are found in conjunction

with sebaceous skin tumours and internal malignancies in Muir-Torre syndrome. This syndrome is a variant of the hereditary nonpolyposis colon cancer (HNPCC) syndrome and is inherited in an autosomal dominant pattern. Patients with Muir-Torre syndrome have germline mutations in their DNA mismatch repair genes. Several researchers have utilised microsatellite instability to document mutations in MSH-2 and MLH-1 mismatch repair genes in lesions from patients with both Muir-Torre syndrome and HNPCC (Machin et al. 2002).

DNA repair defects also characterise xeroderma pigmentosum, a syndrome in which keratoacanthomas are seen with actinic keratosis, basal cell carcinoma, squamous cell carcinomas and melanomas on sun-exposed skin.

Ferguson-Smith keratoacanthomas also demonstrate an autosomal dominant pattern of inheritance, and KAs of the Witten-Zak type have been reported in families.

Activated ras genes have been detected in several tumours including keratoacanthoma. RAS is a family of proteins involved in cell signal transduction that normally cycle between active and inactive states. Mutations in the ras gene can lead to proteins that are disproportionately active and thus tumorigenic. In a study by Peng et al., rabbits were altered to express human EJras, a RAS mutant, and all of these transgenic rabbits developed keratoacanthomas approximately 3 days after birth. Additionally, nearly all of these lesions spontaneously regressed. Clearly, mutations in this family of RAS proteins have the potential to explain KA formation in humans.

Vemurafenib, a fibrosarcoma kinase B (BRAF) inhibitor, is the first molecularly targeted therapy for the treatment of advanced-stage melanoma licensed in the USA and Europe. Its mechanism of action involves selective inhibition of the mutated BRAF V600E kinase that leads to reduced signalling through the aberrant mitogen-activated protein kinase (MAPK) pathway. Vemurafenib use can be associated with the development of cutaneous neoplasms such as squamous cell carcinoma and keratoacanthoma as a side effect. These lesions often arise weeks after initiation of therapy often in sun-exposed areas. The precise mechanism by which BRAF inhibition promotes the appearance of keratinocyte neoplasms is not yet fully understood (Fig. 48.2). However, the prevailing hypothesis is that in the context of a hyperactive mutant RAS gene and a normal BRAF gene, BRAF inhibitors, including vemurafenib, paradoxically activate ERK signalling by promoting the formation of CRAF-containing dimers, leading to hyperproliferation and tumour formation. Su and colleagues provide evidence supporting such a mechanism by showing that 60 % of the cSCCs and KAs in vemurafenib recipients had RAS mutations (mostly in HRAS) – a rate higher than the 3–40 % usually seen in sporadic cutaneous squamous cell carcinomas. Furthermore, cells overexpressing mutant RAS hyperproliferated in the presence of the drug, and skin tumours developed sooner in mice with Hras mutations induced by a vemurafenib analogue.

Clinical Presentation

Keratoacanthoma is a lesion that undergoes three phases: proliferation, maturation and regression. These phases correlate with both its clinical and histological appearances. In the early proliferative phase, KA appears as a flesh-toned to pink bud, dome- or berry-shaped papule that grows rapidly over the course of several weeks into a firm nodule that often has scale on top. During the maturation phase, a central, firmly embedded keratin plug develops (Figs. 48.1 and 48.2). This plug may appear verrucous, may grow to resemble a cutaneous horn (Fig. 48.2) or may become more darkly pigmented with the appearance of a necrotic centre. The firmly embedded keratinous plug cannot be dislodged with ease. The periphery of the lesion is often erythematous and slopes down to merge with the surrounding normal skin.

The tumour is usually not fixed to deeper structures. In the regression phase, the lesion involutes and eventually expels its keratinous centre. Regression usually results initially in a saucer-shaped depression when the plug is dislodged; this evolves into an atrophic, hypopigmented, depressed scar. KA often traverses its entire lifecycle within 2–6 months.

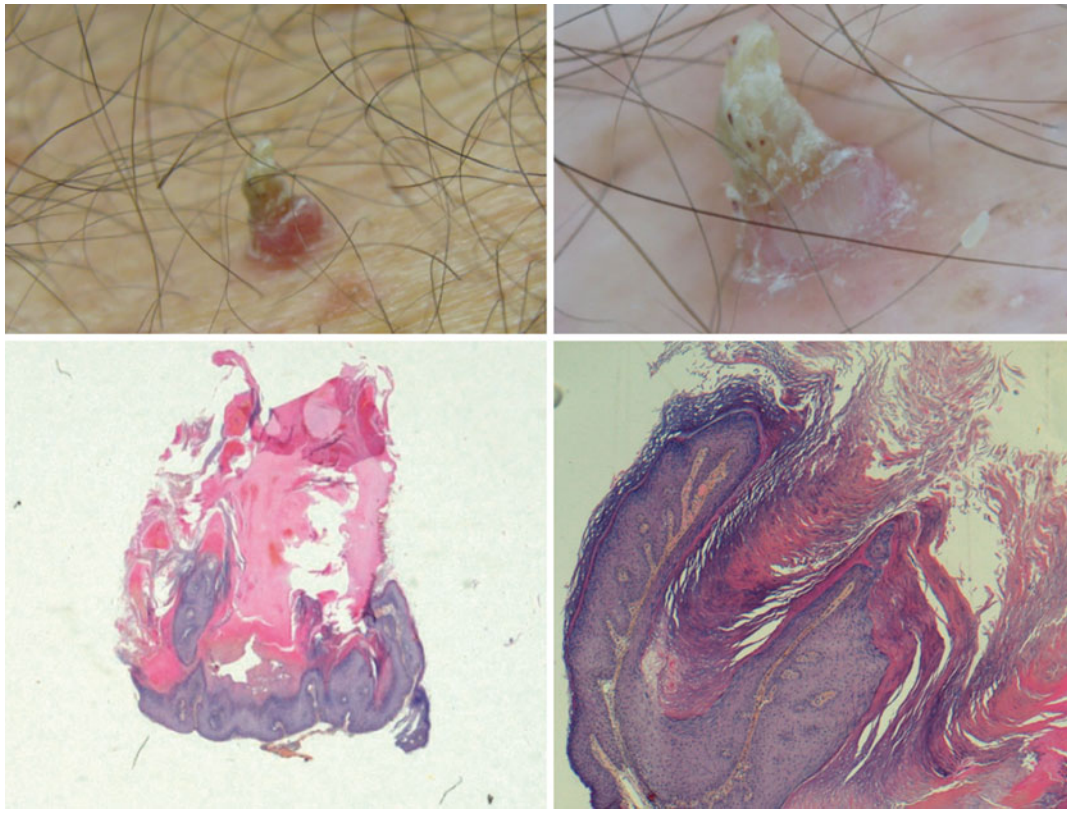

Fig. 48.2 Clinical (*upper left*) and dermoscopy (*upper right*) images of a keratinasing tumour induced during treatment with BRAF inhibitor. Clinically the lesion shows a bright pink elevated tumour with a central horn. Dermoscopy shows a lesion filled by keratin, hair pin vessels and blood spots. The histologic diagnosis is based on the architectural pattern of the lesion at scanning magnification (*down left*). The centre of the lesion shows a crater filled with eosinophilic keratin. Over the sides of the crater, a "lip" or "marginal buttress" of epithelium extends over the keratin-filled crater. At the base and sides of the crater (*down right*), the epithelium is acanthotic and composed of keratinocytes which are highly keratinised and have an eosinophilic, glassy cytoplasm with mild cytologic atypia

Under dermoscopy classical mature KAs are characterised by the presence of hairpin vessels surrounding the centre of the lesion filled by keratin. Hairpin vessels are surrounded by a whitish halo as in other keratinising tumours (Figs. 48.2 and 48.3). Recently, Rosendal et al. described the main dermoscopic criteria present in keratoacanthomas and squamous cell carcinomas, adding to the classical criteria the presence of white circles and blood spots. Central keratin was more common in keratoacanthoma than in SCC (51.2 % vs 30.0 %, $P=0.03$) with highest sensitivity for keratoacanthoma SCC (79 %), and white circles had the highest specificity (87 %). In a multivariate model, white circles, keratin and blood spots were independent predictors of SCC and keratoacanthoma.

Solitary Keratoacanthoma

Solitary keratoacanthoma is the most common form of this tumour. It occurs most often on the sun-exposed, hair-bearing skin, especially the face and dorsal hands, of adults with fair complexion. Solitary keratoacanthoma has the classic appearance of a rapidly growing hemispheric nodule (2–6 weeks) with a central keratin-filled crater that spontaneously regresses over a period of months. Lesions tend to be single, but there

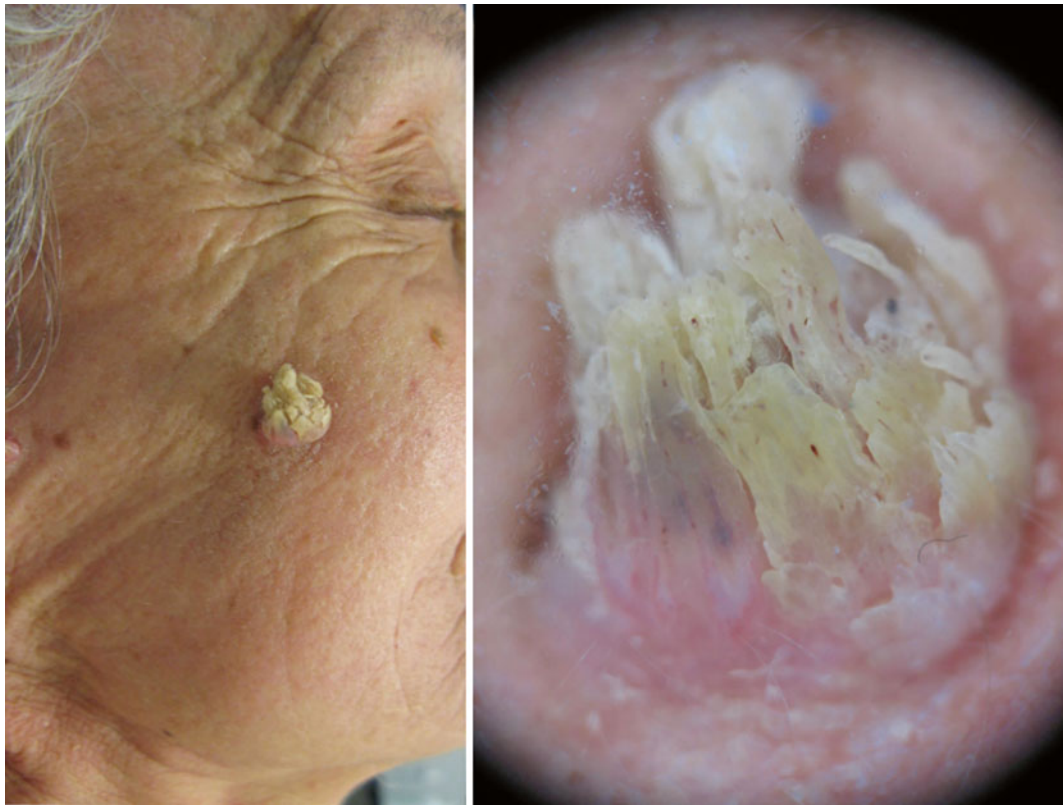

Fig. 48.3 Clinical (*left*) and dermoscopy (*right*) images of a keratinasing tumour induced during treatment with BRAF inhibitor. Clinically the lesion shows a bright pink elevated tumour with a central horn. Dermoscopy shows a lesion filled by keratin, hair pin vessels and blood spots

can be several lesions or additional lesion formation over the course of the patient's lifetime. It has been estimated that some 5 % of treated lesions recur. Invasion along nerve trunks has been documented and may result in recurrence after a seemingly adequate excision.

Giant Keratoacanthoma

A KA is considered giant if it grows larger than 3 cm in diameter. Giant keratoacanthoma may be locally invasive and disfiguring or may remain superficially situated. In spite of its size, it can still demonstrate complete, spontaneous regression.

Keratoacanthoma Centrifugum

Keratoacanthoma centrifugum marginatum is a rare, most commonly solitary, large lesion demonstrating a plaque-like appearance with central clearing and scarring. The diameter is similar to or larger than giant KA, but the proportions have changed so that the lesion is flat and atrophic in the centre with a raised rim that grows outwards and demonstrates keratin production. The dorsum of the hands and pretibial regions are favoured sites. Keratoacanthoma centrifugum marginatum often does not regress and can pose a significant therapeutic challenge.

Subungual Keratoacanthoma

Subungual keratoacanthoma is a rare tumour derived from the nail bed. It causes significant tissue destruction and does not regress. These lesions, classically, cause cup-shaped osteolysis without periosteal reaction in the underlying distal phalanx due to pressure erosion. Other

symptoms include local swelling, erythema, pain, nail bed deformity and in some cases bacterial superinfection. It may occur on the proximal nail fold and may involve nails of the fingers or toes, although they are seen most often on the thumb, index and middle fingers of patients in the third through seventh decades.

Multiple Keratoacanthoma Syndromes

Ferguson-Smith-Type Keratoacanthomas

Multiple KAs of the Ferguson-Smith type are an autosomal dominant disorder seen most commonly in males (3:1 predominance) with an onset in the second and third decades of life. The lesions occur first in small crops and are self-healing with scar formation. Sun-exposed sites are favoured, especially the ears and nose, and in most cases scalp lesions occur. The lesions tend to recur periodically throughout life, and later developing lesions have a lower tendency to spontaneously regress.

Generalised Eruptive Keratoacanthomas of Grzybowski

Grzybowski first described a very rare and sporadic form of eruptive keratoacanthomas in which thousands of small 1–5 mm KAs appear simultaneously or progressively. The lesions are more concentrated on sun-exposed skin, but also involve the oral mucosa, larynx and intertriginous areas. The lesions can appear in groups or clusters and demonstrate Koebnerization. Because of the severe facial involvement and resultant scarring, patients exhibit masked facies and ectropion. This variant has been reported in white, Asian and black patients with equal incidence in men and women.

Witten and Zak-Type Keratoacanthomas

In Witten and Zak-type keratoacanthomas, there is a combination of both Ferguson-Smith-type lesions and the smaller eruptive Grzybowski-type lesions. This variant has been reported in multiple siblings of the same family.

Histology

The histologic diagnosis is based on the architectural pattern of the lesion, which is best evaluated at scanning magnification (Fig. 48.2). This is true at each stage of the lesion's evolution.

The centre of the lesion shows a crater filled with eosinophilic keratin, with orthokeratotic and parakeratotic cells. Over the sides of the crater, which seems to have been formed by the invagination of the epidermis, a "lip" or "marginal buttress" of epithelium extends over the keratin-filled crater. At the base and sides of the crater, the epithelium is acanthotic and composed of keratinocytes which are highly keratinised and have an eosinophilic, glassy cytoplasm. Mild cytologic atypia is common. Mitotic figures, necrotic and dyskeratotic keratinocytes and acantholytic keratinocytes are prominent. Microabscesses of neutrophils often admixed with eosinophils are noted within the hyperplastic epidermis.

The surrounding dermis has a moderately dense perivascular or lichenoid mixed inflammatory infiltrate composed of lymphocytes, eosinophils and plasma cells.

The most definitive histologic feature is evidence of terminal differentiation, where the scalloped outer border of the tumour has lost its infiltrative character and is reduced to a thin rim of keratinising cells lining a large keratin-filled crater.

There are no histologic findings proven to predict biologic behaviour. The number of mitotic figures, perineural invasion and extension into subcutaneous tissue do not appear to differentiate between those lesions that will involute spontaneously and those that will persist.

Some reported metastases of keratoacanthoma to the lymph node have retained the architectural and cytologic features of the primary fully developed lesion.

The differential diagnosis with well-differentiated squamous cell carcinoma is sometimes difficult. Unfortunately, there is no single diagnostic marker study to date that can reliably differentiate KA from SCC.

Interestingly, recently a study was carried out to assess syndecan-1 (CD 138) and Ki-67 expression to differentiate keratoacanthoma

(22 samples) from squamous cell carcinoma (17 samples). Syndecan-1 is an adhesion molecule whose expression appears to be inversely correlated with tumour invasiveness. Elevated Ki-67 expression is indicative of a high proliferation index, a feature of malignant tumours. According to the results of this study, syndecan-1 expression is markedly diminished, and Ki-67 expression is significantly increased in SCC compared to KA.

General Principles of Treatment

Although keratoacanthomas usually spontaneously involute, it is impossible to predict how long this will take. If no therapeutic intervention is implemented, the patient may be faced with a destructive growth of a tumour which has a limited tendency to metastasise. More importantly, SCC cannot always be ruled out. Therefore, excisional biopsy should be considered in most cases. Surgery limits the progression and invasion of the lesion and allows for definitive diagnosis. Mohs micrographic surgery has also met with good success in removal of lesions from the head and neck and of recurrent lesions.

Nonsurgical therapy may also be considered in certain anatomical sites to preserve function or to improve cosmetic outcome.

Preferred treatment options vary depending on size and location of the lesion, as well as experience by the physician with each modality.

Intralesional injection of 5-FU solution, 50 mg/mL at weekly intervals; bleomycin 0.5 mg/mL; or methotrexate 25 mg/mL can be effective. For a typical lesion four injections along the base at each pole are recommended.

Topical photodynamic therapy with delta aminolevulinic acid has been successful for solitary and giant KA.

Low-dose systemic methotrexate may be considered if there is no response to intralesional injection or if multiple lesions are present and there is no contraindication.

Both etretinate and isotretinoin in oral doses of 1 mg/kg/day have been reported with good outcome in the treatment of recurrent and multiple KA syndromes.

Topical 5 % imiquimod has been reported as another successful alternative for the treatment of keratoacanthoma.

Excision is recommended if there is not at least 50 % involution of the lesion after 3 weeks.

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Leg Ulcers

49

Markus Streit and Claudia Blazek

Abbreviations

ABI or ABPI	Ankle-brachial pressure index
DVT	Venous thrombosis
ESWT	Extracorporeal shock wave therapy
MPFF	Micronised purified flavonoid fraction
NPWT	Negative-pressure wound therapy
PAOD	Peripheral arterial occlusive disease
PG	Pyoderma gangrenosum
VAC	Vacuum-assisted closure
VAD	Venoactive drugs
wIRA	Water-filtered infrared A

Key Points

- A leg ulcer is a wound located on the lower leg caused by different underlying diseases.
- Vascular diseases dominate the variety of pathologies, but also dermatological, metabolic, haematological, infectious or other disorders can be causative.
- Leg ulcers tend to evolve as chronic wounds, which have failed to heal within an expected time.
- Clinical knowledge and assessment is imperative for correct diagnosis.
- Treatment of leg ulcers encompasses the treatment of the underlying disease and local wound care.

Definition and Epidemiology

Leg ulcers can be defined as any wound located above the foot and under the knee (1). Ulcers on the foot and toes should better be denoted as foot ulcers although they are often numbered among leg ulcers. Leg ulcers – and foot ulcers – most often are chronic wounds. Such wounds have failed to proceed through an orderly and timely process to produce anatomic and functional integrity. The time frame in which a wound is expected to heal is variably estimated by different authors, ranging from 3 weeks up to 3 months. The delay of wound healing can be explained by different factors (e.g. lack of oxygen, bacterial toxins, increased proteinase levels), which are the consequence of a disease that in general is also the cause of the wound.

There are a large number of diseases that can induce a leg ulcer: Vascular, dermatological, metabolic, haematological or infectious diseases can be the cause but also neuropathies, malignancies

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_49, © Springer-Verlag Berlin Heidelberg 2015

and chemical or physical exposure. An overview of underlying diseases is shown in Table 49.1. A chronic wound can only heal if the underlying disease is controlled; therefore it is mandatory to know the cause of a wound and treat it correctly!

Most studies have shown that a venous aetiology (varicose or postphlebitic) is most common in leg ulcers (70–90 %). However a pure venous aetiology should not be overestimated: An additional arterial component can be found in 10–20 % of venous leg ulcers. A recent population-based study among 250,000 people in London found only 43 % pure venous ulcers but a multifactorial aetiology in 35 % (Moffat et al. 2004).

The prevalence of leg and foot ulcers was investigated in large epidemiologic studies in the 1990s analysing more than 230,000 people. An overall prevalence was found in up to 0.3 %, with a prevalence of venous ulcers of 0.16 %. More recent data from Germany have confirmed these data, showing a prevalence of an active venous ulcer in 0.1 % of a general population (more that 3,000 subjects) (Rabe et al. 2003). In elderly people the prevalence is higher (up to 0.3 % in the cited Bonn vein study) with a predominance of females.

Leg ulcers are a major public health concern, representing about 2 % of the UK healthcare budget with costs of £400 million. In Germany annual costs of over two billion Euros were calculated.

Due to the fact that leg ulcer is caused by a huge number of different diseases involving different medical specialities, a multidisciplinary approach is important. A close collaboration of dermatologists, angiologists, vascular and plastic surgeons, internists, rheumatologist and others is a precondition when dealing with leg ulcers.

But also the interprofessional aspect is of relevance: Wound nurses today are experts for the treatment of leg ulcers. Their suggestions for a treatment plan should be taken into account.

Diagnosis

All diagnostic measures should first aim to find the cause of leg ulcer and to establish the diagnosis of the underlying disease!

As most leg ulcers have a venous or arterial aetiology, the first step should always be to *confirm a venous origin and rule out an arterial involvement*. For this purpose, clinical characteristics are important and most helpful.

If a venous and/or arterial origin is not obvious or another aetiology is clinically suspected, diagnostic procedures have to be performed that allow diagnosis of suspected diseases.

Diagnostic steps include the following.

Medical History

Basic information should comprise duration of ulceration, date and modalities of onset, change of shape, characteristics of pain, history of previous ulcers and recurrences and former treatments.

To confirm *venous origin*, personal and family history of venous disease is of interest, e.g. occurrence of varicose veins, earlier venous thrombosis (DVT), former treatments (surgical interventions) and forms of compressions therapy.

To rule out *peripheral arterial occlusive disease* (*PAOD*), one has to ask for intermittent claudication (occurrence of crampy pain in the calf or thigh during walking) or rest pain in the legs (improvement with walking). Risk factors for vascular disease have to be recorded, e.g. arterial hypertension, diabetes mellitus, hypercholesterolaemia and nicotine consumption.

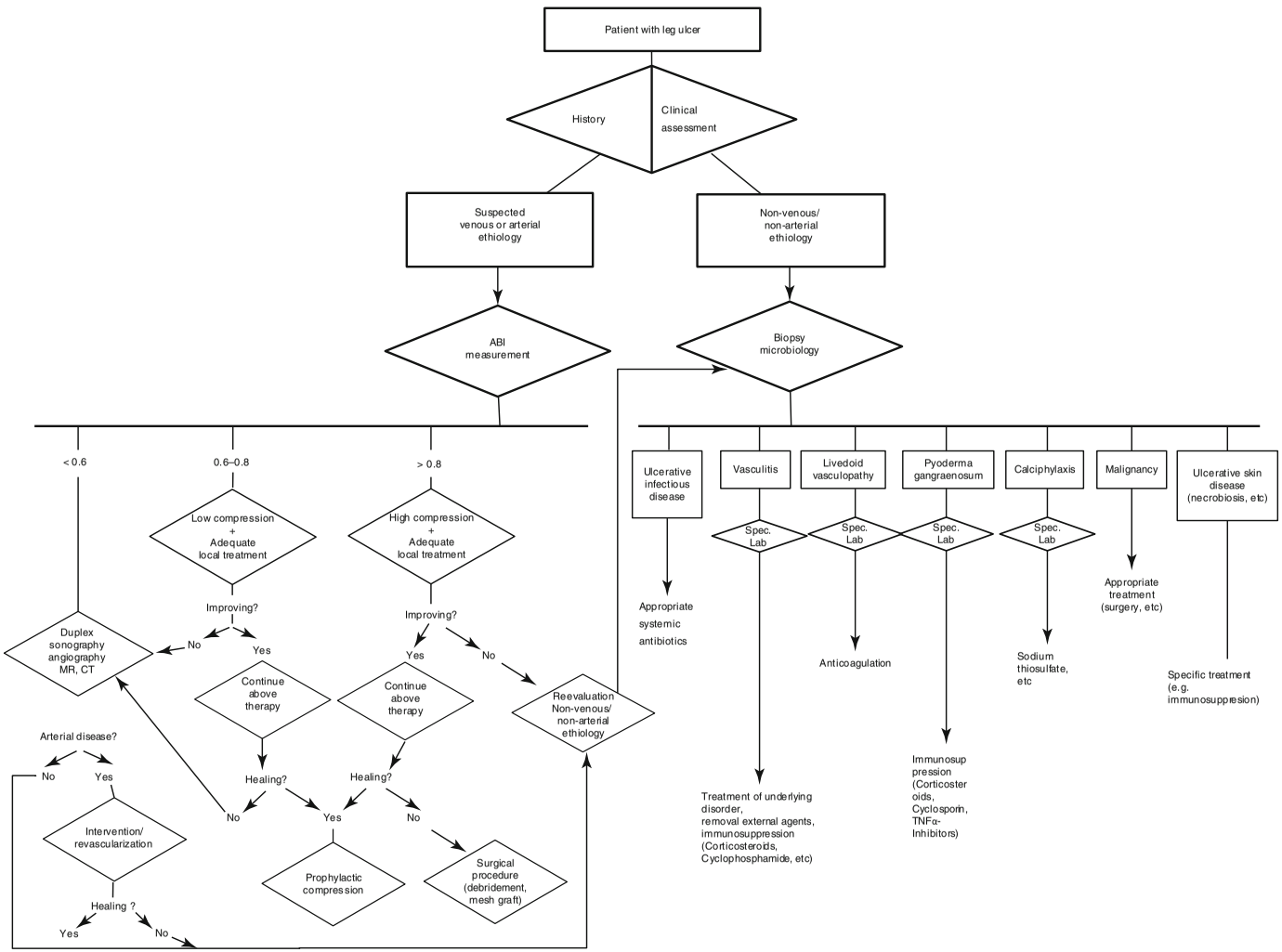
Recording of known diseases, allergies and drug intake is compulsory. Because patients with leg ulcers most often are elder people, information about life situation, impaired mobility and adequate nutrition is of great importance.

Clinical Assessment

The clinical aspect of a leg ulcer is often diagnostic for an underlying disease. Therefore it is crucial to be familiar with typical clinical signs:

- To confirm *venous origin* at a glance, localisation of ulcers is of primary interest: Venous ulcers are typically located around the medial ankle. Lateral or other localisation may occur, in particular in case of lesser saphenous vein insufficiency.
- Most helpful in diagnosing a venous origin of an ulcer are characteristic cutaneous signs of

Table 49.1 Algorithmic steps to achieve correct treatment of a leg ulcer. Rhomboid boxes: diagnostic step or intervention



chronic venous insufficiency, the underlying disease of venous ulcers. These skin changes on the lower leg were listed by Widmer in the 1970s in his classification of chronic venous insufficiency and define stages I and II of the disorder (Widmer and Wandeler 1978):

Look for ankle swelling, pretibial pitting edema and varicose veins, especially corona phlebectasia. Redness and dryness with scaling are signs of venous stasis eczema, small red and brownish spots are typical for purpura jaune d'ocre which can lead to hyperpigmentation. Diffuse redness resembling erysipela is indicative for hypodermitis. Dermatofibrosclerosis and atrophie blanche are typical for longstanding venous insufficiency. – The mentioned clinical signs also define clinical stages C1-4 of the CEAP classification that has been established in the nineties and is today widely accepted for the classification of chronic venous insufficiency (Ad hoc committee American Venous Forum. Classification and Grading of Chronic Venous Disease in the Lower Limbs: A Consensus Statement. Maui, Hawaii, 6th Annual Meeting February 22–25, 1994). (Eklof et al. 2004)

- Pathophysiologically chronic venous insufficiency results from venous hypertension induced by superficial and/or deep venous reflux. Both are mainly consecutive to valvular and/or perforator impairment (destruction in postphlebitic syndrome; incompetence due to venous dilatation) and dysfunction of muscular and articular pump (which supports recirculation of blood from foot to heart).
- Venous hypertension induces major microcirculatory disorders:
  - Dilatation, lengthening and microthrombosis of capillaries.
  - Distension of venular endothelial pores, allowing large plasmatic molecules to escape into the interstitial fluid and thereby inducing pericapillary deposits of fibrin. Increased oncotic pressure then favours the subsequent development of oedema, lymphatic overload and lymphangiopathy.
  - Accumulation and "trapping" of white blood cells in the distal medial part of the dependent legs of CVI patients, plugging of capillaries and releasing of cytokines as well as toxic metabolites.
  - Fibrosis and thickening of the fascia superficialis of the leg, histologically well demonstrated, altering calf muscle pump function.

Taken together, these alterations disturb oxygen diffusion and metabolic exchanges, inducing hypoxia, anoxia and leg ulcers.

- An *arterial involvement* has to be suspected when an ulcer is localised on the lateral aspect of the lower leg and when foot pulses are absent. Arterial ulcers are often more painful than venous ulcers.
- A very painful ulcer on the distal portion of the lower leg above the lateral malleolus with necrotic wound ground and livedoid borders is typical for *Martorell's ulcer* (*hypertensive leg ulcer*). Stenosing arteriolosclerosis is causative for the infarction of the skin that leads to ulceration; foot pulses may be palpable. Arterial hypertension and diabetes mellitus are underlying diseases.
- Ulcers with an atypical localisation, with rolled or everted wound edge, atypical granulation tissue (with hypertrophic, transparent aspect) and an increase of size despite adequate treatment are suggestive for *ulcerative malignancy*. Malignant neoplasias are the cause of a leg ulcer in up to 2.2 %. Basal cell carcinomas can be found most often. Squamous cell carcinoma can occur de novo or arise in long-standing chronic wounds due to "Marjolin transformation". In non-healing ulcers with no suspicious features, carcinoma can be found in 37.5 % (Miller et al. 2004).
- Disseminated necrotic lesions and ulcerations on both legs surrounded by flea bite-like, small red lesions are typical for *small vessel vasculitis*. The small red purple lesions that do not blanch when pressed are diagnostic: Such lesions (petechiae) are caused by extravasation of blood into the skin. This may result from hyper- and hypocoagulable states or vascular pathology. Petechiae that are palpable are indicative for vascular inflammation and therefore almost diagnostic for vasculitis afflicting small cutaneous vessels (palpable

purpura). Petechial lesions may become necrotic and ulcerate. Vasculitic ulcers usually are very painful.

- When ulcers are bizarrely shaped – often with a dendritic form – and surrounded by a purplish discoloration of the skin in a mottled reticulated pattern, *ulcerating livedo reticularis* can be diagnosed. The discoloration (reticular livedo) is caused by swelling of venules due to thrombotic obliteration of capillaries. A variety of diseases can lead to vasoocclusion of small vessels: haematological diseases (e.g. cryoglobulinaemia), autoimmune conditions with vasculitis (e.g. polyarteritis nodosa, systemic lupus erythematosus, etc.) and others.
- Reticular livedo together with atrophie blanche and episodic painful ulcers is diagnostic for *livedoid vasculopathy*. The disease is most often associated with coagulopathies.
- Livedo reticularis, painful panniculitis and large necrotic ulcers are the cardinal signs of *calciphylaxis*. In calciphylaxis pathological calcification of small arteries and fat tissue leads to thrombosis and skin necrosis. The disease most often occurs in patients on dialysis (stage 5 chronic kidney disease) and the term calcific uremic arteriolopathy (CUA) is equally used. However other risk factors have also been identified (elevated serum calcium and phosphate levels, hyperparathyroidism, obesity and type 2 diabetes mellitus, oral anticoagulation with coumarins, arterial hypertension and others). Calciphylaxis is extremely painful and necrosis and ulcerations can rapidly spread out.
- Another form of very painful ulcer that can occur on the lower leg shows undermined violaceous borders and a purulent, cleft wound ground, resembling dirty honeycombs. This corresponds to the classical picture of *pyoderma gangrenosum*, which typically has started with a small, red papule or pustule – looking like a bite reaction – changing into an ulcerative lesion with rapid centrifugal enlargement. Pyoderma gangrenosum is a non-infectious reactive neutrophilic dermatosis that is associated with inflammatory bowel disease, rheumatological and haematological disease and malignancy.
- Disseminated round, punched out lesions with a crusted necrotic surface are typical for *ecthyma gangrenosum*, an ulcerative infectious pyoderma of the skin caused by bacteria (*Pseudomonas*, *Streptococci*, *Staphylococci*). Patients often suffer from a haematological disease or receive immunosuppressive drugs. Diabetes and malnutrition may also favour occurrence of infection.
- Round ulcers with centrifugal enlargement over weeks and with a history of insect bite are suggestive for *leishmaniasis*. Infection is caused by protozoan parasites that are transmitted by the bite of sandflies.
- Round superficial ulcerations could be caused by bullous skin diseases even in the absence of visible blisters. *Bullous pemphigoid*, an autoimmunobullous disorder, can present solely on the legs. Autoantibodies against epidermal basal membrane induce bullous inflammation.
- Ulcerations occurring in well-circumscribed plaque-like areas on the shin with active, more indurated borders and waxy, strophic centres are typical for *necrobiosis lipoidica*. Initially, the underlying skin lesions are reddish brown but progressively become more yellow, shiny and atrophic in appearance. Necrobiosis lipoidica is a disorder of collagen degeneration.
- Ulcers on the feet and toes are typical for *diabetic foot syndrome*. As this article only deals with leg ulcers, the problem will not be discussed further.

Non-invasive Apparative Investigations

Ankle-Brachial Pressure index (ABI or ABPI)

In all leg ulcers at least this apparative investigation should be performed to exclude arterial disease. ABI stands for assessment of the ratio of blood pressure in the lower leg (ankle) to blood pressure in the arm (brachial): ABI = P leg/P arm.

It is a simple method that requires a Doppler ultrasound blood flow detector (Doppler probe) and a sphygmomanometer (blood pressure cuff). Ankle pressure is measured by slowly inflating

the blood pressure cuff around the distal lower leg and indicating at which pressure the pulse of distal pedal arteries ceases. For calculation of the ratio, the higher systolic reading of the left and right arm brachial arteries is generally used in the assessment and the higher of the two values of pressures measured in the posterior tibial artery and dorsalis pedis artery.

An ABI of less than 0.9 indicates an arterial disease. Of practical importance: Below a threshold of 0.8 compression therapy has to be performed with caution.

An ankle pressure of less than 50 mmHg demonstrates critical ischaemia. This is also the case with a toe systolic pressure below 30 mmHg.

Doppler and Duplex Investigation

Doppler probe offers a cheap and simple technique to diagnose alterations in the venous or arterial system; however sensitivity and specificity are low and therefore the Doppler is not advised any more in the diagnostic of leg ulcers for routine investigations (Guidelines for diagnostics and treatments of venous leg ulcers developed by the Guideline Subcommittee of the European Dermatology Forum 2013).

Duplex sonography (the combination of B-mode echography and Doppler sonography) in contrast has a high sensitivity and specificity in the diagnosis of venous or arterial thrombosis, arterial occlusion or stenosis and is most commonly used to visualise the superficial and deep venous system (e.g. venous directional flow, valve incompetence) of the leg. It is the preferred technique for patients with a vascular leg ulcer (Guidelines for diagnostics and treatments of venous leg ulcers developed by the Guideline Subcommittee of the European Dermatology Forum 2013).

A duplex sonography should be performed in all patients with venous or arterial ulcer when an intervention is a realistic option.

Pulse Volume Recording (PVR)

If arterial disease is suspected, this non-invasive diagnostic test can evaluate arterial circulation, which is measured at multiple sites of the leg according to the vascular segments. The test is based on pressure ratios and flow assessment and allows a more precise location of the arterial disease. The PVR may be non-diagnostic in patients with advanced vessel calcification as in diabetes or hypertension, due to atherosclerosis. In unclear cases, further tests like magnetic resonance imaging (MRI) are required.

Microbiology

All chronic wounds are contaminated or colonised by bacteria or yeasts. Therefore a routine swab from the wound ground for microbiological investigations is meaningless, if there is not a suspect of a critical colonisation that impairs wound healing or an obvious wound infection can be detected. In this case identification of microbes is important for the choice of antibiotics.

In countries with a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), routine swabs may be important to identify patients for hygienic reasons.

Histopathological Investigations

Ulcers with atypical appearance or inadequate response to treatment are suspicious for malignancy. A biopsy from the edge of the wound should be advocated for any ulcer that fails to respond to appropriate treatment to rule out malignancy.

A number of underlying diseases of leg ulcers can only be diagnosed histologically: This applies for all forms of vasculitis (especially small vessel vasculitis), calciphylaxis and ulcerating dermatoses (e.g. necrobiosis lipoidica, sarcoidosis). For other diseases like pyoderma gangrenosum, histopathological findings are important to support the clinical suspect.

Special investigations are required for some rare disorders: The diagnosis of leishmaniasis requires Giemsa's stain and/or polymerase chain reaction (PCR) assays from tissue; atypical mycobacteriosis can only be detected in Ziehl–Neelsen stain and by PCR. For the diagnosis of autoimmunobullous disorders, a direct immunofluorescence is mandatory.

These examples may underline the importance of clinical knowledge. Diagnostic investigations in the direction of rare diseases would not be performed without a corresponding clinical suspect.

Laboratory Investigations

It is debatable whether blood tests should be performed initially in all patients with leg ulcers.

It may be useful to have information from the beginning about a patient's blood count, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), HBA1c, total protein and basic coagulation parameters.

In some cases laboratory findings however are imperative:

- In case of a wound infection (with erysipelas or phlegmon/cellulitis), differential blood count, CRP and ERS are relevant for diagnosis and monitoring of the course.
- In patients with PAOD, one should know the values of risk factors (cholesterol, glucose/HbA1c) and also values that are of interest for further interventions, e.g. angiography, angioplasty or surgery (creatinine and coagulation parameters/INR).
- When vasculitis is suspected, laboratory tests are important to diagnose the aetiology of vasculitis but also to assess acuteness and extent of the disease. Serological tests include titres of antinuclear antibodies (ANA), dsDNA, cANCA, pANCA and rheumatoid factor (RF); serology for hepatitis B and C; creatinine/urea, muscle enzymes (CK, aldolase), complement, evidence of cryoglobulins and antiphospholipid antibodies.
- If a vasoocclusive disease with hypercoagulable/hypocoagulable state is suspected (e.g. livedo vasculopathy), additional assessments are relevant to rule out coagulopathy (prothrombin time, partial thromboplastin time, proteins C and S, homocysteine, antithrombin III, APC resistance, lupus anticoagulant).
- Calciphylaxis requires special assessment of serum calcium and phosphate, parathormone, HbA1c and albumin.
- The diagnosis of pyoderma gangrenosum obliges to search for associated internal diseases.

Angiography: Arteriography and Phlebography

With angiography the inside of blood vessels can be visualised. This is performed by injecting a contrast agent into the blood vessel and imaging using X-ray–based techniques.

Phlebography is the technique in which contrast fluid is injected into the venous vascular system, either from distal (ascending phlebography) or from proximal by performing a Valsalva manoeuvre (descending phlebography). Phlebography has largely been replaced by duplex diagnostic and is not considered the diagnostic of first choice for venous leg ulcers. It should only be used for special indications (Guidelines for diagnostics and treatments of venous leg ulcers developed by the Guideline Subcommittee of the European Dermatology Forum 2013).

Intra-arterial angiography refers to the visualisation of the arterial system with access gained through an artery, most commonly through the femoral artery. Angiography is performed to show stenosis of arteries in suspected peripheral arterial occlusive disease, which can be treated in the same session with angioplasty. For pure diagnostic measures, arterial duplex has become popular and also CT and MR angiography.

General Principles of Treatment

Treatment of leg ulcers is based on two pillars: The first comprises *treatment of underlying disease*, and the second encompasses *local wound care*.

The first step in the management of leg ulcers should always target at recognition and treatment of underlying diseases. As mentioned above, wound healing is only possible if the cause of the wound is sufficiently controlled. In the treatment of venous ulcers, in a Cochrane review, evidence for faster healing has been demonstrated for compression therapy (O'Meara et al. 2012), which is the treatment of underlying chronic venous insufficiency. In contrast the type of dressing applied beneath compression had not been shown to affect ulcer healing in another Cochrane review (Palfreyman et al. 2006).

Dealing mainly with elder patients that suffer from other diseases, one should not forget to look for concomitant diseases. These may have an influence on wound healing and should be treated: cardiac insufficiency, diabetes, obesity,

malnutrition, hypertension arthropathies, autoimmune disorders and others.

Treatment of Underlying Disease

Venous Ulcers: Treatment of Chronic Venous Insufficiency

The underlying disease of venous ulcer is chronic venous insufficiency, which can be treated noninterventionally or interventionally. Noninterventional treatments include compression therapy and medical treatments; interventional treatment encompasses all forms of invasive procedures from endovenous ablation techniques to surgery.

Compression Therapy

Compression therapy is an empirically originated treatment: Bandages are applied to exert pressure on tissue. Compression therapy is indicated in all forms of chronic venous insufficiency; it is and will remain the keystone of treatment for chronic venous insufficiency. Compression therapy reduces oedema, leads to constriction of venous lumina and thus reduces venous blood capacity. It enhances blood velocity in both superficial and deep venous compartments, improves pump function and reduces venous reflux. Reduction of capillary pressure corrects microcirculatory dysfunction and improves skin changes like dermatosclerosis.

Compression treatment may be performed with different forms of bandages:

- *Elastic long-stretch bandages* exert almost constant pressure due to their elasticity regardless whether a person is moving, standing or lying.
- *Short-stretch bandages* are less elastic and work on the principle of applying a low amount of pressure when the muscle is resting/not active. When the calf muscle is working, however, high resistance is applied to the muscle, which is known as working pressure.
- Nonelastic bandages like *multilayer bandages* or *Unna's boot* (gauze bandage containing zinc oxide paste) generate most working pressure and support optimally function of calf muscle pump. *Compression stockings* (*hosieries*) are manufactured with elastic materials and are worn knee-high, thigh-high or as pantyhose. They exert a graduated compression, which is strongest distally around the ankle. For elder people they may be difficult to apply by themselves. Compression stockings are mainly indicated for prophylaxis and in practice are generally recommended when an ulcer has healed. In the last ten years, however, special forms of high-compression stockings have been developed that are provided for ulcer treatment.

In a Cochrane systematic review, it could be demonstrated that compression increases ulcer healing rates compared with no compression. Multicomponent systems were more effective than single-component systems, and those multicomponent systems containing an elastic bandage appeared to be more effective than those composed mainly of inelastic constituents. Patients receiving a four-layer bandage healed faster than those with short-stretch bandage, and more patients heal on high-compression stocking systems compared to short-stretch bandage (O'Meara et al. 2012).

Compression therapy is safe; however there are some contraindications: Elastic bandages may not be used in stage III or IV of PAOD and/or below an ABI of <80 mmHg. Nonelastic bandages can still be applied because they do not exert pressure at rest. In case of heart failure, especially in the presence of right heart insufficiency, compression therapy has to be performed with care due to the shift of fluid into central compartments.

With bandage or stockings worn, regular exercise such as walking is imperative. Stimulation of ankle mobility to induce calf muscle pump is essential. Additional application of a bolster to the ulceration may selectively enhance compression.

Medical Treatment: Venoactive Drugs (VAD) and Others

Venoactive drugs (VAD) are a heterogeneous group of medicinal products of plant or synthetic origin, which have effects on oedema and on symptoms related to chronic venous disease. Synonymously used but better discarded are the terms oedema-protective agents, phlebotonics, venotonics, vasoprotectors, phlebotropics and venotropics. VAD include flavonoids (secondary metabolites of plants), e.g. benzopyrones like diosmin, hesperidin or coumarin; rutosides (rutin) and troxerutin; saponins like escin (from horse chestnut); calcium dobesilate; etc. The

main mechanisms of action of VAD is an increase of venous tone that results in restoration of normal blood flow, dispersion of red cell aggregates and better oxygenation. In the treatment of venous leg ulcers, VAD are used adjuvantly together with compression therapy which has to be the first-line treatment.

Micronised purified flavonoid fraction (MPFF) with diosmin and hesperidin has shown an adjuvant effect on healing of leg ulcers in double-blind studies (Guilhou et al. 1997; Roztocyl et al. 2003) and one meta-analysis (Coleridge-Smith et al. 2005), when ulcers were larger than 5 cm^2 and existing for more than 6 months. Pain was relieved in all treated patients.

Long-term administration of rutosides did not prevent leg ulcer relapses in one study (Wright et al. 1991).

Oral anticoagulants, heparin, aspirin, pentoxifylline and prostaglandins have been suggested to improve microcirculation and stanozolol to reduce dermatofibrosclerosis.

Interventional Therapy

Superficial venous insufficiency is a major cause of leg ulcers; up to 60 % of venous ulcers result from greater and/or lesser saphenous insufficiency, as could be demonstrated by duplex investigations in recent series. Superficial venous insufficiency can be treated and corrected by different forms of interventions:

- *Phlebectomy*, *sclerotherapy*, *echo-guided sclerotherapy or endovenous ablation techniques* (*radiofrequency or laser ablation*) of a feeding vein in the neighbourhood of the ulceration are simple and cost-effective treatment that can be performed in an outpatient setting.
- *Flush ligation and stripping* of insufficient greater and/or lesser saphenous veins suppresses reflux and venous hyperpressure. Photoplethysmography (1,2) is useful to determine the impact of venous reflux and can predict the improvement to be achieved with surgical removal of the incompetent vein(s).

The question whether compression and surgery are better treatments for venous ulcers has been answered by the ESCHAR study (Barwell et al. 2004) where the combination of surgery and compression was compared to compression alone in a randomised controlled trial with 40 patients. Healing rates after 6 months were similar in both groups (65 % vs 65 %), but 12-month ulcer recurrence rates were significantly reduced in the combined compression and surgery group (12 % vs 28 %). It could be concluded that most patients with chronic venous ulceration benefit from the addition of simple venous surgery regarding recurrence of ulcer but not concerning healing of the present ulcer.

Some surgical procedures may be indicated in cases of long-lasting venous ulcers with chronic skin changes.

- *Paratibial fasciotomy*, as described by Hach, yields excellent results in post-thrombotic syndromes or in painful atrophie blanche ulcers. It now usually completes perforator dissection and is performed through the same incision. The fascia is split down to the malleolus with long scissors or with a fasciotome. The mode of action is not clearly understood, but it certainly compensates a chronic compartment syndrome, by reequilibrating sub- and epifascial venous pressure. Fibrotic alteration of the fascia induces a fatty degeneration of the muscles and impedes its effect on the venous return. These changes are partially reversible after fasciotomy. Post-operative improvement of the microcirculation is immediate, as demonstrated by tcpO2 measures.
- *Large excision of the ulcer* and surrounding tissues, including the fascia, associated if necessary to endoscopical dissection of perforators, stripping and fasciotomy may be the single solution to definitively heal refractory long-lasting ulcers, which become "autonomous". Long-term results are excellent.
- *Shave excision and grafting* are indicated in circular superficial ulcers on dermatofibrosclerosis.

Arterial Leg Ulcers: Treatment of PAOD

If arterial perfusion is not sufficient for healing, revascularisation is mandatory. It could be demonstrated that wound healing is impaired high above the threshold of chronic critical limb ischaemia. Leg ulcers with an arterial involvement and an ankle pressure below 110 mmHg that do not heal under conservative measures will benefit from revascularisation.

Revascularisation requires angioplasty (PTA or percutaneous transluminal angioplasty, if necessary with stent placement), if solitary occlusions in large arteries are present. Often bypass surgery is needed for arterial reconstruction to circumvent a seriously occluded area of the arterial vasculature.

In leg ulcers meeting the criteria of critical ischaemia, where arterial reconstruction is not possible, intravenous prostacyclin (Ilomedin, Iloprost®) or prostaglandin E (Prostavasin, Alprostadil®) should be considered before amputation is executed.

PAOD requires general measurements: Activity should be recommended, e.g. walking to the point of pain and alternate with rest periods. Risk factors should be minimised: Smoking has be stopped, and arterial hypertension needs medical control, as well as hypercholesterolaemia if dietary measures are not sufficient. Reduction of overweight is another goal. Daily aspirin is recommended for overall cardiovascular care.

Martorell's Ulcer

The most important is to recognise the disorder which is often mistaken for pyoderma gangrenosum or calciphylaxis (which shares identical histological features, e.g. calcified vessels). Best treatment is surgical debridement and split-thickness skin grafting.

Ulcerative Malignancy

Most often basal cell carcinoma and squamous cell carcinoma are the cause of malignant ulceration on the leg. Both are best treated with surgical excision, which normally requires skin grafting of the excisional wound. Radiotherapy is an alternative option when surgical treatment is not possible or reasonable.

Vasculitis

Cutaneous small vessel vasculitis (leukocytoclastic or hypersensitivity vasculitis) is the most common vasculitis seen in clinical practice that leads to vasculitic ulcers. It can be caused by different diseases (autoimmune disorders, systemic vasculitis, Henoch-Schönlein, infection, etc.) but also by external agents (e.g. drug reaction). In most cases (up to 50 %), no cause is identified. Treatment of vasculitis requires treatment of underlying disorder (when identified) or removal of external agents (e.g. drugs). The mainstay of symptomatic treatment is the use of anti-inflammatory/immunosuppressant agents, first of all corticosteroids. In ulcerative and necrotic vasculitis, systemic treatment is the rule, in dosages up to 60–80 mg/day of prednisolone equivalent. An infectious aetiology should always be ruled out before the introduction of immunosuppressive therapy. In severe cases, a combination of corticosteroids and other immunosuppressants like cyclophosphamide may be needed. Mild manifestations of vasculitis with only palpable purpura can be treated locally with steroid ointments/cream. Additional measures like leg elevation and compression of leg lesions may also be helpful (See Chap. 17).

For underlying collagenoses or systemic vasculitis, treatment should be performed according to actual recommendations (Sunderkotter and de Groot 2008).

Livedoid Vasculopathy

As a result of recent research (Kerk and Goerge 2013), livedoid vasculopathy has been defined as a coagulation disorder classified as a vasculopathy different from inflammatory vasculitis. To improve rheology, aspirin and pentoxifylline have been recommended earlier. In view of the basic coagulation disorder, systemic anticoagulation is suggested in recent recommendations (Sunderkotter and de Groot 2008). Treatment experience exists for the use of low molecular weight heparin (e.g. enoxaparin in a daily dosage of 1 mg/kg s.c.).

Calciphylaxis

The appearance of wounds in calciphylaxis with widespread necrosis is seductive for wide surgical debridement. In one of the largest series ($n=64$) in a retrospective study, in fact, 1-year survival was better in patients that received surgical debridement (Weenig et al. 2007). These data should be handled with care. In our own experience and according to other recommendations, wound care should be atraumatic. Extensive wound debridement is strongly discouraged, as even the slightest trauma, such as taking a biopsy, can lead to massive, new ulcerations leading to

new septic foci. The use of antibiotics however is important to prevent sepsis, which is the most dreaded complication of calciphylaxis and the main cause of death.

Another aim is to minimise risk factors: Reduction of serum concentrations of calcium and phosphate is mandatory. The impact of parathyroidectomy is discussed controversially, as there are data that show a benefit (Duffy et al. 2006), whereas others do not (Weenig et al. 2007). Oral anticoagulants should be avoided.

Intravenously applied sodium thiosulphate has become the most favoured treatment in calciphylaxis with documented good outcome. Sodium thiosulphate acts as a calcium-chelating agent which allows for successful mobilisation and clearance of the vascular and soft tissue calcium deposits.

Cinacalcet, which inhibits the production of parathormone by negative feedback, is another therapeutic option, which is often used in combination with sodium thiosulphate.

Bisphosphonate is the third treatment option with documented therapeutic success in many reports.

Pyoderma Gangrenosum (PG)

In active PG – due to pathergy phenomenon – surgical interventions, including aggressive debridement, have to be avoided because of the likely occurrence of new lesions at surgical sites and worsening of the original lesions.

In almost all cases of PG, systemic treatment is indicated. In 2005, an evidence-based review of the literature based on more than 350 patients (Reichrath et al. 2005) recommended only three medical treatments as first-line therapies for PG: daily oral corticosteroids, medium- to high-dose (0.5–1 mg methylprednisolone/kg/day) and pulsed-dose methylprednisolone 1 g/day for 1–5 days and oral daily cyclosporine 5 mg/kg/day. All other medical treatments that are documented in literature for the treatment of PG were considered to be of "experimental" nature in this review: dapsone, cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, clofazimine, thalidomide and intravenous immunoglobulins. One exception was infliximab (TNF-alpha inhibitor) that was evaluated as a first-line therapy but only in cases of PG associated with Crohn's disease. A placebo-controlled trial 1 year later demonstrated that infliximab was superior to placebo in all types of treated PG (Brooklyn et al. 2006). Its application however is in "off-label use".

In small and early lesions and also when systemic treatment is not possible, primary local treatment can be considered. First-line therapy is the use of potent topical or intralesional corticosteroids. Topical tacrolimus and pimecrolimus are other options.

In addition to systemic therapies, local wound care can be conducted with dressings appropriate to wound stage. Alternatively used for local treatment are – among others – benzoyl peroxide, 0.25 % acetic acid and polyhexanide-containing wound solutions that all have an antimicrobial effect and prevent from secondary infection.

Ecthyma Gangrenosum

Appropriate systemic antibiotic treatment should be initiated. It is crucial to have microbiological evidence of causative bacteria.

Bullous Pemphigoid (BP)

Autoimmune bullous dermatosis generally requires an immunosuppressant treatment, lasting for months. Oral steroids are considered the standard treatment. In bullous pemphigoid however potent topical steroids have also proven to be effective. For ulcerative BP on the lower leg, oral steroids can be recommended, starting at a daily dosage of 0.75 mg prednisolone equivalent. To minimise corticosteroid-related adverse effects, adjuvant immunosuppressive drugs may be used (see Chap. 11).

Necrobiosis Lipoidica

There is no standardised treatment for necrobiosis lipoidica. Ulcerative forms are generally difficult to treat.

Systemic corticosteroids are not an attractive option because most patients are diabetics.

Successful treatment has been documented in several case reports for the use of cyclosporine A and for TNF-alpha inhibitors. Topical calcineurin inhibitors are also promising.

Other treatment options are phototherapy (PUVA) and chloroquine.

Local Wound Treatment

In the last century, local wound treatment was performed for decades by applying dry gauze on the wound ground, allowing the wound to dry and to develop a hard crust.

In 1962, in an epochal article in *Nature*, Winter could demonstrate that epithelialisation is retarded by the dry scab which covers a superficial wound, and if the formation of the scab is prevented, the rate of epithelialisation is markedly increased.

Winter's change of paradigm that wound healing is accelerated in a moist wound environment led to the "golden age of moist wound treatment" which went along with the development of new dressings that were applied on the wound to keep it optimally moist: Hydrocolloids, hydrofibre, alginates, foams and many others have become standards in local wound care in the last 50 years.

Recent reviews however have disclosed that the effectiveness of these dressings might be overestimated and evidence for their efficacy is poor: In a systematic Cochrane review assessing the effectiveness of wound dressings for the treatment of venous leg ulcers, no evidence was found for a better efficacy of a special form of wound dressing nor that the type of dressing applied beneath compression did affect ulcer healing (Palfreyman et al. 2006).

In another critical review of the literature on the efficacy of modern dressings in healing chronic and acute wounds, no evidence was found that any of the modern dressings were better than another or better than saline or paraffin gauze (Chaby et al. 2007). And finally two very recent systematic reviews found no current evidence that either alginates or foam dressings were more effective than other wound dressings to treat venous leg ulcers (O'Meara and Martyn-St James 2013a, b).

Despite these findings, the impact of local wound care with regard to wound healing cannot be emphasised enough. Local wound care is more than just applying a wound dressing: Each wound is different and requires an individual approach to care.

For a structured approach to wounds, an international group of wound healing experts has provided a framework for a structured approach to wound bed preparation more than 10 years ago (Schultz et al. 2003); this approach represents a basis for optimising the management of open chronic wounds. The concept of wound bed preparation can be described by the acronym TIME, which stands in today's definition for Tissue management (T), Inflammation and infection control (I), Moisture balance (M) and Epithelial (edge) advancement (E) (European Wound Management Association (EWMA). Position Document. 2004).

TIME has become an internationally accepted approach to chronic wounds in the last 10 years and is also the topic of a position paper of the European Wound Management Association (EWMA) (2004).

TIME Framework: An Approach to Treat Chronic Wounds

T = Tissue Management

Tissue management means removal of non-viable tissue (debridement). The presence of necrotic or compromised tissue is common in chronic non-healing wounds, and its removal has many beneficial effects. It takes away non-vascularised tissue, bacteria and cells that impede the healing process. Unlike acute wounds, which usually only require debridement once, chronic wounds may require repeated debridement.

The balance of necrotic burden can be achieved with different forms of debridement:

- For *sharp superficial debridement*, curettes, scalpel or scissors are used. Local anaesthesia may be required. With a ring curette, it could be demonstrated that a single treatment accelerated healing of venous leg ulcers.
- *Surgical debridement* with removal of deep structures has to be executed in an operating theatre in general or regional anaesthesia.
- *Hydrosurgical debridement* with fluid jet technology is comparable to sharp and surgical debridement. Most often local anaesthesia is required.
- Other physical forms of debridement include *ultrasound* and *CO2 laser*.
- *Autolytic debridement* is performed with dressings with a high water content, such as hydrogels and hydrocolloids. Enzymatic activity in wound fluid leads to lysis of fibrin

or necrotic tissue. Autolytic debridement is slow and often not effective.

- *Enzymatic debridement* can be induced by proteolytic enzymes in ointments or solutions. Proteases are derived from animals, plants or bacteria. Clostridiopeptidase A, a bacterial collagenase, and streptokinase, an inducer of plasmin which degrades fibrin, are both commercially available.
- For *biosurgical debridement*, maggots (fly larvae of *Lucilia sericata*) are used that produce proteolytic enzymes. Maggots are raised in a sterile environment and are placed on the wound, under a loose bandage in a cagelike dressing, where they selectively degrade dead or dying tissue. To reduce pain, maggots can be placed in a bag or pouch on the wound to avoid direct contact to the wound ground. The efficacy of maggot debridement therapy has been demonstrated in leg ulcers (Dumville et al. 2009), pressure ulcers (Sherman 2002) and diabetic foot ulcers (Sherman 2003). The treatment is safe, but acceptance of patients may be problematic.

I = Inflammation and Infection Control

All chronic wounds are colonised by bacterial or fungal microorganisms. Bacteria may stimulate a persisting inflammation and lead to the production of inflammatory mediators and proteolytic enzymes, thus promoting chronicity of wounds. Evidence shows that a bacterial burden of 10^5 organisms or more per gram of tissue seriously impairs healing.

A bacterial overload with $>10^5$ microorganisms/gram tissue – in the absence of systemic signs of infections – is referred to as critical colonisation. As mentioned previously, microbiological investigations (swab) should be limited to situations where there is a clear indication that the bacterial load is implicated in delayed healing.

In all chronic wounds, non-specific antimicrobial measures are reasonable to restore bacterial balance: This includes removing of nonvital tissue, exudate control, regular cleansing with sterile saline and/or superficial debridement.

If a critical colonisation is suspected, specific antimicrobial treatment is indicated and is most often performed with antiseptics like polyhexanide, octenidine or silver-containing wound dressings, even if evidence from systematic reviews is low (Storm-Versloot et al. 2010).

Biguanide antiseptics polyhexanide and octenidine, both with bactericidal effect against gram-positive and gram-negative bacteria and also fungicidal properties, can be used as solution: When changing dressings, a moist compress is applied and kept on the wound for 3–5 (octenidine) or 10–15 min (polyhexanide). Both antiseptics can also be applied together with modern wound dressings (hydrofibres, alginates, foam substances).

Silver, which demonstrates good antimicrobial efficacy against gram-negative and gram-positive bacteria, can be applied on wounds as silver nitrate solution or silver sulphadiazine cream. Most frequently used today is silver incorporated in any form of wound dressing (e.g. foam, hydrofibre, hydrocolloid).

Antiseptic treatment can also be conducted with iodine-containing products (PVP-iodine/povidone-iodine as solution or as a hydrosomal wound gel or cadexomer-iodine), honey or honey-containing dressings or acetic acid solution (<1 % applied for 3–5 min).

Systemic antibiotics may occasionally be indicated in critical colonisation, when local antiseptic treatment is insufficient. An uncontrolled use increases bacterial resistance. Symptomatic infection with erysipelas, cellulitis, fever and systemic signs in laboratory investigation has to be treated with systemic antibiotics. For the selection of appropriate antibiotics, a microbiological diagnosis is relevant.

M = Moist Control

Dressing

In the course of normal healing, a wound goes through different phases (inflammation–proliferation–reparation/maturation/remodelling). In these phases a varying amount of exudate is produced, with the peak in the inflammatory phase. Chronic wounds – due to chronic inflammation – produce chronic exudate, which causes the breakdown of extracellular matrix proteins and growth factors, prolongs inflammation, inhibits cell proliferation and leads to the degradation of tissue matrix. Chronic exudate delays healing and causes

maceration of the surrounding skin. The management of exudate therefore is crucial.

Compression therapy is one important measure to reduce exudate, not only in venous ulcers, but in the treatment of all chronic wounds – if there is no relevant arterial involvement.

To control exudate, selection of an appropriate dressing is relevant. Modern dressings are all able to keep a wound moist, but they differ in the degree of absorbing exudate. As exudate production correlates with the wound stages, the aspect of the wound ground may be helpful to estimate exudate release: A yellow colour and a sloughy wound ground are typical for the inflammatory phase which may go together with heavy exudate production. Red colour means granulation tissue and less exudate, while pink is the colour of epithelialisation.

Wounds with high exudate production (early inflammatory phase) can be treated with foams, hydrofibre dressings and alginates. They all have a good capacity to absorb exudate.

- *Foam dressings* are sheets of foamed polyurethane or silicone. They have a variable thickness and structure and are highly absorbent but can transmit moisture vapour and oxygen. In many countries they have become most popular in modern wound care.
- *Hydrofibre* dressings are almost entirely composed of sodium carboxymethylcellulose fibres. They absorb exudate immediately and form a soft coherent gel. They retain exudate within their structure even under compression and do not allow horizontal spreading of fluid, thus protecting the surrounding skin from maceration.
- *Alginates* are biodegradable fibre products derived from brown seaweed. Alginates can absorb 15–20 times their weight of fluid. They partly dissolve on contact with wound fluid to form a hydrophilic gel.

If relevant bacterial load is suspected, silver-impregnated foam, hydrofibre or alginate dressings may be considered.

Wounds with less or little exudate can be treated with hydrocolloid dressings, low-adherent dressings or films:

- *Hydrocolloids* consist of a layer of hydrophilic colloidal gel-forming particles, made of sodium carboxymethylcellulose, gelatin, pectin, elastomers and adhesives that are bonded to a carrier of semipermeable film or a foam sheet. Hydrocolloids absorb liquid and form a gel on the wound surface that maintains an optimal moist environment. This promotes granulation, mediates local fibrinolysis, stimulates capillary proliferation, enhances the concentration of growth factors within the wound fluid and increases the rate of re-epithelialisation. Hydrocolloids should be left on the wound for at least 2–3 days. When dressings are changed, the gel in the dressing, which may be yellow and malodorous, may be mistaken for infection.
- *Low-adherent dressings* are designed to reduce adherence at the wound bed. They are manufactured in the form of tulles, which are open-weave cloth soaked in soft paraffin or chlorhexidine. They allow exudate to pass through into a secondary dressing.
- *Semipermeable films* consist of sterile plastic sheets of polyurethane coated with hypoallergenic acrylic adhesive and are used mainly as a transparent primary wound cover. Although they are impermeable to fluids and bacteria, they are permeable to air and water vapour.

Dressings have to be changed according to the stage of the wound. In exudative ulcers, they should be changed quite regularly, whereas in later healing stages, it is preferable to avoid frequent changes of dressing, as this interferes with healing and may compromise newly formed tissue, disturb the patient's life and enhance the costs of treatment.

Negative-Pressure Wound Therapy (NPWT) or Vacuum-Assisted Closure (VAC)

NPWT or VAC can be used on almost any wound and provides optimal exudate control and promotion of granulation. The primary intention is to remove chronic oedema and fluid from exudative wounds, stimulate granulation, increase local blood flow, impede nosocomial infection of the wound and isolate infected ulcers. A foam dressing under hermetical occlusion is applied on the ulcer and connected with an aspirating device assuring a controlled continuous or intermittent sub-atmospheric pressure (between 55 and 200 mmHg below ambient pressure). This technique may induce granulation in refractory

venous ulcers, decubitus, infected wounds or even in arterial ulceration.

Surrounding Tissues

When exudate is not sufficiently controlled, maceration may occur around the margins of the wound. It is manifested as white, soggy tissue. For protection, zinc paste may be used or liquid film-forming acrylate.

If contact dermatitis is observed, local corticosteroids are indicated for a short-term use. Patients with leg ulcers frequently acquire clinically relevant contact sensitisation. In patch testing, sensitisation can be found in up to two-thirds of patients. Sensitisations are often found for balsam of Peru, amechol, fragrance mix, wool wax alcohols and rosins but also to wound dressing materials.

E = Edge Effect

Effective healing requires the re-establishment of an intact epithelium. If the epidermal margin fails to migrate across the wound bed, there are many possible reasons, including hypoxia, infection, desiccation, dressing trauma, overgrowth of hyperkeratosis and callus at the wound margin. Careful clinical observation can help to determine the cause.

Surgical Local Wound Treatment

Skin grafting can dramatically shorten the time to complete healing. The wound has to be well conditioned, with a good granulation tissue in the wound ground.

Pinch grafting (or Reverdin graft) may be performed in outpatients. Small bits of partial- or full-thickness skin from a healthy area are obtained by elevating the skin with a needle and cutting across its base. The pinch is removed and seeded in the site to be covered.

Split-thickness and meshed grafts are indicated in large ulcers, where healing by secondary intention would last for months. Meshed grafts are also used to cover a wound after deep debridement or large excision of a fibrotic ulcer bed.

Advanced Wound Treatments

Besides conventional local wound treatment, a number of new therapeutic modalities exist that can be summarised as advanced treatments. Some of them have been used for years while others are still experimental. We will focus on treatments that have been established and are already widely used:

Growth Factors

Growth factors are of great importance in normal wound healing. They are produced by many cells involved in different wound phases. It is suggested that in chronic wounds, degradation of growth factors by up-regulated proteases is one factor that is responsible for the delay in healing.

In a number of experimental approaches, exogenous growth factors were supplied to the wound microenvironment to stimulate healing. An efficacy in wound healing could only be demonstrated for platelet-derived growth factor (Wieman et al. 1998). Until today a recombinant form of PDGF-BB (becaplermin) is the only growth factor that was licensed and distributed for topical application in diabetic ulcers.

Protease Inhibition

A new generation of wound dressings was developed to interact with the wound to stimulate healing. Examples are protease-modulating dressings, which stimulate healing by inactivating excess of proteases (Cullen et al. 2002).

Tissue-Engineered Skin Equivalents

For years wound research has tried to create "artificial" living skin substitutes. A number of epidermal, dermal or bi-layered skin equivalents have been developed. Most of them are meant for acute wounds, especially burn wounds. For the treatment of leg ulcers, two skin equivalents are commercially available:

- *Apligraf* is a living bilayered skin equivalent that consists of an epidermal layer derived from human keratinocytes and a dermal layer containing human fibroblasts and bovine collagen. It was demonstrated that the skin equivalent that can be easily applied on a conditioned wound improves wound healing in venous leg ulcers and diabetic foot ulcers (Falanga et al. 1998; Veves et al. 2001).
- EpiDex is an autologous epidermal equivalent containing keratinocytes from the patient's own outer root sheath (ORS). To cultivate epidermal

equivalents, the necessary cells are extracted by plucking the patient's anagen head hairs. The outer root sheath of isolated hair follicles contains precursor cells for epidermal keratinocytes. It could be shown that EpiDex was as effective as split-thickness skin autografting in the promotion of healing and complete closure of recalcitrant vascular leg ulcers (Tausche et al. 2003; Ortega-Zilic et al. 2010).

Water-Filtered Infrared A (wIRA)

Water-filtered infrared A (wIRA) radiation can improve the healing of acute and chronic wounds both by thermal and thermic as well as by non-thermal and nonthermic effects. wIRA increases tissue temperature, oxygen partial pressure and perfusion. Application of wIRA proved to be effective for the treatment of chronic venous stasis ulcers.

Extracorporeal Shock Waves

Extracorporeal shock waves are a sequence of sonic pulses characterised by high peak pressure over 100 MPa, fast pressure rise and short life-cycle. In urology, extracorporeal shock wave lithotripsy (ESWL) has been successfully used for years for the treatment of urolithiasis. Extracorporeal shock wave therapy (ESWT) can also be used for recalcitrant skin ulcers. Several studies in the last 10 years have shown that ESWT promotes angiogenesis, increases perfusion in ischaemic tissues, decreases inflammation, enhances cell differentiation and accelerates wound healing (Stieger et al. 2013).

Future

In adult organisms, stem cells that can divide and differentiate into specialised cell types act as a repair system for the body. It sounds promising to apply stem cells in a wound where they can differentiate into cells that are required for the respective wound stage. It was demonstrated that application of stem cells derived from bone marrow aspirate – delivered in a fibrin spray – was able to accelerate wound healing (Falanga et al. 2007). Another interesting approach is application of stem cells in a biomatrix to treat wounds (Vojtassák et al. 2006).

Finally there are high expectations in gene therapy: This treatment uses DNA that encodes a protein required for treatment of a disease. To get the DNA inside cells of the body, DNA is packed within a vector. Inside the cells, DNA becomes expressed and starts producing the therapeutic protein. To treat wounds, locally applied genes will induce production of growth factors and cytokines in cells of the wound. This has been demonstrated for PDGF-B, PDGF-A, VEGF and EGF (Eming et al. 2007).

The future of wound treatment looks promising (Figs. 49.1, 49.2, 49.3, 49.4, 49.5, and 49.6).

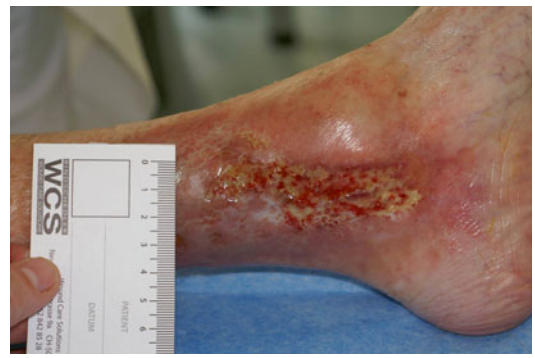


Fig. 49.1 Venous leg ulcer loco classico around the medial ankle

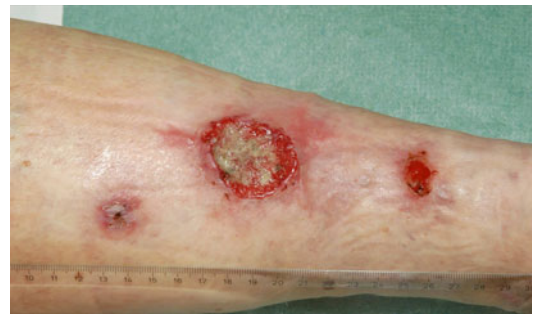


Fig. 49.2 Ulcerative basal cell carcinomas on the lower leg

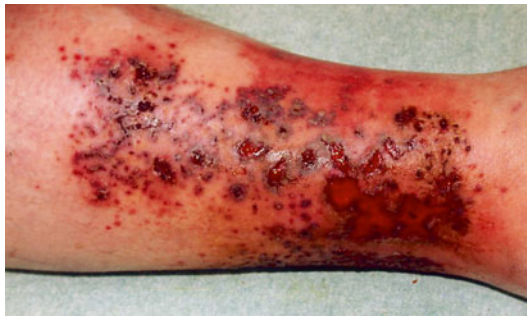


Fig. 49.3 Necrotic lesions and ulcerations due to small vessel vasculitis

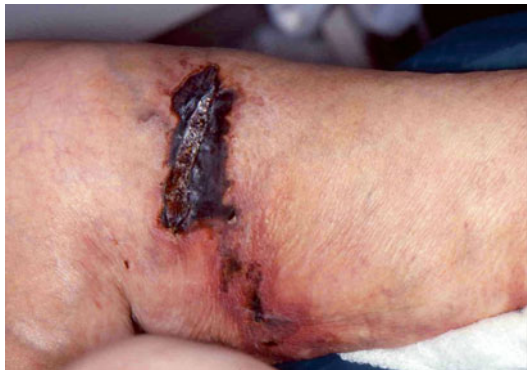


Fig. 49.4 Painful necrotic ulcer with livedoid extension caused by calciphylaxis

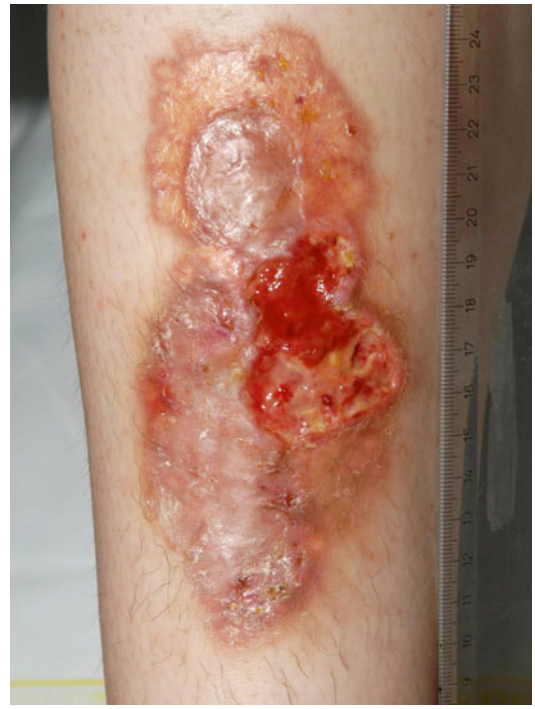


Fig. 49.6 Ulcerative necrobiosis lipoidica

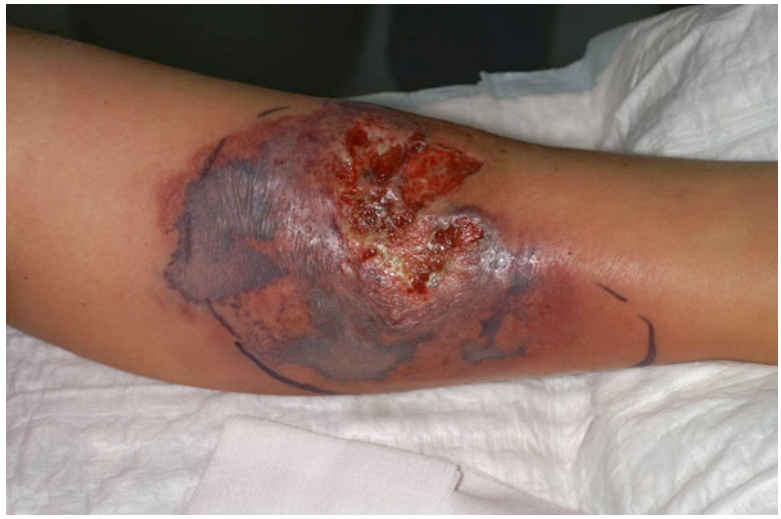


Fig. 49.5 Pyoderma gangrenosum

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Leishmaniasis

50

Meltem Onder and Mehmet Ali Gürer

Key Points

- Leishmaniasis usually affects the face and leaves a depressed scar.
- Leishmaniasis is diagnosed by the presence of the leishmania parasites in a superficial smear or biopsy of the ulcer.
- Treatment depends on the clinical form of the disease.
- Intralesional antimonial (0.2–0.4 ml sodium stibogluconate intradermally three times a week for a total of 15 injections) is advocated.
- 20 % paromomycin sulfate is a topical medication.
- Cryotherapy with liquid nitrogen (−195C) can be applied once or twice weekly up to 6 weeks. The combination of superficial cryotherapy and intralesional antimony is more effective than each technique used alone.
- Thermotherapy with radio-frequency waves is effective as antimony therapy.
- Systemic use of antimonials, amphotericin-B, dapsone, allopurinol, and rifampicin has shown effective activity against leishmania.
- The most successful therapy is intralesional therapy because of its efficacy, absence of toxicity, and low cost.

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Definition and Epidemiology

Leishmaniasis is a protozoan disease with different clinical manifestations depending both on the infecting species of leishmania and on the immune response of the host. Its transmission occurs through the bite of a sandfly infected with leishmania parasites. It occurs in two forms, visceral and cutaneous leishmaniasis. Visceral leishmaniasis, also known as *kala-azar*, is a systemic disease, and it is usually diagnosed by the presence the organisms in the spleen, lymph gland, or bone marrow aspirates. Cutaneous leishmaniasis usually occurs in the form of an ulcerated nodule on the skin.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_50, © Springer-Verlag Berlin Heidelberg 2015

It is seen in all races and both sexes. It is a common disease especially in the south-east of Anatolia in Asia. Approximately 400,000 new cases occur each year, and 400 million people are at risk of the disease.

Basic Concepts of Pathogenesis

Leishmaniasis is caused by parasites of the *genus Leishmania*. Sandflies from the *genus Phlebotomus* transmit the disease. Only the female sandflies are bloodsucking, and they prefer to feed at night. The leishmania parasite exists in two forms, the promastigote or leptomonal form and the amastigote or leishmanial form. The first one is seen in the gut of the sandfly. It is flagellated and extracellular. The amastigote form occurs in the human host where the organism exists intracellularly and nonflagellated. The transmission occurs when the exposed area of the skin is bitten by an infected sandfly; at that time, the organism is engulfed by dermal macrophages. The sandfly becomes a vector by either biting the lesions of infected humans or feeding on animals which harbor the organism.

Clinical Presentation

Leishmaniasis usually affects the face, neck, and arms and legs which are easily bitten by a vector (Figs. 50.1, 50.2, and 50.3). The bite commonly presents as a solitary red papule which enlarges to a plaque or nodule. The lesion often develops into an ulcer, which is well demarcated. Itching pain is very mild. After approximately 6–12 months, the ulcer spontaneously regresses. It leaves a depressed scar with hypo- or hyperpigmentation. The wound may become superinfected, leading to misdiagnosis. A generalized papular eruption may also develop representing a hypersensitivity reaction.

In AIDS patients, atypical manifestations of cutaneous leishmaniasis occur as an opportunistic infection. One to 3 % of AIDS patients in endemic areas suffer from visceral leishmaniasis.

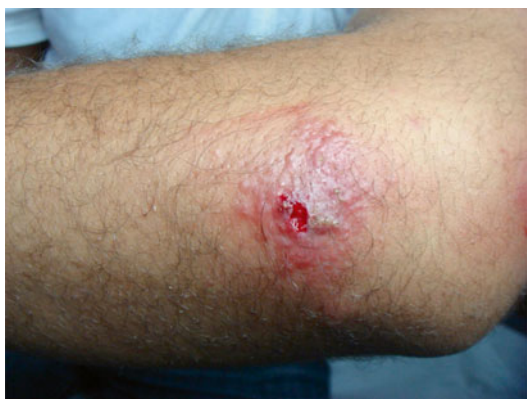

Fig. 50.1 Leishmaniasis (Courtesy of Prof Dr. Hamdi Memisoglu Adana, Turkey)

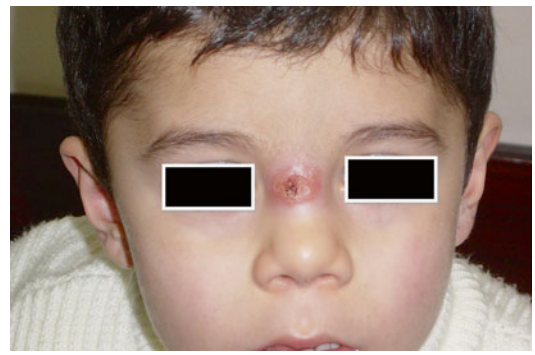

Fig. 50.2 Leishmaniasis in a child (Courtesy of Prof Dr. Hamdi Memisoglu Adana, Turkey)

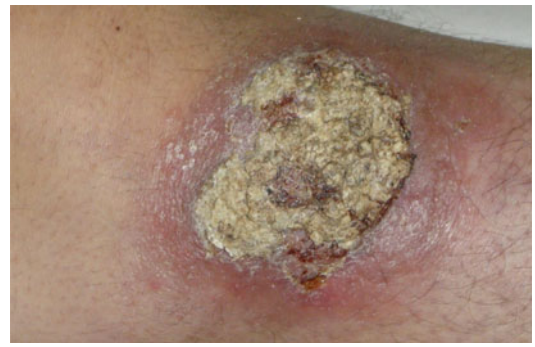

Fig. 50.3 Leishmaniasis (Courtesy of Prof Dr. Hamdi Memisoglu Adana, Turkey)

Diagnosis

Leishmaniasis is diagnosed by demonstrating the organisms in a superficial smear or biopsy of the ulcer. The smears stained with Giemsa or Wright's

stain are often not satisfactory, because the lesion usually contains secondary infection. Moreover, the parasites are found much deeper in the tissue.

Skin biopsy reveals epidermal or dermal changes depending on the type and stage of the disease. Epidermal changes are hyperkeratosis, parakeratosis, and follicular plugging. Epidermal atrophy, acanthosis, may be seen. The basal layer may be degenerated. In the dermis, there is predominantly a mononuclear infiltrate consisting primarily of lymphocytes and histiocytes. The histiocytes may be filled with leishmaniasis bodies.

In suspected cases, both biopsy and touch preparation (imprint) from a biopsy specimen improve the sensitivity of diagnosis.

The intradermal leishmanin test (Montenegro reaction) and other serologic tests are of little value in regions where the disease is endemic because of previous exposure to the parasite. Immunofluorescence studies should be interpreted with caution and only if antibody levels are very high. Cultures of aspirated material from the lesions on NNN (Nicolle, Novy, MacNeal) blood agar were found to be moderately sensitive monoclonal antibodies to parasite surface antigens and have been used to identify leishmania species. Polymerase chain reaction (PCR) can be used to distinguish between the different species of *Leishmania*.

Differential Diagnosis

The natural history of cutaneous leishmaniasis is characteristic. It should be suspected in any patient with chronic inflammatory skin lesions who has visited or resided in the areas where leishmaniasis is endemic. The disease is on the rise due to travel, immigration, and military activity. The differential diagnosis may differ depending on the location of skin manifestations. Lip leishmanias is fairly common. It resembles herpes labialis, syphilitic chancre, squamous cell carcinoma, and fixed drug eruption. The differential diagnosis can be summarized in Table 50.1.

Table 50.1 The differential diagnosis of leishmaniasis

Acute infections	
Fungal	
Sporotrichosis	Microbiology, culture
Blastomycosis	Microbiology, culture
Bacterial	
Mycobacteriosis	
Leprosy	Microbiology, culture
Lupus vulgaris	Diascopia, histopathology
Tuberculosis verrucosa	Violaceous border
Treponematoses	
Yaws	
Pinta	
Syphilitic gumma	
Staphylococcal/streptococcal pyodermas	
Impetigo	
Ecthyma	
Furunculosis	
Insect bite	
Viral	
Chronic infections	
Inflammatory	
Sarcoidosis	
Discoid lupus erythematosus	Histopathology
Foreign body granuloma	
Keloids	
Neoplastic	
Cutaneous T cell lymphoma	Histopathology
Jessner's lymphocytic infiltrate	Histopathology
Basal cell carcinoma	Histopathology
Keratoacanthoma	Histopathology

General Principles of Treatment

- Leishmaniasis is a worldwide health problem and there is no ideal therapy. It depends on the clinical form of the disease.
- The important measures to control leishmaniasis in areas where it is endemic are health education, elimination, or control of reservoir and hosts and vectors and early treatment of patients.

- Patients with lesions on the face or another cosmetically important area should be treated to reduce the size of the resultant scar.
- The most successful therapy is intralesional therapy. Systemic chemotherapy is recommended for very extensive lesions. Uncomplicated lesions do not need to be treated aggressively. Simple excision, cryosurgery, and topical therapy are usually sufficient.

Recommended Therapies

(a) *Systemic chemotherapy*
- I. Antimonials
  - Sodium stibogluconate (Pentostam®)
  - Meglumine antimoniate (Glucantime®)
- II. Amphotericin-B, dapsone, allopurinol, rifampicin, and isoniaside
- III. Pentamidine
- IV. Azole derivatives
  Ketoconazole-itraconazole-terbinafine
- V. Others
  Trimethoprim-sulfamethoxazole
  Metronidazole
  Monomycin
  Methyluracil
  Mebendazole
  Levamisole
  Furazolidone
  Miltefosine

(b) *Intralesional therapy*
- I. Antimonials
- II. Emetine hydrochloride
- III. Mepacrine
- IV. Hypertonic sodium chloride solution

(c) *Topical therapy*
- I. Paromomycin
- II. Diminazene aceturate
- III. Chlorpromazine
- IV. Local application of meglumine antimoniate under occlusive dressing

(d) *Local measures* (*physical*)
- I. Cryotherapy
- II. CO_2 laser
- III. Excision
- IV. Localized heat
- V. Photodynamic therapy

Systemic Chemotherapy

Antimonials have been used to treat most forms of leishmaniasis. They inhibit the amastigote's glycolytic activity and fatty acid oxidation. Two available preparations of pentavalent antimony are sodium stibogluconate (Pentostam ®) and meglumine antimoniate (Glucantime ®). The recommended dosage is 20 mg/kg per day for 20 days intravenously or intramuscularly. The parenteral route of administration is expensive and impractical in rural areas in which leishmaniasis is so prevalent. Moreover, the side effects, such as arthralgias, reversible elevations of hepatocellular enzymes, leukopenia, thrombocytopenia, and electrocardiogram changes, make systemic antimonials an unattractive choice for the treatment. All side effects resolve spontaneously after treatment. Glucantime remains the first-line treatment for cutaneous leishmaniasis.

Several oral agents have been tried instead of the parenteral antimonials. Amphotericin-B, dapsone, and allopurinol have shown effective activity against leishmania organism. Rifampicin 1,200 mg/day in two divided doses is well tolerated. It is simple to administer, cheap, more effective, and less toxic than other available oral drugs.

Pentamidine at a dose of 3–4 mg/kg once weekly for at least 4 months may help in diffuse cutaneous leishmaniasis.

A 600 mg dose of ketoconazole has been shown to be effective. Itraconazole 7 mg/kg per day for 4–8 weeks has been encouraging, but it cannot be used as the single agent.

Miltefosine is an alkyl phospholipid (hexadecylphosphocholine); at a dose of 50–100 mg/day, it can be used for 28 days. The limitations are relatively high cost, gastrointestinal side effects, and occasional hepatotoxicity and nephrotoxicity.

Intralesional Therapy

Intralesional antimonial regimen involves the application of 0.2–0.4 ml sodium stibogluconate intradermally three times a week for a total 15 injection. The recurrence rate with this regimen is only 4 %. It is advocated,

because of its efficacy, absence of toxicity, and low cost.

Topical Therapy

Today topically applied drugs are being used to minimize systemic toxicity and concentrate medication of the specific sites on the skin. Recently paromomycin sulfate 20 % was found to be a promising topical medication. It is an aminoglycoside and has an antibiotic spectrum. It is applied twice daily for 10–20 days. Some redness and irritation can be seen.

Local Measures

Cryotherapy, local excision, CO_2 lasers, and localized heat have all been tried with variable results. Freezing the lesions for 30–60 s until 2 mm margins are obtained has proved lethal to leishmania organisms. Liquid nitrogen is a relatively simple and safe alternative with few or no systemic adverse effects.

Thermotherapy, using radio-frequency waves (three treatments of 50 °C for 30 s at 7 day intervals), is effective, although the device is expensive.

Photodynamic therapy

After curettage of the lesion, topical application of methyl-amino-oxo-pentanoate (MAOP) for 3 h, followed by photodynamic red light, is used effectively.

Alternative and Experimental Treatments

Interferon

More recently subcutaneous injection of IFN-γ has proved effective for regression of lesions by stimulating the macrophages of the Th1 line.

Vaccination

It has been performed on animal models and human beings with virulent promastigotes. Reduced rates of subsequent injection have been noted in the vaccinated populations. The development of an effective, noninfectious vaccine is problematic.

Immunotherapy

The mixture of heat killed cultured leishmania promastigotes plus live lyophilized Bacille de Calmette et Guérin (BCG) can be combined for chemotherapy. It is recommended as a single intradermal injection and applied every 6 weeks.

Sitamaquine (WR 6026)

This is a primaquine analogue, *an 8-aminoquinoline derivative*, *is a once-a-day oral treatment for visceral leishmaniasis that* has shown effectiveness in animal models (Loiseau et al. 2011).

Liposomal Amphotericin

This has proved effective, but it is undergoing clinical trials.

Oral Zinc Sulfate

5 mg/kg of zinc sulfate orally can be recommended in the prophylaxis of cutaneous leishmaniasis (Sharquie et al. 2001).

A Therapeutic Algorithm

Global incidence of leishmaniasis is estimated at two million cases per year; approximately three fourths are cases of cutaneous leishmaniasis (CL). Treatment of CL should be decided by the clinical lesions and etiological species (Table 50.2). There are number of therapies for various forms of leishmaniasis and the preferences for first line and second line vary on the type of disease and are often guided by regional practice. In Table 50.3 recommended treatment dose, duration, main side effects, and risks are summarized. Basic treatment options regarding childhood, pregnancy, and lesions type like simple and complex may change.

Table 50.4 summarizes these options.

The growing resistance of parasite to antileishmanial drugs suggests that the currently used monotherapy needs to be reviewed. Local cryotherapy can be combined with intralesional treatment options and oral treatments. Combination

Table 50.2 Leishmanial parasites and treatment regimens

Species	Treatment
L. Major (Middle East and Africa)	Local
	Cryotherapy
	Topical paromomycin
	Intralesional stibogluconate(Sb)
	Intralesional Sb+cryotherapy
	Heat therapy
	Systemic
	Fluconazole
	Systemic stibogluconate
	Systemic stibogluconate+pentoxifylline
L. Tropica (Middle East and the Mediterranean)	Local
	Topical paromomycin
	Intralesional stibogluconate(Sb)
	Intralesional Sb+cryotherapy
	Systemic
	Systemic stibogluconate
	Systemic stibogluconate+pentoxifylline
	Amphotericin
	Allopurinol
All species and recurrences	Amphotericin or liposomal amphotericin
	Systemic stibogluconate
	Topical imiquimod
	Miltefosine
	Immunotherapy

Table 50.3 Dosage recommended period of treatment

Treatment	Dose	Duration	Risks, side effects
Local injection of pentavalent antimonials	IL, IM 1 ml/cm^2	Per week until recovery	Local side effects,
Meglumine antimoniate (Glucantime^R)	For infants 10 mg/kg/day		Hepatic renal failure
Stibogluconate (Pentostam^R)			Drug resistance
			Contraindication: pregnancy
Doxycycline	200 mg/day	15–30 days	Phototoxicity
Azithromycin	500 mg/day	5 days/4 months	Recurrence
Pentamidine	IM 2–4 mg/kg	3 days per week	Hypertension
			Tachycardia
			Skin rush
			Renal failure
			Pancreatic toxicity
Paromomycin	15 mg/kg/day	20 days	Erythema
Pentoxifylline	400 mg/oral/day	30 days	Recurrence (combination requires)
Allopurinol	20 mg/kg/day	30 days	Cardiotoxicity, elevation of liver test values
Metronidazole	1.5 g/day	15–30 days	Recurrence (combination requires)

Table 50.3 (continued)

Treatment	Dose	Duration	Risks, side effects
Amphotericin B	2.5–5 mg/kg/day	15–30 days	Renal insufficiency, electrolyte problem
Ketoconazole	100–400 mg/day	28 days	Hepatotoxicity
Fluconazole	200 mg/day	6 weeks	Hepatotoxicity
Itraconazole	400 mg/day	8 weeks	High costs and recurrence risk
CO_2 laser	Pulse 0.5–5 s	Every week	Local anesthesia is required
Electrotherapy	5–15 miliamper, 40 W	4–6 weeks	Local side effects
Cryotherapy	15–20 s freezing	2–3 months weekly	Hypopigmentation, satellite lesion
Imiquimod	5 % cream	20 days	Expensive in poor countries
Thermotherapy	39–40 °C	20 days	Painful
Miltefosine	50–100 mg/kg/day	30 days	Digestive troubles, increasing transaminases
			Abortion in pregnant women, high cost

Table 50.4 Basic treatment options

Simple lesion	*Complex lesion*
Cryotherapy	Amphotericin B
Thermotherapy	Ketoconazole, itraconazole, fluconazole
Intralesional antimonials	Miltefosine
Childhood	*Pregnancy*
Cryotherapy	Only local treatment
Intralesional antimonials	
Miltefosine (up 3 years)	

therapy with amphotericin B and miltefosine is also recommended.

Prevention

The preventive treatment is collective, and it is based on the eradication of the vector, eradication of the reservoir, and protection against the bite of sandfly. Eradication of the reservoir is important with the diagnosis and treatment of affected humans and killing the infected dogs in endemic zones. The use of powerful insecticides is recommended. Avoidance of outdoor activities during which the Phlebotomi are most active, wearing protective clothing, and installing mosquito nets around beds, doors, and windows are also very important.

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Lentigo Maligna

51

Jean Kanitakis

Key Points

- Lentigo maligna is a form of melanoma in situ appearing on chronically sun-exposed areas in elderly patients. It may progress, albeit slowly, to an invasive melanoma (lentigo maligna melanoma). The diagnosis of lentigo maligna requires adequate biopsy and histological examination.
- High levels of evidence based on prospective studies or randomised controlled trials are not available to establish definite recommendations for the management of lentigo maligna.
- The preferred treatment ensuring the lowest rate of recurrences is surgical excision with tumour-free margins. This can be performed as standard local excision with predefined safety margins, staged surgical excision or Mohs micrographic surgery (traditional or "slow"). The latter margin-controlled techniques are associated with the lowest recurrence rates.
- Nonsurgical treatments can be applied when surgical excision is incomplete or not possible because of anatomic/functional concerns, patient's age and/or comorbidities. They include mainly imiquimod, radiotherapy and cryotherapy. These options do not allow histological verification of margin clearance and have therefore higher recurrence rates.

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Definition and Epidemiology

Lentigo maligna (LM), also known as malignant freckle, Hutchinson's melanotic freckle and melanosis circumscripta precancerosa of Dubreuilh, is a clinicopathologic subtype of malignant melanoma (MM), accounting for 4–15 % of all MM cases. Although its precise prevalence is unknown, this seems to be increasing as a consequence of population ageing and increased sun exposure over the past decades. LM has long been considered as a precursor of MM, but the current trend is to consider it as a type of MM in situ in a radial growth phase. Clinically, it manifests as an asymmetric flat macule with irregular contours. It is light or dark brown in colour, often with several hues including black or whitish areas, reflecting partial regression, and may

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_51, © Springer-Verlag Berlin Heidelberg 2015

exceptionally be completely amelanotic. It develops on chronically sun-exposed body zones, typically the face (cheeks, forehead, temple, periocular skin) and more rarely on extrafacial sun-exposed body zones (arms, legs) of middle-aged and elderly patients with fair skin showing signs of sun damage (Fig. 51.1). LM may be difficult to distinguish clinically from solar lentigo, early seborrheic keratosis, pigmented actinic keratosis and lichen planus-like keratosis. Although the vast majority of solar lentigos are benign, they may rarely progress to LM. LM expands radially over months or years and may in the long term invade the dermis (vertical growth phase), thereby progressing to lentigo maligna melanoma (LMM), which has potential for metastatic spread and can cause death. This progression manifests clinically with the development of a thickened zone or a raised nodule. The rate of progression is poorly quantified. The lifetime risk has been reported to be as low as 5 % and as high as 50 %. The time to progression may vary from a few months to over 30 years; therefore, this progression may be unlikely within the lifespan of elderly people.

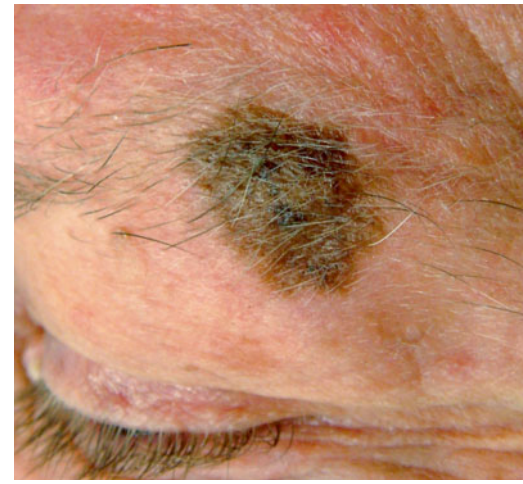

Fig. 51.1 Lentigo maligna: acquired pigmented macule with irregular contours and heterogeneous-speckled brown colour on the forehead of a skin type II Caucasian man

Diagnosis

The diagnosis of LM (and LMM) can be suggested clinically and may be supported by non-invasive imaging techniques such as dermatoscopy and in vivo reflectance confocal microscopy. By dermatoscopy, LM shows asymmetrical pigmented follicular openings, zones of rhomboidal pigmentation, annular-granular structures and grey pseudo-network. In vivo confocal reflectance microscopy shows epidermal disarray, pagetoid infiltration by large (>20 μm) round refractile cells and non-edged dermal papillae. Even though non-invasive imaging methods are useful in the diagnosis of LM, biopsy and histological examination are required to establish a definitive diagnosis. Although for suspicious lesions an excisional biopsy is recommended because it is easier to interpret pathologically and minimises the risk of missing the worst area of the tumour (including LMM), this is often not feasible for large lesions located on the face, as is often the case of LM. An incisional or punch skin biopsy is acceptable and should be taken from the clinically most suspicious area (most infiltrated/palpable, darkest or with the highest pigmentary irregularity). Biopsy of more than one site can reduce the risk of missing subclinical dermal microinvasion (LMM). Indeed, up to 22 % of cases diagnosed as LM by incisional biopsy are reclassified as LMM upon examination of the completely excised lesion. Non-invasive imaging techniques (such as Wood lamp illumination, dermatoscopy and in vivo reflectance confocal microscopy) are helpful to define the most informative area wherefrom the biopsy should be taken and to define the infraclinical limits of the lesion, which is useful for the further surgical treatment of the lesion as atypical melanocytes characteristic of LM may extend far beyond the clinically visible limits of the lesion.

Histopathological examination of LM shows a lentiginous proliferation of atypical, often spindle-shaped melanocytes within the basal epidermal layer; these often have a vacuolated

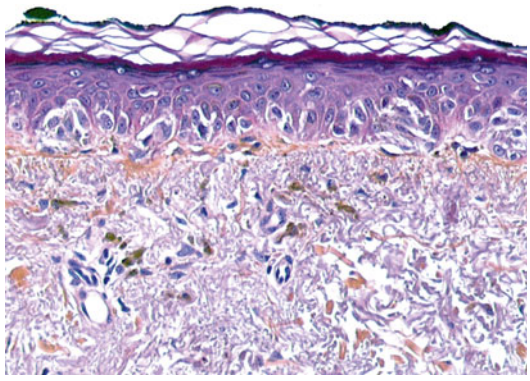

Fig. 51.2 Lentigo maligna: microscopic examination shows a lentiginous proliferation of atypical melanocytes in the basal cell layer of the epidermis, tending to form small nests. Note the presence of epidermal atrophy (manifesting with flattening of the dermal-epidermal junction), heavy elastosis and melanophages in the dermis (haematoxylin-eosin-saffron stain)

cytoplasm and a basophilic nucleus that may be pycnotic or multiple (Fig. 51.2). Atypical melanocytes are also found in the basal layer of the epithelial sheath of hair follicles and are responsible for recurrences following superficial treatment modalities that do not penetrate deeper than the epidermis. In more advanced stages, atypical melanocytes cluster in irregular nests that initially locate in the basal epidermal layer and later may invade the upper epidermis and eventually also the dermis (vertical growth phase, LMM) (Fig. 51.3). Associated histologic findings include an atrophic epidermis with a flattened dermal-epidermal junction, actinic elastosis in the underlying dermis (reflecting chronic sun exposure) and the presence of melanophages along with a mild lymphocytic infiltrate in the papillary dermis. LM should be differentiated from simple (non-malignant) atypical melanocytic hyperplasia, often noted in chronically sun-exposed facial skin of elderly people; this distinction is often difficult, especially in the initial stages of LM.

LM most commonly carries mutations in the *c-kit* gene, unlike other commoner forms of melanoma (SSM, nodular) that have activating mutations in the BRAF gene.

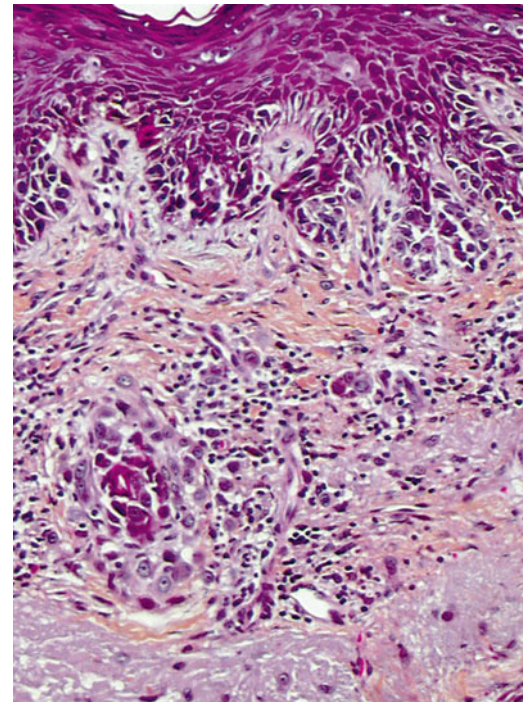

Fig. 51.3 Lentigo maligna melanoma: note similar findings as those seen in Fig. 51.2, along with the presence of atypical melanocytes invading the dermis (haematoxylin-eosin-saffron stain)

Workup

After a diagnosis of LM is established, a thorough history should be obtained and a complete physical examination performed, including total body examination and palpation of lymph node basins, both regional and distant. In asymptomatic patients with localised in situ MM (including LM), baseline routine laboratory tests and imaging studies are generally not recommended and should only be performed in the presence of clinically suspicious signs and symptoms.

General Principles of Treatment

There are no prospective studies or randomised controlled trials allowing to establish definite guidelines for the management of LM. It is however generally admitted that the best treatment of

LM is complete surgical excision. This allows histological examination of the whole tumour, therefore minimising the risk of missing an invasive zone, and allows examination of the margins to ensure that they are tumour-free. Surgical excision achieves thereby the lowest risk for disease recurrence. However, clinical factors such as the age of the patient, the patient's life expectancy and comorbidities and the size and location of the lesion may impact on the way LM is managed. Alternative destructive or medical therapeutic modalities can be proposed when surgery is not a feasible option. The best treatment should be tailored to each individual patient, possibly in the setting of a multidisciplinary oncology team, the aim being to obtain the best risk-benefit ratio in each case.

Surgical Excision

As with all clinicopathologic subtypes of MM, complete surgical excision with clear histologic margins is considered the best treatment of LM as it achieves the highest clearance rates. The definite surgical excision should preferably be performed within 4–6 weeks following diagnosis. The challenge is to excise the lesion completely (i.e. with tumour-free margins) while respecting the anatomy of the face and conserving a maximum of healthy tissue, so as to obtain the best possible aesthetic and functional results. Surgical excision can be performed with technical variations, such as standard excision with adequate safety margins, and margin-controlled techniques, such as staged surgical excision (SSE) and Mohs micrographic surgery (MMS).

Standard excision is a one-stage excision using predefined safety margins. It is suitable for well-defined, relatively small LM. The size of safety margins has been debated. Most consensus guidelines (Australian-New Zealand, European, National Comprehensive Cancer Network (NCCN), British Association of Dermatologists (BAD)) recommend for in situ MM (to which LM belongs) excision margins of 5 mm around the visible lesion. However, LM often shows subclinical extension of atypical melanocytes, which may be present several cm beyond the visible lesion, so that 5 mm margins are often insufficient to achieve histologically negative margins. A recent study found that surgical margins larger than 5 mm are required in 26.5 % of primary and in 69.2 % of recurrent LM. Another study using MMS found that margins of 6 and 9 mm achieved complete excision of in situ MM in 86 and 98.9 % of cases, respectively, and therefore suggested 9 mm excision margins. Another study found that the mean total surgical margin required for complete LM excision was 7.1 mm. On the basis of these observations, the NCCN recommends for large in situ MM (LM-type) surgical margins greater than 5 mm to achieve histologically negative margins. The AAD recommends margins 5–10 mm for in situ MM. The French Standard, Options and Recommendations guidelines recommend lateral excision margins of 10 mm; when this margin is unfeasible because of anatomic or functional limitations, a margin of 5 mm is acceptable, pending strict microscopic control of the entire tumour margin, either using SSE or MMS prior to definitive wound closure. The deep margin should include the subcutis but not the aponeurosis since removing this structure does not improve the rate of recurrence or survival. With simple surgical excision, the clearance rates range from 24 to 70 % and recurrences from 8 to 20 % of cases.

Margin-controlled excisions (SSE and MMS) are indicated in the case of large LM with ill-defined clinical borders. They are associated with the lowest recurrence rates for LM. SSE comprises several consecutive stages of excision, with each subsequent stage defined by the histologic findings of the previous stage. The first stage(s) consist(s) in excision of peripheral margins, if necessary in multiple steps, until histologically tumour-free ones are obtained. Various techniques of margin examination have been developed, such as square/geometric, perimeter, contoured and total circumferential margin control. The "spaghetti" technique is a recent variation of SSE that does not require specific training

of surgeons and pathologists and does not leave patients with an open wound before final reconstruction. The last stage of SSE consists in excision of the central portion of the tumour, after tumour-free margins have been excised. After complete excision the reconstruction is usually performed with flaps or grafts. Recurrence rates with SSE are reportedly lower than 10 %, and in one comparative study they were significantly lower than those obtained with MMS.

MMS is a specialised form of SSE using (conventionally) frozen sections for immediate histologic analysis or permanent, formalin-fixed-paraffin-embedded sections, offering better tumour cell visualisation (called "slow Mohs"). Immunohistochemical stains for melanocytic antigens (such as MART1/Melan-A and HMB-45) can be used to improve visualisation of atypical melanocytes, especially when frozen sections are used (intraoperatively). MMS allows smaller initial margins than standard excision and therefore has the advantage of sparing healthy tissue (although in the case of LM the difference with SSE regarding postsurgical lesion size may not be significant); furthermore, the traditional MMS involves real-time assessment of tissue samples and therefore allows complete tumour excision in 1 day. The recurrence rate in most studies is lower than 7 %, usually in the order of 4–5 %.

Nonsurgical Treatments

Although surgical excision is the mainstay of LM treatment, this may be challenging because LM frequently develops near critical anatomical structures of the face. Therefore, nonsurgical treatments may be envisaged in some clinical scenarios, namely, for unresectable tumours where complete excision would entail unacceptable mutilations or in elderly or frail patients when comorbidities or advanced age render surgery impossible. These nonsurgical modalities carry a higher risk of recurrence, mostly because of the lack of histological tumour assessment, a fact also exposing to the risk of missing invasive MM (LMM).

Imiquimod (IMQ)

IMQ (1-(2-2methylpropyl)-1H-imidazo[4,5-c] quinolin-4-amine) is a synthetic Toll-like receptor 7-agonist approved for the topical treatment of genital warts and superficial (pre)malignant keratinocytic neoplasms, i.e. actinic keratoses and superficial basal cell carcinomas. It acts as an immune-response modifier by stimulating skin macrophages to secrete cytokines (including TNFα, IFN-α, IFN-γ, IL-6, IL-1b, IL-8, IL-12, GM-CSF, G-CSF) directed against tumour cells. Local side effects (severe inflammatory reaction, burning sensation, erosions) are frequent but can usually be managed, if necessary, with local anti-inflammatory products.

IMQ has been used with variable results in the treatment of LM as a primary treatment when surgery is not realisable (e.g. for periocular tumours), before SSE, or as an adjuvant treatment in selected patients with positive margins after optimal surgery or after laser ablation. The dosing scheme is application of IMQ 5 % cream from daily to three times weekly over several weeks (6–44), with treatment margins up to 2 cm around the visible lesion. Complete clinical responses have been reported in 40–93 % of patients, although histological clearance rates are lower (persistent disease is found in approximately 25 % of patients). Furthermore, the follow-up time in most studies was rather short (less than 3 years). Progression to LMM has also occurred under IMQ treatment. The development of an inflammatory reaction to IMQ seems to be a predictor of clinical and histological clearance, contrary to treatment duration and lesion size. Long-term follow-up (at least 5 years) and post-treatment biopsies are recommended, even in the absence of a clinical recurrence.

IMQ can be associated with local applications of tazarotene 0.1 % gel (twice weekly). This has resulted in a slightly better (although statistically nonsignificant) rate of clearance (78 % vs. 64 %), probably due to a decrease of stratum corneum cohesion, thereby allowing better penetration of IMQ. IMQ can also be used in association with laser ablation or cryotherapy ("cryo-immunological treatment").

Radiotherapy (RT)

RT is rarely indicated as a primary treatment in MM in general but may be envisaged in elderly patients with surgically unresectable disease. It may also be used as adjuvant treatment after surgical excision when tumour-free margins have not been obtained. RT has the advantage over surgery in conserving normal tissue within the treatment field, therefore achieving good functional and cosmetic results. Either low-energy Grenz rays or superficial RT can be used, administered in fractionated doses so as to take advantage of the difference in repair capacity between normal and neoplastic cells. The total dose varies from 35 to 160 Gy and is delivered in 5–20 fractions. The radiation field must be large enough to avoid recurrences, in the order of 10–20 mm around the visible lesion. The radiation should be penetrating enough so as to reach deeply seated melanocytes (namely, those within hair follicles), as radiation energy attenuates with increasing depth; 5 mm is considered to be adequate in most cases. The recurrence rate of RT (infield or marginal) is 5–10 % at 3 years. Salvage is possible in the majority of these cases by further RT, surgery or other therapies. Progression to LMM has been observed in 1.4 % of cases at 3 years, and the outcome in these cases is poor. RT is well tolerated; however, side effects (such as fibrosis with possible ectropion, hypopigmentation, telangiectases and alopecia) may occur.

Cryotherapy/Cryosurgery

This technique involves application of a cryogenic agent, usually liquid nitrogen, to the skin in order to destroy superficially located pathologic cells. In LM, the treatment relies on the fact that melanocytes are sensitive to freezing and are destroyed at temperatures between −4 and −7 °C, i.e. higher than those destroying keratinocytes (−20 to −30 °C). The liquid nitrogen can be applied with a cotton swab or as spray. Most studies have involved small patient series. Two to three freeze–thaw cycles (occasionally under local anaesthesia) and 5–10 mm lesion margins are usually applied. A clinical clearance rate of 60 % or higher has been achieved, although data are insufficient to determine a histological clearance rate. On the other hand, even with "aggressive" cryotherapy, the recurrence rates may be high (up to 40 %). This treatment may make subsequent progression difficult to detect and may be complicated by the development of amelanotic MM. Side effects include hyper- or hypopigmentation of the treated area. Cryosurgery can be combined with continuous treatment with IMQ ("cryo-immunological treatment").

Other Treatments

Other treatment modalities have been tried for LM but are not included in current consensus recommendations. They include:

Laser therapy: several types of lasers (argon, carbon dioxide, Q-switched ruby, Q-switched neodymium-doped yttrium aluminium garnet, alexandrite lasers and various combinations) have been used. Potential advantages of laser treatment include less pain, better cosmetic results compared with surgery, speed of therapy and less post-treatment care. Despite lateral margins of 5 mm, the recurrence rates are rather high (23–38 %), probably because the laser beam may not reach a sufficient depth to destroy deeply seated atypical melanocytes, namely, within hair follicles. This drawback outweighs the advantages of laser therapy that may nevertheless be proposed as an alternative treatment in patients in whom surgery or RT is declined or carries significant morbidity. The combination of ablative laser therapy followed by IMQ has recently been advocated.

Curettage and electrosurgery have been used in a limited number of patients. Not surprisingly, high recurrence rates were observed.

Topical azelaic acid (AZA) is a dicarboxylic acid that competitively inhibits tyrosinase in vitro. It has been used to treat LM (applications of 15–20 % cream for up to 3 months) with local disease control; however, progression to invasive melanoma has also been reported.

Topical 5-fluoro-uracil is an antineoplastic pyrimidine analogue used locally for the treatment of actinic keratoses and superficial basal cell carcinomas. Limited data exist for its use in LM

treatment (twice daily application of 5 % cream for 6–13 weeks). Efficacy is very limited because recurrences are very common.

Topical cidofovir 1% is an acyclic nucleoside analogue of deoxycytidine monophosphate that can be used topically for the treatment of DNA virus-induced infections (molluscum contagiosum, HPV warts, herpes simplex). It has proven effective in a small number of basal and squamous cell carcinomas and has also been successful in two cases of recurring LM; it may act by blocking DNA synthesis.

Finally, elderly patients with facial LM that are not suspicious of containing an invasive zone, and who cannot be treated by surgery or alternative nonsurgical methods because of comorbidities or complexity of wound repair, may be carefully monitored with non-invasive techniques (macroscopic and dermatoscopic photography, in vivo reflectance microscopy). Biopsy should be performed if changes in size or pigmentation are noted.

Treatment of Lentigo Maligna Melanoma (LMM)

LM that has progressed into the invasive phase (LMM) behaves as other MM subtypes and therefore should be treated similarly to other MM forms, although the localisation on the face and the often large size of the lesion often poses difficult functional and anatomic problems. The therapeutic decision should be taken on an individual patient, preferably after discussion in the setting of a multidisciplinary oncology team.

Follow-Up

The aim of follow-up in MM is early detection of recurrences or disease progression, early diagnosis of new primary MM (reportedly occurring in 10 % of patients), psychosocial support and providing education on self-examination of the patient and his first-degree relatives. The frequency and extent of follow-up examinations depend on the risk of each individual patient. Since LM has no risk of metastasis, some advocate that no follow-up is necessary, apart from a return visit after complete excision to check the whole skin for further primary MM and to teach self-examination for a new primary MM. However, most guidelines recommend patient monthly self-skin examination and at least annual skin examination for life for all patients diagnosed with in situ MM. The frequency of this examination may be increased (up to four times per year) depending on the individual risks of the patient to develop recurrences and/or new MM, such as personal or family history of MM and the patient's ability and awareness to detect signs and symptoms of the disease.

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Leprosy (Hansen's Disease)

52

Clio Dessinioti and Andreas D. Katsambas

Key Points

- Leprosy (Hansen's disease) is a chronic granulomatous bacterial infection caused by the bacillus *Mycobacterium leprae* (*M. leprae*).
- The transmissibility of *M. leprae* is low.
- The disease mainly affects the skin and the peripheral nerves.
- Lepromatous leprosy (LL) is characterized by positive bacteriology and negative Mitsuda reaction due to the absence of specific cell-mediated immunity.
- Tuberculoid leprosy (TL) is stable, rarely contagious, and may even be self-limiting. There is negative bacteriology and positive Mitsuda reaction, and granulomas are typically found on biopsy.
- The duration and type of drug therapy is based on the classification of leprosy as paucibacillary or multibacillary.
- Leprosy is curable.
- Multidrug therapy (MDT) treatment is a highly effective cure for leprosy.
- Reversal reactions and erythema nodosum leprosum (ENL) can be treated using oral corticosteroids.
- For severe ENL, thalidomide is the treatment of choice.

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Definition and Epidemiology

Leprosy is a chronic granulomatous bacterial infection that primarily affects the skin and peripheral nerves. It is one of the world's oldest documented diseases with the first known written mention of the disease dating 600 BC. Leprosy is also called Hansen's disease after Gerhard Henrik Armauer Hansen (1841–1912), a Norwegian physician known for the identification of *Mycobacterium leprae* (*M. leprae*), an obligate intracellular, acid-fast, rod-shaped bacillus, as the causative agent of leprosy in 1874. *M. leprae* multiplies slowly (approximately every 12 days) and the incubation period of the disease is about 5 years. Symptoms can take as long as 20 years to appear.

By 2005, the global prevalence of leprosy had fallen to about 300,000 due to the available multidrug therapy. As reported by WHO, official figures from 115 countries showed the global registered prevalence of leprosy at 189,018 at the end of 2012, and during the same year, 232,857 new cases were reported. Elimination of leprosy globally was achieved in the year 2000 (i.e. a prevalence rate of leprosy

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_52, © Springer-Verlag Berlin Heidelberg 2015

less than 1 case per 10,000 persons at global level). High endemicity still remains in some areas of many countries, including Angola, Bangladesh, Brazil, China, Democratic Republic of Congo, Ethiopia, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, the Philippines, South Sudan, Sri Lanka, Sudan, and the United Republic of Tanzania.

Basic Concepts of Pathogenesis

M. leprae is an acid-alcohol-fast, gram-positive obligate intracellular bacillus that shows tropism for cells of the reticuloendothelial system and peripheral nervous system. It preferentially infects cold areas of the body such as the skin, nasal mucosa, and peripheral superficial nerves.

The transmissibility of *M. leprae* is low. The mode of transmission and infection with *M. leprae* remains unclear, but it has been postulated to occur from person to person via respiratory droplets, from the nose and mouth, during close and frequent contacts with untreated cases. Household contact studies have shown that multibacillary (MB) cases with a higher bacillary load display a higher transmission potential as compared to paucibacillary (PB) cases.

Leprosy displays a wide spectrum of clinical forms depending on the immunological status of mainly T-helper (Th) type cell-mediated immunity. The cytokine interferon-gamma (IFN-γ) plays an important role in the activation of natural killer (NK) cells and the induction of Th1 cells. A meta-analysis by Silva et al. included 1,573 patients and 1,914 controls and reported that carriers of the IFN-γ +874T allele (12q14.1), which has been correlated with high interferon-γ levels, may be protected from developing leprosy (pooled OR = 0.83, 95 % CI 0.72–0.96, $p = 0.011$). Familial aggregation studies and segregation analyses support a genetic basis for the human susceptibility to leprosy. A two-stage model has been proposed with a first set of genetic factors controlling susceptibility to preclinical disease and a second set of genes controlling the clinical polarization into PB or MB leprosy.

Clinical Presentation

Leprosy is a multi-organ infectious disease that can cause severe disability. The development of skin, nerve, and eye lesions and other symptoms can delay for 20 or more years after the onset of infection.

Clinical forms of leprosy are a part of a disease spectrum. In 1966, Ridley and Jopling have proposed a classification of leprosy into five groups based on clinical, histological, bacteriological, and immunological criteria (Fig. 52.1). Lepromatous leprosy (LL) is considered to be at the systemic and infectious end of the spectrum and correlates with an absence of an immune response to *M. leprae* antigens. LL affects the skin and peripheral nerves and presents with annular infiltrated, usually anaesthetic plaques. The lepromatous pole of the spectrum (lepromatous leprosy and borderline lepromatous cases) is characterized by confluent papules and nodules; marked, diffuse infiltration of the skin; leonine facies; and madarosis (Fig. 52.2). Lesions are usually symmetrical and bilateral. The lepromatous pole is characterized by greater nerve involvement and more severe disability. Histoid leprosy is a variant of lepromatous leprosy, presenting with shiny, skin-coloured or erythematous papules, nodules, or plaques. It may occur after inadequate antileprosy treatment or due to dapsone-resistant mutation or de novo.

Tuberculoid leprosy (TT) form correlates with cell-mediated immunity to *M. leprae*. The borderline forms [borderline tuberculoid (BT), borderline borderline (BB; also termed mid-borderline), and borderline lepromatous (BL)] have some cell-mediated immunity and are often immunologically unstable. At the tuberculoid pole (tuberculoid and borderline tuberculoid cases), there are a few well-defined, hypopigmented anaesthetic macules or plaques with elevated, erythematous borders and sometimes atrophic centres. This form is associated with anhidrosis and loss of adnexal structures. Since there is adequate immune response, lesions are not usually large or numerous and TT may resolve spontaneously.

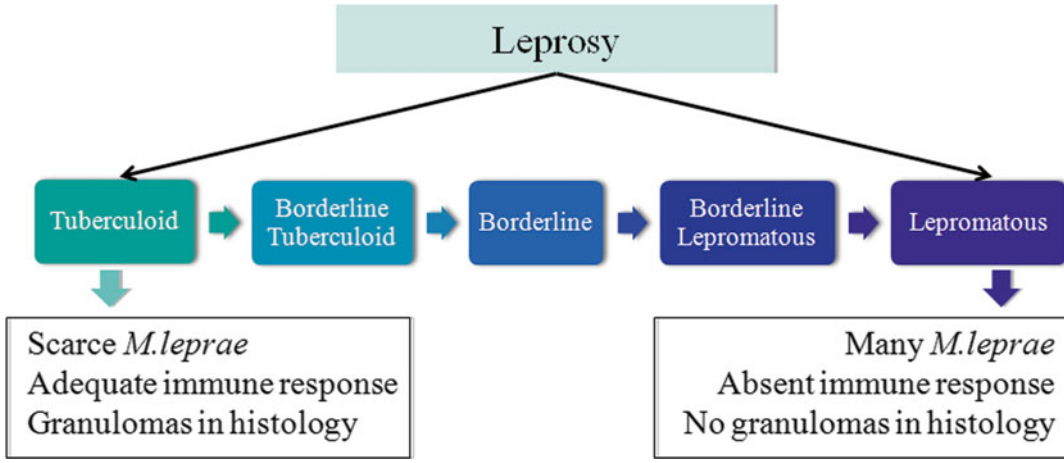

Fig. 52.1 Forms of leprosy

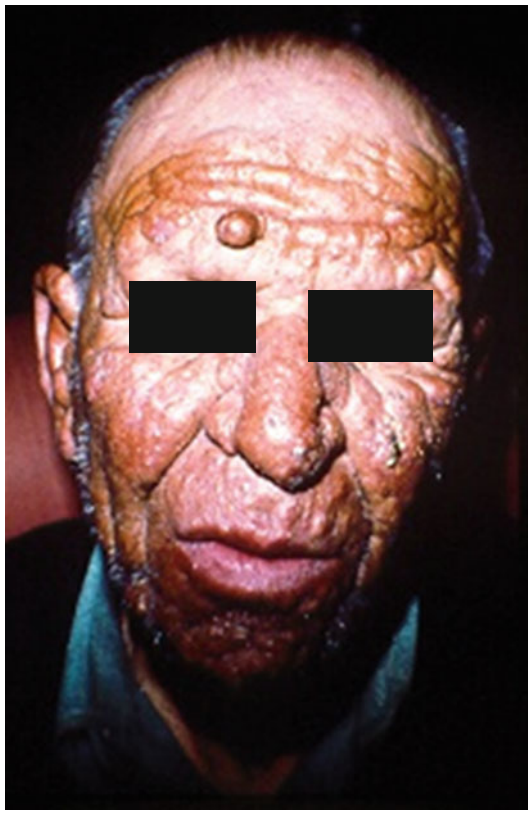

Fig. 52.2 Lepromatous leprosy with leonine face

Leprosy may affect cutaneous peripheral nerves, primarily the posterior tibial, cubital, medial, and lateral peroneal nerves, making them palpable during physical examination. There may be numbness, anhidrosis, and motor and thermal sensory impairment. Other affected organs in leprosy include the musculoskeletal system (95 %) with osteoporosis and non-specific symptoms due to nerve damage, the testis with atrophy and acute orchitis in patients with the lepromatous form, and the eye with lagophthalmos, keratitis, entropion, optic nerve damage, or loss of vision (Table 52.1).

Leprosy is classified into two subtypes, paucibacillary (PB) or multibacillary (MB) leprosy with MB patients manifesting a greater number of lesions, extent of nerve involvement, and bacillary load.

All types of leprosy have been reported in patients with HIV infection.

Leprosy Reactions

Leprosy may be complicated by episodes of immunological instability, such as those caused by antileprosy medication, stress, or pregnancy, termed 'reactions'. During reactions, leprosy patients are at higher risk of developing nerve damage. Type 1 reactions are caused by delayed-type hypersensitivity to *M. leprae* antigens, while type 2 reactions (erythema nodosum leprosum) by immune complex formation. If these reactions occur during MDT, the treatment should be continued and additional therapy for the reactions is advised.

Table 52.1 Clinical manifestations of leprosy

Skin	In tuberculoid leprosy: few anaesthetic erythematosquamous lesions
	In lepromatous leprosy: numerous symmetrical, annular, papulonodular lesions
Cutaneous peripheral nerves (posterior tibial, cubital, medial, and lateral peroneal)[a]	Thickening and palpable during physical examination
	Numbness
	Anhidrosis
	Motor and thermal sensory impairment
	Deformities
Musculoskeletal system (95 %)[b]	Non-specific findings
	Fractures
	Deformities due to nerve damage osteoporosis
Upper respiratory tract[b]	Nose deformities
	Mouth
	Larynx
	Pharynx
Testis[b]	Testicular atrophy
	Acute orchitis (lepromatous leprosy, erythema nodosum leprosum)
Eye[b]	Lagophthalmos
	Keratitis, iritis, uveitis
	Entropion
	Damage of the optic nerve
	Vision loss

[a]In tuberculoid leprosy, rapid, serious, asymmetrical nerve involvement; in lepromatous leprosy, slow and symmetrical nerve involvement
[b]Affected in lepromatous leprosy

Type 1 Reactions

Type 1 reactions include upgrading or reversal reactions and downgrading reaction. Reversal reaction is a delayed type IV hypersensitivity reaction that arises when borderline leprosy shifts towards borderline lepromatous leprosy during treatment. Type 1 reactions are due to the development of an appropriate immune response and the production of tumour necrosis factor-alpha (TNFα) and IFN-γ. The reaction is characterized by oedema and erythema of existing skin lesions, development of new skin lesions, neuritis, and additional sensory and motor loss.

The downgrading reaction occurs in untreated borderline patients and is characterized by appearance of new skin lesions and a shift towards the lepromatous pole.

Treatment of type 1 reaction includes nonsteroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids with tapering after clinical improvement is achieved.

Type 2 Reactions (Erythema Nodosum Leprosum)

Type 2 leprae reaction manifests clinically as erythema nodosum leprosum (ENL). It is a Th2-mediated type III hypersensitivity reaction due to immune complex deposition associated with systemic toxicity and elevated tumour necrosis factor levels. ENL is due to immunological response to high loads of *M. leprae* in skin tissue, and it develops mainly in leprosy patients classified as BL or LL, belonging to the multibacillary (MB) group, as defined by WHO. Incidence rates of ENL in person years at risk (PYAR) have been reported to range from 1 to 8 per 100 PYAR. In their systematic review, Voorend et al. reported that in most studies, the incidence of ENL during multidrug therapy (MDT) was at least twice as high than at the time of the initial diagnosis and was the highest during the first year of MDT. Other risk factors for the development of ENL include a bacteriological index (BI) of six (associated with up to 8.6 times higher risk), lepromatous leprosy, pregnancy, and lactation. ENL presents with fever and painful subcutaneous nodules on the face or the extensor surfaces of the limbs, while there may also be nerve and eye lesions. Neuritis, iritis, iridocyclitis, arthralgia, and glomerulonephritis may occur. ENL is often recurrent and may become chronic.

Thalidomide is the drug of choice for severe ENL, with its beneficial effect being attributed to anti-TNFα action. Due to the documented teratogenic effects of thalidomide, it is not proposed for women of childbearing potential. Short

courses of oral corticosteroids may be used in cases of moderate ENL or contraindication for thalidomide use. In the case of recurrent or chronic ENL, clofazimine may be beneficial.

Leprosy of Lucio and Latapí

Leprosy of Lucio and Latapí is prevalent in Mexico and the Caribbean. It is considered to be the most anergic form in the immunologic spectrum of the disease, and it is characterized by generalized infiltration of the skin and absence of nodules. Lucio's phenomenon is a late stage reaction in which haemorrhagic infarcts occur due to heavy colonization of endothelial cells by *M. leprae* in infarcted and clinically normal-appearing skin.

Diagnosis

Under the global initiative for eradicating leprosy in countries where the disease is endemic, diagnosis is based on clinical signs and smear tests, although other methods, such as serology, have become available.

The WHO case definition of leprosy is *M. leprae* infection in an individual who has not completed a course of treatment and has one or more of the following:

- Hypopigmented or reddish skin lesions with loss of sensation
- Involvement of the peripheral nerves as demonstrated by their thickening and associated loss of sensation
- Skin smear positive for acid-fast bacilli

Laboratory studies include the following:

- Skin biopsy, nasal smears, or both are used to assess for acid-fast bacilli using Fite stain.
- Serologic assays can be used to detect phenolic glycolipid-1 (specific for *M. leprae*).

The smear test has a specificity of 100 % and a sensitivity of 50 %. A smear can be obtained from the nasal mucosa, an ear lobe, and/or skin lesions and stained with Ziehl-Neelsen stain. The current system for classifying patients as either paucibacillary or multibacillary is based on skin smears. Ridley's logarithmic scale, or bacterial index (BI), is used to interpret the smear test results. Patients with negative smears at all sites are classified as having paucibacillary leprosy, while those with positive smears at any site are classified as having multibacillary disease.

Histologically, the morphology and cellular composition of the infiltrate in cutaneous leprosy lesions depends on the intensity of cell-mediated immunity. In TL, there are granulomas of activated macrophages (epithelioid cells) with CD4+ T cells in the centre of the aggregates of epithelioid cells and CD8+ T cells surrounding the granuloma. By contrast, in LL, both T-cell types are diffusely distributed without a specific organization.

The intradermal lepromin test uses inactivated *M. leprae* extracted from lepromas. After intradermal injection of 0.1 mL of the antigen (lepromin) in the flexor surface of the forearm, the reaction is interpreted. The early (Fernández) reaction is read at 24 or 48 h. The late (Mitsuda) reaction is read at 21 days and indicates resistance to the bacillus. A nodule measuring more than 5 mm indicates positivity. These tests are not diagnostic, and they are used for classification and prognostic purposes.

PCR detection of the bacillus is a highly specific and sensitive but expensive technique.

LL is characterized by positive bacteriology and negative Mitsuda reaction due to the absence of specific cell-mediated immunity. TL is stable and rarely contagious and may even be self-limiting. There is negative bacteriology and positive Mitsuda reaction, and granulomas are typically found on biopsy.

Differential Diagnosis

Leprosy should be differentially diagnosed from other granulomatous skin diseases such as sarcoidosis, cutaneous tuberculosis (lupus vulgaris), and other skin disease with infiltrated plaques/nodules such as cutaneous T-cell

lymphoma (mycosis fungoides) and deep fungal infections:

- Sarcoidosis: may present with annular plaques and/or nodules. However, there is a different histology.
- Lupus vulgaris: it is caused by *M. tuberculosis*, different histology.
- Mycosis fungoides: different histology, immunohistochemistry.
- Deep fungal skin infections: histology, culture and stains for fungi.
- Leishmaniasis: histology, culture for *Leishmania*.
- Molluscum contagiosum: histology.
- Primary amyloidosis: histology.
- Hereditary neuropathies: nerve biopsy.

Table 52.2 Standard MDT regimens for adults proposed by WHO

Multibacillary (MB) leprosy	
Rifampicin	600 mg once a month
Dapsone	100 mg daily
Clofazimine	300 mg once a month and 50 mg daily
Duration	12 months
Paucibacillary (PB) leprosy	
Rifampicin	600 mg once a month
Dapsone	100 mg daily
Duration	6 months
Single-skin-lesion paucibacillary leprosy	
Rifampicin	600 mg
Ofloxacin	400 mg
Minocycline	100 mg
Taken as a single dose	

General Principles of Treatment

Leprosy is curable and early treatment can prevent disability. Untreated, leprosy can cause progressive and permanent damage to the skin, nerves, limbs, and eyes. Standard treatment is multidrug therapy (MDT), including the combination of the antibiotics rifampicin and dapsone, with or without clofazimine, depending on the bacillary load. Since the introduction of multidrug therapy in 1981 by the World Health Organization (WHO), the global burden of leprosy has steadily declined. The duration and type of drug therapy is based on the classification of leprosy as paucibacillary or multibacillary (Table 52.2). When classification is in doubt, the patient should be treated as having multibacillary disease.

First-Line Drugs

Rifampicin is derived from *Streptomyces* fungi. It has antibacterial action and inhibits RNA synthesis. It is given once a month. It causes red coloration of urine, sweat, tears, and faeces.

Clofazimine binds DNA, generates cytotoxic superoxide radicals, and has anti-inflammatory properties. It is most active when administered daily. It causes a reversible brownish black discoloration and dryness of skin. Its use is associated with a lower incidence of erythema nodosum leprosum.

Dapsone is a sulphonamide whose antibacterial mechanism relies on p-aminobenzoic acid (PABA) antagonism and inhibition of folate synthesis. It is associated with haemolysis (mainly in patients with glucose-6-phosphate dehydrogenase deficiency), peripheral neuropathy, and erythema nodosum leprosum. Resistance to rifampicin and to dapsone has been described.

The daily combination of dapsone and clofazimine is highly bactericidal. This combination is capable of eliminating any rifampicin-resistant mutants in an untreated MB leprosy patient within 3–6 months. Based on results from several studies showing that MB leprosy patients who received less than 24 monthly doses of MDT responded as favourably as those who received 24 or more doses of MDT, the 7th WHO Expert Committee considered that the duration of MDT treatment of MB leprosy can be reduced to 12 months.

According to WHO, MB patients starting with a high BI may have a higher risk of developing reactions and nerve damage during the second year than those patients starting with a low bacterial index. High-BI patients who do not show improvement, with evidence of deterioration, will need an additional 12 months of MDT for multibacillary leprosy.

After completion of the WHO MDT regimens, the risk of relapse is considered to be negligible, and it is proposed that it is not necessary to continue active post-MDT surveillance. Patients should be taught to recognize early signs of possible relapses and to report promptly for treatment. Relapse in MB leprosy is defined as the multiplication of *M. leprae*, suspected by the marked increase (at least 2+ over the previous value) in the BI at any single site, usually with evidence of clinical worsening (new skin patches or nodules and/or new nerve damage).

Household contacts of patients with leprosy are at risk for the development of the disease and they should be examined for evidence of leprosy. Chemoprophylaxis with rifampicin or other antileprosy drugs is not recommended by WHO for contacts of leprosy patients in leprosy control programmes.

Supportive Measures

In order to improve the functional ability in patients with leprosy, supportive measures include physical therapy, reconstructive surgery, nerve and tendon transplants, and surgical release of contractures.

Vaccines

In some regions the BCG vaccine is administered to children under the age of 12 years who are in contact with relatives who have leprosy.

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Lichen Planus

53

Alfredo Rebora

Key Points

- Lichen planus (LP) is an acquired chronic disease characterized by small cutaneous papules and mucosal striae affecting 0.3–0.8 % of the population.
- Topical treatments are usually employed on limited lesions, especially the oral ones. The most useful medications are corticosteroids and tacrolimus.
- Systemic treatments are rarely needed. Oral cyclosporine is probably the most active.
- Biologics are interesting but only exceptionally needed.

Definition and Epidemiology

Lichen planus (LP) is an acquired chronic disease characterized by small cutaneous papules and mucosal striae. It affects 0.3–0.8 % of the population, occurring in all races and both genders. Children are rarely affected.

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Basic Concepts of Pathogenesis

LP is a specific pattern of cell-mediated cutaneous hypersensitivity to a variety of antigens expressed on keratinocytes (possibly on other epitheliocytes as well), which are the target of CD8 lymphotoxicity. Antigens may be viruses (hepatitis C and hepatitis B virus in the Mediterranean countries, the USA, and Japan), drugs, and contact antigens. LP may associate with visceral diseases, in particular chronic active hepatitis, primary biliary cirrhosis (in the UK), and ulcerative colitis and with other autoimmune disorders of the same cell-mediated nature, like alopecia areata.

Clinical Presentation

Lesions are small violet, polygonal papules, which coalesce into larger papules and plaques. On their surface, a whitish reticulum can be observed. On the skin, a typical site is the volar aspect of the wrist, but widespread lesions are not uncommon. Mucosae are often involved, usually by the whitish reticulum, more rarely by erosions (Figs. 53.1 and 53.2). Nail plates may be dystrophic. Clinical features vary according to the body region. On the shins, LP is verrucous, while on the scalp it presents as a scarring alopecia plaque. Unusual varieties include:

- Annular LP of the scrotum
- Ulcerative form of the sole
- Lichen planopilaris

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_53, © Springer-Verlag Berlin Heidelberg 2015

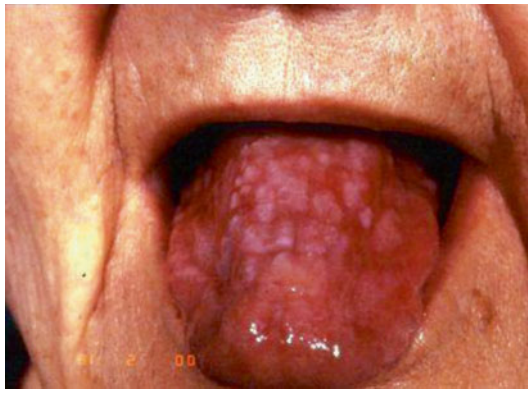

Fig. 53.1 Nonerosive oral lichen planus. Note the whitish irregular plaques on the dorsal surface of the tongue

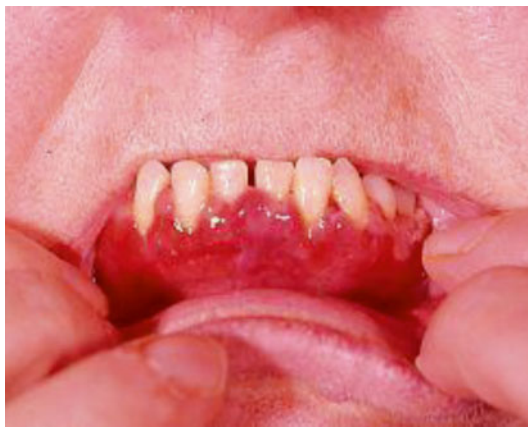

Fig. 53.2 Erosive oral lichen planus. Gums are intensely erythematous and deepithelialized

- Vesicobullous lichen
- Pigmentary forms (lichen actinicus, lichen pigmentosus)

The course is chronic, accompanied by pruritus of varying severity. Mucosal erosion may result in squamous cell carcinoma.

Diagnosis

Diagnosis is mainly clinical. Histopathology may help in doubtful cases but is mandatory in erosive forms. It reveals a typical mononuclear infiltrate (CD4-positive initially then CD8-positive), which impinges the keratinocyte basal line, disorganizing the epidermal architecture. Immunofluorescence shows an IgM deposit at the dermoepidermal junction.

Differential Diagnosis

- Lichenoid drug eruptions: they show parakeratosis and eosinophils in the infiltrate.
- Lupus erythematosus: a lupus band in direct immunofluorescence is distinctive, but there may be overlapping cases.
- Secondary syphilis: lymph nodes are constantly involved and serology is distinctive.
- Psoriasis: there are parakeratotic scales and a typical histopathology.
- Leukoplakia: often asymmetrical, with a rough velvet surface and dysplasias on histopathology.
- Candidiasis: whitish patches are easily removed; there is a severe immunodeficiency.
- Erythema multiforme: skin lesions are target-like and histopathology is distinctive.
- Bullous diseases: histopathology and direct immunofluorescence are distinctive.

General Principles of Treatment

Usually, LP is a chronic but benign and often symptomless disease, which does not require systemic treatment. As an immune disease, LP responds to all immunosuppressants. Those should be used only if a severe visceral involvement is documented or whenever the mucosal erosions prevent eating and speaking.

Topical Treatments

A number of medications have been tried and recommended. They are summarized in Table 53.1.

Topical Corticosteroids

Corticosteroids are in most cases the treatment of choice, but there is no convincing evidence of their efficacy in the literature (Cribier et al. 1998). Class I and II corticosteroids should preferably

Table 53.1 Treatments

Corticosteroids	Retinoids	Calcineurin inhibitors	Physical	Others
Triamcinolone acetonide	Tretinoin	CyA A	Laser therapy	Aloe vera
Fluocinolone acetonide	Tazarotene	Pimecrolimus	Photodynamic therapy	Hyaluronic acid
Fluocinonide	Isotretinon	Tacrolimus		Calcipotriol
Clobetasol proprionate	Fenretinide	Sirolimus		Mesalazine
Fluticasone proprionate				Thalidomide
Betamethasone phosphate				Amlexanox
Mometasone furoate				Tetracycline
				Herbal medicines
				Extracorporeal photochemotherapy

be employed. Occlusive dressings with class I drugs are recommended on verrucous plaques. Intralesional preparations have been advocated, but they should be used only in very resistant verrucous plaques. They have been useful in pitted nails, but discomfort discourages the patients. In any case, injectable triamcinolone, properly diluted, is preferable (5–0 mg per mL injection and 0.5–1 mL per 2 cm lesion). On lichen planopilaris of the scalp, corticosteroids may be more useful at the periphery of the plaque rather in its center, which is usually scarring. Foamy preparations of betamethasone or clobetasol are useful in this particular location.

Oral mucosal lesions (OLP) occur in 50–70 % of the patients with LP, affecting 2 % of the population with the highest incidence in women (2:1), in the age range from 40 to 70 years. It is understandable therefore that most of the literature is devoted to oral lesions rather than to other locations. Topical steroids are still the widely accepted first-line therapy for erosive OLP. A recent Cochrane collaboration systematic review found, however, only weak evidence for their effectiveness (Thongprasom et al. 2011). The lack of good-quality well-conducted trials and the small number of participants prevented good evidence to be obtained. In any case, none of the studies involved genital or oesophageal disease.

Several side effects are reported. With topical corticosteroids, the main side effects are oral candidiasis and dyspepsia, but even a severe neuropsychiatric disorder has been reported due to the exceeding absorption of clobetasol through the oral mucosa. Fluticasone propionate spray caused nausea, swollen mouth, bad taste and smell, dry mouth, and a sore throat in a small proportion of participants.

Anecdotal reports describe the efficacy of the injections of triamcinolone within the lesion of OLP. In a study of 11 patients with lichen of the nail plate (Abell 1973), 5 mg/mL were injected in the posterior nail fold at intervals of 2–4 weeks. Seven of them greatly improved, but eight experienced relapses after about 1 year.

Retinoids

A recent literature review (Petruzzi et al. 2013) of data on topical retinoids in patients with OLP found 16 studies with 280 patients topically treated with different classes of retinoids. Isotretinoin 0.1 % gel is the most frequently employed one, but tretinoin (0.025 %), tazarotene, and fenretinide have been also tried.

In a double-blind study, ten patients with biopsy-proven OLP were treated for 4 months with 0.1 % isotretinoin gel and another ten patients with placebo. All patients treated with isotretinoin showed a significant improvement of the oral lesions, whereas in the placebo group, the size of the lesions remained the same (Piattelli et al. 2007). The best concentration has been also studied in 70 OLP patients who were randomly divided into two groups with 0.05 and 0.18 % drug concentrations. None of the cases of reticular LP improved, while in 26 patients with the

atrophic-erosive forms (at 0.18 % concentration) and in nine patients (at 0.05 % concentration), the erosions or ulcers disappeared both clinically and histologically. The disappearance of dysplastic phenomena was observed at 0.18 % concentration. Topical application of the drug was accompanied by a transitory increase in soreness and pain, as well as greater sensitivity to hot foods. The presence of dysplastic features, however, raises some doubts on the correct diagnosis (Scardina et al. 2006).

Tretinoin in an oral base 0.05 % was compared in a randomized controlled study with fluocinolone acetonide 0.1 % in the treatment of atrophic and erosive OLP. Of 33 patients, 18 improved with fluocinolone acetonide, whereas 15 patients receiving topical retinoic acid showed little change. The difference was significant. In a randomized, placebo-controlled study, 12 patients with OLP were randomly treated with tazarotene gel 0.1 % b.i.d. or with placebo for eight consecutive weeks. The tazarotene group had their lesions significantly reduced as compared with the control group (Petruzzi et al. 2002).

Fenretinide was used in a small heterogeneous study (eight patients) and two of them had complete remission after 1 month.

Cyclosporin A

Four controlled trials evaluated topical CyA (Eisen et al. 1990; Sieg et al. 1995; Lopez Lopez and Rosello Llabrés 1995; Harpenau et al. 1995). Three washes per day (1,500 mg/day) proved beneficial in 16 OLP patients. In another trial, no difference between CyA and triamcinolone paste was noted in 13 patients. Likewise, there was no difference in comparing an oil-based CyA solution (50 mg three times daily) with an aqueous 1 % triamcinolone acetonide solution in 20 patients. A significant difference was instead found when 14 patients with erosive OLP treated with 5 mL of CyA (500 mg) were compared with placebo after 4 weeks of treatment.

Multiple, small, uncontrolled trials studied topical CyA on OLP, while only one evaluated its effect under occlusion in chronic hypertrophic LP. The different forms of OLP, the different modalities of application (mouthwash, manual administration with local massage), the different doses (50–1,500 mg/day), and vehicles all bias the results. Those are favorable in most studies, although poor efficacy was also reported in three. Also genital LP seems to benefit from topical CyA, but a case of squamous cell carcinoma was registered during treatment. Efficacy seems to be dose dependent (1,550 mg/day), but not blood level dependent. CyA A solution significantly reduced pain in erosive OLP over 0.1 % triamcinolone acetonide in orabase; the study, however, was very small (11 patients). A significant difference was seen in favor of the 1.5 % CyA gel compared to 0.025 % clobetasol propionate gel. However, seven patients with long-standing atrophic/erosive OLP were treated for 4 weeks with CyA A as a mouthwash. At the end of the 3-month follow-up period, no improvement was recorded. In any case, the evidence to support the contention that topical cyclosporine reduces pain and clinical signs of oral lichen planus has been defined as weak and unreliable (Le Cleach and Chosidow 2012).

Calcineurin Inhibitors

A recent systematic review for calcineurin inhibitors examined 5 double-blind studies, 1 investigator-blinded study, 10 open prospective studies, 6 retrospective studies, and 28 case reports (Cheng et al. 2012).

Strong evidence (double-blind and open studies) (level A) has been found for tacrolimus ointment in OLP, with efficacy at least equal to topical clobetasol propionate 0.05 % ointment. Blood levels of tacrolimus are demonstrable but without clinically significant adverse events. Strong evidence (level A) has been also found for pimecrolimus 1 % cream with efficacy equal to that of topical triamcinolone acetonide 0.1 % paste. For vulvovaginal LP, pimecrolimus was superior to placebo in one double-blind study but less active than clobetasol (Goldstein et al. 2011). Only case reports support the efficacy of topical calcineurin inhibitors in cutaneous LP.

Topical rapamycin (1 mg/ml) was studied in an open prospective study involving seven women with oral and vulvar erosive lesions twice a day for 3 months. Complete remission was obtained in four women. Only one had stopped treatment due to local discomfort. Only one woman had detectable blood sirolimus level (Soria et al. 2009).

Other Topical Preparations

Calcipotriol

Eighteen LP patients applied calcipotriol ointment twice daily. Of the 16 patients that completed the study, 5 obtained complete clearing of the lesions, while 4 had partial improvement. No improvement was observed in seven. In a randomized open-label trial, 15 LP patients were given calcipotriol 50 μg/g and 16 betamethasone 0.1 % ointment twice daily for 12 weeks. Calcipotriol was no more effective than betamethasone (Theng et al. 2004).

Mesalazine

Mesalazine (5-aminosalicylic acid) 5 % was compared with clobetasol propionate 0.05 % in 25 patients with OLP. Both preparations were active without statistical difference. Mesalazine resulted in total remission in 57 % of patients. Only 9 % of patients had no benefit (Sardella et al. 1998).

Thalidomide

In a randomized double-blind, positive-control trial, 24 patients received thalidomide 1 % paste vs. dexamethasone 0.043 % paste of controls. After 1 month of treatment, 66.7 % of thalidomide patients had fully healed. The erosive area size and the Visual Analogue Scale scores were similar between groups. Only two patients in each group experienced discomfort with treatment (Wu et al. 2010).

Amlexanox

Amlexanox is an anti-inflammatory drug which selectively inhibits TBK1 and IKK-ε. It has been studied in a randomized, positive-controlled clinical trial in which 20 patients with erosive OLP received amlexanox paste and 18 dexamethasone paste. After 7 days of treatment, both groups showed significant reduction in erosive area. None of the patients had severe adverse reactions (Fu et al.2012).

Aloe Vera

Aloe vera gel was tried in a randomized, double-blind study involving 40 patients with OLP (18 erosive, 14 atrophic). After 8 weeks of therapy, aloe vera gel proved more effective than triamcinolone acetonide (Choonhakarn et al. 2010). In another double-blind, placebo-controlled trial, 27 patients with OLP applied *Aloe vera* twice daily for 8 weeks. Lesions disappeared in two patients treated with *Aloe vera* vs. none of the placebo group.

Hyaluronic Acid

In a blinded parallel-group randomized clinical trial (Woo 1985), a local hyaluronic acid preparation (0.2 %) was evaluated in 120 patients with erosive OLP four to five times daily for 28 days. In patients treated with hyaluronic acid, a decrease of pain for up to 4 h post application and a reduction of ulcerative areas were registered (Nolan et al. 2009).

Tetracycline

A 78-year-old woman with erosive OLP gargled a 0.25 % tetracycline solution three times a day. Within a week there was a considerable relief from pain, and after 6 weeks the erosions had disappeared.

Herbal Medicines

Zheng et al. investigated the concomitant administration of the Chinese herb *Liuwei Dihuang* and retinoic acid cream in 43 patients with OLP with more effective results than retinoic acid cream alone, particularly in patients with a shorter history of lichen. Lichen pemphigoides, however, has been reported to occur after Chinese herb medication.

Physical Treatments

Laser Therapy

A diode laser (940 nm) was also successfully used to relieve symptoms in a single case of LP.

The excimer laser 308 nm UVB was used in 8 patients with OLP with 9–32 applications and fluency 75–175 mJ/cm^2. Six patients improved, with

complete remission in two. One patient relapsed after 4 weeks (Köllner et al. 2003). Also Trehan and Taylor (2004) successfully managed nine patients with the excimer laser therapy (initial fluencies 100 mJ/cm^2). Unsatisfactory results have been instead reported in four patients treated with the 308 nm excimer laser twice a week for 12 sessions. The lowest dose was 50 mJ/cm^2, increased by 50 mJ/cm^2 every two sessions up to 200 mJ/cm^2. Only one patient showed positive results.

A total of 82 lesions of OLP of 30 patients were treated in an open study (Cafaro et al. 2013) with low-level laser therapy delivered with a 980 nm gallium-aluminum arsenide diode laser. Eighteen patients (60 %) obtained a total resolution of the clinical signs, ten patients (33.3 %) a partial resolution, and two patients (6.6 %) did not respond at all. In another study, low-level laser therapy proved as effective as topical corticosteroid therapy without any adverse effects.

The CO2 laser was investigated in 39 superficial OLP lesions (1.5–2.0 J/mm^2). During a mean follow-up period of 8 years, 24 lesions showed no more signs of pain or burning sensation. In all patients, the treatment led to complete epithelialization in 3 weeks (Van der Hem et al. 2008).

Photodynamic Therapy

Twenty-three patients with OLP were submitted to photodynamic therapy performed using a semiconductor laser, with power up to 300 mW and a wavelength of 660 nm. After treatment, improvement was observed in 39 sites, including 14 with complete regression. The reduction in the size of lesions was statistically significant in both genders and in smokers and nonsmokers. On the gums and tongue, the effect was slighter and not statistically significant.

Extracorporeal Photochemotherapy

Extracorporeal photochemotherapy (ECP) or photopheresis efficacy has been studied in four patients with erosive OLP. All patients improved their symptoms and lesions after seven to nine cycles. Guyot et al. (2007) submitted 20 patients with erosive OLP to ECP twice weekly for 3 weeks while the following sessions were planned according to clinical improvement. All patients reported clinical improvements. In another study ECP has been used successfully in the treatment of two patients with erosive OLP and cortico-resistant LP.

The Problem of Carcinogenicity of Calcineurin Inhibitors

Approximately 1–5 % of oral LP lesions will develop squamous cell carcinoma (SCC) of the mouth. Also about 1–3 % of vulval LP lesions develop into SCC and a small, but unknown, percentage of penile LP lesions transform into SCC. High-risk factors include smoking, excessive alcohol ingestion, erosive or atrophic clinical types, presence of erythroplakic lesions (reddened patches with a velvety surface found in the mouth), and sites involving the tongue, gingival, or buccal mucosa. No risk factors are known for progression of vulval LP into SCC. In a 7-year prospective study on 327 OLP patients, 8 patients developed an SCC in OLP areas (0.36 %/year) during a mean follow-up of 81.7 months, especially in women.

In 2006, the Food and Drug Administration warned about the potential cancer risk with topical calcineurin inhibitors tacrolimus and pimecrolimus. The reasons were an animal study indicating a risk for malignant transformation and lack of long-term studies on the safety of tacrolimus in treatment of atopic dermatitis. The advice to physicians was to use tacrolimus only as a second-line agent for short-term and intermittent treatment. The European Medicines Agency followed the same strategy.

Such strategy raised a discussion in which the reliability of the OLP diagnosis and whether the lesion would have become malignant even without tacrolimus were debated.

As Eisemberg (2000) put it, often "the microscopy not only fails to confirm the given diagnoses of antecedent OLP, but also it depicts previously unappreciated maturation abnormalities that augur malignant potential." In other words, "if the reported carcinomas evolved from atypical or dysplastic lesions that were confused with OLP at outset, the

case for malignant degeneration in OLP is decidedly undermined." I came recently across a case in which a patient was treated for OLP on the basis of a microscopic description and developed SCC. Further histological sections demonstrated that the original "OLP" was in fact already SCC. The asymmetry of the clinical lesions is against OLP diagnosis as they are the presence of dysplasia and the absence of persistent reticular striations in the periphery. As for the second point, the problem is whether or not tacrolimus may enhance SCC risk. Fleischer (2006) emphasized that not a single SCC case has been found in data from randomized control studies and that the risk is smaller than with use of topical steroids. In fact, topical steroids, which are usually recommended in OLP, are not free from risk of cancer (about 5 % in lichen sclerosus), and the incidence of lymphomas in the general population is far higher than in patients treated with topical tacrolimus. In conclusion, OLP, especially in its erosive variety, compromises the quality of life of the patient and even prevents any social activity (pain, severe dysphagia, fetid breath) demanding a treatment. Calcineurin inhibitors could be regarded at least as safe as topical steroids.

Systemic Treatments

Rarely LP requires systemic treatment. In the office patients, lesions are usually limited in size and spread; pruritus is hardly a real problem and the quality of life is commonly preserved. That is probably the reason why large controlled studies are scarce in the literature. Nonetheless, a number of systemic drugs have been proposed (Fig. 53.3).

Corticosteroids

Corticosteroids are the treatment of choice for most dermatologists, but surprisingly enough until recently, there were no double-blind placebo-controlled randomized studies to support such a practice. Two large studies have been recently conducted. In the first study by Kelett and Ead (1990), 38 patients received either prednisolone (30 mg/day) or placebo for 10 days. After 2 years, LP cleared in 18 weeks with prednisolone and, surprisingly, also in 29 weeks with placebo. Only three failed to clear with placebo. Probably because the treatment was stopped without tapering, severe relapses occurred. In the second study (Pitche et al. 2007), 73 patients with generalized cutaneous LP received three injections of betamethasone every 2 weeks. At 6 weeks, 84 % cleared and 8 % partially remitted. The failure rate was of 8.2 %. At 6 months, the relapse rate was 31.5 %. No major side effects were reported.

Cyclosporin A

Being specifically aimed at cell-mediated hypersensitivity reactions, systemic CyA is expected to be the drug of choice on severe cutaneous LP. It may be surprising therefore that only four small uncontrolled series and one anecdotal case are available. In a total of 21 patients treated with 1–6 mg/kg/day, the lesions cleared in a mean of 6 weeks. No relapse were noted after several months of follow-up in most patients. Lower doses 1–2.5 mg/kg/day proved to be equally effective.

Azathioprine

Azathioprine (50–100 mg/day) may be used in erosive OLP with chronic active hepatitis. Usually, transaminase level and oral lesions improve simultaneously. If the patient is hepatitis C virus positive, however, immunosuppressive treatments should be avoided to prevent hepatocarcinoma to develop. In any case, favorable therapeutic effects for LP found in the literature reach only a low quality of evidence (level C).

Thalidomide and Analogues

Oral administration of thalidomide seems to be effective in two short series and in anecdotal reports. Moura et al. (2009) treated eight patients with cutaneous LP with 100 mg/day. Five (62.5 %)

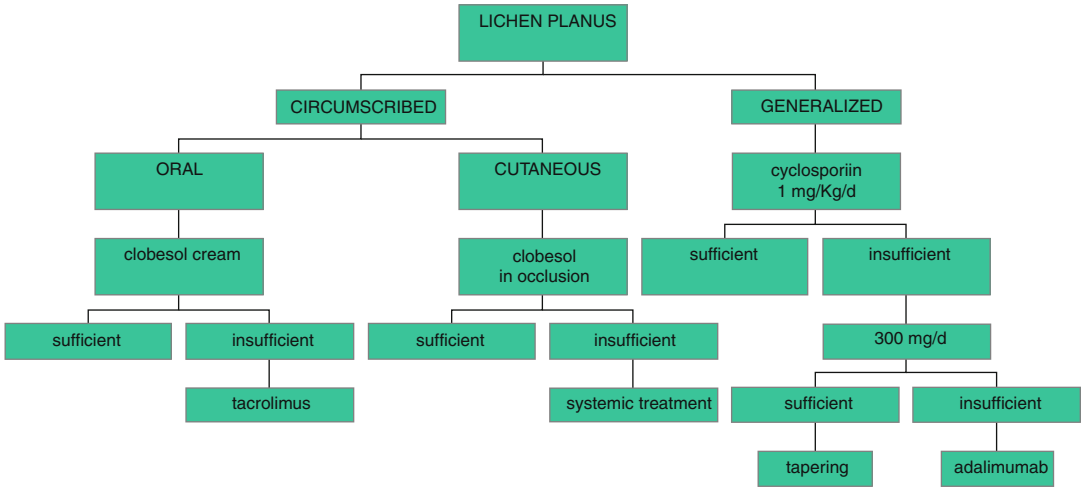

Fig. 53.3 Therapeutic algorithm

patients completed the trial. Three withdrew mainly due to neuropathy affecting the legs and weakness after the first days of treatment. These symptoms spontaneously regressed within days after treatment was stopped. Mean time for complete remission was 3 months. No recurrences were seen at follow-up 1 and 6 months after the end of treatment.

Macario-Barrel et al. (2003) used thalidomide in six patients with severe erosive OLP resistant to oral corticosteroids. They started at 50–100 mg/day to taper to the minimal effective dose. Complete healing of erosive lesions was observed in four patients after a mean duration of 4 months.

Perez reported a patient with generalized LP who, after treatment with thalidomide (initial doses 300 mg/day for 2 weeks and 200 mg/day for further 10 weeks), had his lesions cleared. Naafs and Faber (1985) treated one patient with oral LP in whom clearance was achieved. Another patient with generalized LP failed.

Dereure et al. (1996) treated two patients with severe erosive OLP with 150 mg thalidomide per day with impressive improvement in 4 months in the first case and with nearly complete healing in 3 months in the second. Tapering to 50 mg did not cause relapse. Side effects were minimal, except a mild reduction of T lymphocytes in the first case. Camisa and Popovsky (2000) used thalidomide in a patient with mild OLP at a starting dosage of 50 mg/day for 2 weeks and gradually increased the dosage over 3 months to 200 mg/day. Improvement was noted after 4 months. At the 11th month, the desquamative gingivitis and striae were nearly cleared. Dizziness, edema of the lower extremities, and a mild rash of the face and trunk recommended decrease to 100 mg/day.

Hydroxychloroquine

Although well known to include LP as adverse effect, hydroxychloroquine has been used in OLP at 200–400 mg/day for 6 months as a monotherapy in ten patients. Nine had an excellent response to therapy. Erosions required 3–6 months to clear. There were no adverse effects.

A 9-year-old girl with actinic LP was treated with hydroxychloroquine 200 mg daily for 3 months with complete and no relapse in the following years. The study was biased by the addition with 0.1 % methylprednisolone aceponate ointment for 2 weeks and with photoprotective measures (Ramírez et al. 2012).

A retrospective review by Chiang et al. (2010) of 40 patients with lichen planopilaris (or frontal fibrosing alopecia) who had been treated with hydroxychloroquine for up to 12 months found that after 6 months, 69 % had reduced symptoms and signs, a percentage that rose to 83 % at 12 months.

Retinal adverse effects should be considered, however, as they are often unpredictable and should be thoroughly monitored.

Retinoids

Etretinate provides more side effects than benefits. Five open studies have tested the efficacy of etretinate 0.6–1 mg/kg per day in 58 cases of oral LP (Miyagaki et al. 2013). Results were good in four of the five studies. In a series of ten patients, the benefits were minimal. In the only small controlled trial, 28 patients with OLP were treated with 75 mg/day etretinate vs. placebo for 2 months followed by crossover with etretinate in nine cases. Six stopped the treatment prematurely because of side effects. This therapy improved 93 % of lesions vs. 5 % of control lesions in the control group. Relapses occurred, 3 months after the end of treatment, in 66 % of cases.

In addition, scattered anecdotal reports can be found. A 68-year-old woman with oral and cutaneous LP and thymoma underwent thymectomy. Cutaneous LP lesions subsided spontaneously while oral lesions did not. Oral lesions responded well to oral etretinate therapy. No information on dosage are provided (Miyagaki et al. 2013). Another Japanese woman with ulcerative LP of the sole and Sjogren syndrome was treated with etretinate 30 mg/day for 2 months with nearly resolution of the ulcer (Tsuboi and Katsuoka 2007).

Oral tretinoin has been studied by three open studies. Doses ranged from 10 to 60 mg/day (Ott et al. 1996). Favorable results have been reported, but clinical data and criteria of efficacy are scantily mentioned; dosages are diverse, and topical tretinoin has been added, all biasing the assessment of tretinoin efficacy.

Oral isotretinoin has been reported anecdotally (Handler 1984), and in two small series, the dosage was 0.5 mg/kg/day and was effective in two cases. Benefits were minimal in the series of six patients.

Systemic therapy with acitretin 25 mg daily should be considered for patients with severe refractory LP. In the only placebo-controlled double-blind trial published so far, 65 patients with cutaneous LP were treated with 30 mg/day acitretin for 8 weeks. Sixty-four percent of them significantly improved vs. 13 % of controls. Clearance was doubtful, however, as papules persisted in most patients as one figure clearly shows. The trial had some defects as neither criteria for remission and improvement were detailed nor the duration and the extent of the lesions. Six of eight patients with LP treated with 50 mg/day acitretin for 8 weeks had a dramatic improvement, as did a boy with exanthematous LP (Brockowet al. 1997). A case of refractory hypertrophic LP, reported by Jaime et al. (2011), was treated with acitretin 40 mg/day and achieved total resolution on the upper limbs and partial resolution on the lower limbs after 9 months of therapy.

Because of the systemic side effects, acitretin has been replaced by oral alitretinoin. In one anecdotal report, a patient was treated with 30 mg/day with good results within 4 weeks. No severe side effects were registered, but oral striae and dysphagia recurred during treatment and LP relapsed after 4 months (Kolios et al. 2013).

Recently, some reports of recalcitrant lichen planus successfully treated with alitretinoin have been published (Kolios et al. 2013; Brehmer et al. 2011).

Temarotene obtained complete or nearly complete remission after 2–3 months in 10/13 patients. Dosage was 800–4,800 ng for between 31 and 441 days. Nausea and vomiting, with a transient increase of transaminase blood levels, afflicted six patients (Bollag and Ott 1989).

Dapsone

Dapsone (50–150 mg/day) proved to be more effective than topical corticosteroids in a prospective trial with 75 patients and in 2 isolated cases of recalcitrant erosive oral LP (Chopra et al. 1999). Attention should be paid to older patients for dapsone systemic side effects (hemolysis, methemoglobinemia). Its use is recommended in children and in bullous cases.

Methotrexate (MTX)

Only small retrospective series are available in the literature. Eleven patients with generalized

LP were treated with MTX 15–20 mg/week. Mucocutaneous lesions and pruritus improved within the first month in all patients, and complete response was achieved in ten patients at the end of the first month. Only one patient discontinued MTX because of intolerable adverse effects (nausea and fatigue) at the fourth week (Turan et al. 2009).

Adverse effects are in fact common, but they have been found only mild in a double-blind controlled study (Hazra et al. 2013) on 44 patients with LP treated with MTX (10 mg) (23 patients) or mini-pulse betamethasone (5 mg) (21 patients). Anemia (14.2 %), edema (57.1 %), dyspepsia 15 (71.4 %), acne 10 (47.6 %), mooning face 8 (38.1 %), striae 8 (38.1 %), menstrual abnormality (71.4 %), and hypertrichosis 4 (19.0 %) developed only with betamethasone. Intermittent diarrhea, headache, nausea, and fatigue were complained with both drugs but more often with betamethasone. Abnormality in platelet count and SGPT were registered only with MTX.

Tetracycline

In an open-label clinical trial, 15 patients with LP were treated with tetracycline 500 mg or doxycycline 100 mg, both twice daily. Of the 13 subjects who completed the study, 6 (46 %) reported no response to either doxycycline or tetracycline, 6 (46 %) a partial response, while only 1 experienced a complete remission in a mean treatment period for responders which was 3.6 months (range 1–6) (Hantash and Kanzler 2007).

An anecdotal report of a woman with lichen pemphigoides suggested the efficacy of doxycycline 200 mg/day and nicotinamide 1,500 mg/day, though the therapy included also intralesional triamcinolone.

Griseofulvin

Griseofulvin was largely studied in the past though no definitive conclusions were allowed. Griseofulvin, 1,000 mg/day, was given for 1–10 months in 15 patients with cutaneous LP and in 25 patients with cutaneous LP (Levy et al. 1986). In the first open study, 12 % of the patients improved and 12 % experienced exacerbation of the disease. In the second study, 86 % of the patients had complete disappearance of the lesions after a 3-month delay. A study included two groups of 17 patients receiving either placebo or griseofulvin for 4–6 weeks. A partial regression was observed in 71 % of griseofulvin-treated patients vs. 30 % of controls. In the second study, 44 patients with cutaneous LP were treated with griseofulvin, 1 g/day or placebo for 8 weeks. Griseofulvin resulted in "complete improvement" in 82 % of patients and partial remission in 18 %, whereas partial remission occurred in only 23 % of placebo-treated patients. A case of intensely pruritic acute eruptive LP in a 51-year-old male failed to respond to griseofulvin, and of seven OLP cases treated with 500 mg/day griseofulvin for more than 2 months, none improved and four worsened.

Levamisole

Levamisole hydrochloride has been tried in two studies, but in one it is not known whether the patients improved and in another it was associated with prednisolone (Lu et al. 1995).

Curcuminoids

Curcuminoids (diferuloylmethane) are components of turmeric (*Curcuma longa*) that has anti-inflammatory properties and has been used in Indian traditional medicine for centuries. A randomized, double-blind, placebo-controlled clinical trial on 20 OLP patients compared 6,000 mg/day curcuminoids in three divided doses to placebo. The curcuminoids group showed a greater and significant reduction in erythema and total modified Oral Mucositis Index score and proportion showing improvement in the numerical rating scale of OLP signs and symptoms and total Modified Oral Mucositis Index score. Adverse effects were uncommon in both groups (Chainani-Wu et al. 2012).

Metronidazole

As LP is a standard Th1 cell-mediated reaction to a variety of antigens, it is of no surprise that cutaneous and oral lesions improved as the results of treatment of intestinal giardiasis with oral metronidazole. In an open-label trial (Rasi et al. 2010), 49 LP patients were given metronidazole, 750 mg/day. Forty-one percent of lesions fully cleared, 33 % had partial healing, and 26 % did not improve. In mucosal lesion, the overall response was 67 %. In another open study, 19 LP patients were treated with 1 g metronidazole for 20–60 days and were followed up for a period of 5–36 months. Complete response was observed in 13 patients. Lesions worsened in 1 of the 4 nonresponders.

Itraconazole

A prospective, open-label study of itraconazole 400 mg/day for 1 week of each month for 3 months in 16 patients with severe LP reported complete cessation of new lesions in 77.7 %, complete relief of pruritus in 55 %, and complete flattening of lesions in 33 %. The mechanism of action is believed to be due to the immunomodulatory effects of itraconazole (Khandpur et al. 2009).

Fumarate

In a retrospective study, two of three LP patients showed complete clearance of their lesions after being treated with fumarate (max three tablets a day for 8 months). In one case, side effect led to discontinuation.

Biologics

As the serum levels of TNF-alpha is higher in LP patients, some TNF-alpha inhibitors have been tried in particularly severe LP patients. Results are in general encouraging, although some relapses and even a rebound effect have been registered at the drug withdrawal (Table 53.2). Another apparent contradiction rests on the fairly frequent occurrence of LP as side effects of TNF-alpha inhibitors used for other reasons. Less understandable is why B-cell inhibitors like rituximab and mycophenolate mofetil can work in a Th1-mediated disease as LP. In any case, biologics should be used only as ultima ratio when all other therapies have failed or cannot be used.

UV Phototherapy

Narrowband UVB

Twenty patients with disseminated LP were included in a retrospective study treated with narrowband UVB thrice a week according to the standard protocol for psoriasis. Complete response was obtained in 11 patients and partial response in 4 after 3 months, with an accumulated dose of UVB of 36 ± 4.8 J/cm^2. Another retrospective analysis of 43 patients with generalized LP treated by narrowband UVB revealed that complete response was achieved in 70 % of cases. In a randomized study, 46 patients with generalized LP were treated with either systemic prednisolone 0.3 mg/kg for 6 weeks or narrowband UVB (max 9 J/cm three times a week for 6 weeks). Narrowband UVB was significantly more effective than systemic steroids (Iraji et al. 2011).

PUVA

In a retrospective study, 28 patients with disseminated LP treated with PUVA and 13 treated with UVB-311 nm were compared. All 15 patients treated with oral PUVA had a complete (10) or partial (5) clinical response. The ten patients treated with UVB-311 nm showed complete (4) or partial (6) clinical response. The initial response to PUVA was significantly superior. After a mean follow-up period of 20.5 and 35.7 months, respectively, the disease relapsed in 7 of 15 PUVA-treated patients in 3 and 3 of 10 UVB-311 nm-treated patients (Wackernagel et al. 2007).

Table 53.2 Biologics in LP

Drug	Author	Year	Cases	Type of LP	Dose	Duration (wks)	Result
Adalimumab	Chao	2009	1	LP + OLP		22	CR
	Ho and Hantash	2011	1	Vulvovaginal gingival syndrome	160 mg SC	12	CR
	Holló et al.	2012	1	LP	80 mg SC	24	CR
Alefacept	Fivenson and Mathes	2006	2	LP + OLP	15 mg/wk IM	12–20	CR
	Chang et al.	2008	7	Erosive	15 mg/wk IM	12	2 CR, 5 NR
Basiliximab	Rebora et al.	2002	1	Erosive	20 mg/ 4 days apart IV	1	CR but rebound in 4 wks
Efalizumab	Cheng and Mann	2006	1	Erosive	0.7–1 mg/Kg wk SC	10	PR
	Hefferman et al.	2007	4	Erosive	0.7–1 mg/Kg wk SC	11	PR
	Boehm and Luger	2007	1	LP	0.7–1 mg/Kg wk SC	4	CR
Etanercept	Yarom	2007	1	Erosive	25 mg/wk SC		PR but relapse
	Irla et al.	2010	1	Nail LP	25–50 mg/wk SC	24–36	PR
Infliximab	Muller et al.	2008	1	Erosive			PR
Rituximab	Parmentier et al.	2008	1		375 mg/m^2/wk IV	12	CR (relapse at 10th month)
	Erras et al.	2011	1	LPP	1 g/wk IV	24	CR
Mycophenolate mofetil	Brehmer et al.	2011	16	LPP		>24	5 CR,5PR,2NR.4WD
	Emad et al.	2012	1	LP	1.5 g/day	24	PR[a]
	Wee et al.	2012	10	Erosive	2 g/day	3.7 years	7CR, 3 PR
BCG-PSN	Xiong et al.	2009	31	Erosive	0.5 ml every other day	2	CR (87 %)

LP lichen planus, *OLP* oral LP, *LPP* lichen planopilaris, *wks* weeks, *CR* complete remission, *PR* partial remission, *NR* nonresponder, *WD* withdrawal, *SC* subcutaneous, *IV* intravenous

[a]+systemic steroids

Conclusions

Generalized LP is rare and commonplace patients do not need particular treatments. This is probably the reason why most of the studies are based on very small populations. Recruiting larger populations and following them up for a long time is not a cheap endeavor. As a consequence, one may suspect that the few studies existing in the literature, which may be considered of level A, are probably supported by the firm that manufactures the studied drug. A conflict of interest may bias their results.

Keeping this on mind, acitretin is the first line of treatment for cutaneous LP. Systemic corticosteroids are the second-line treatment, and all other drugs or procedures, including PUVA and narrowband UVB, are still awaiting rigorous placebo-controlled randomized trials.

Oral LP, instead, especially in its erosive form, is the real therapeutic challenge, since it is painful, prevents eating and speaking, exhales a fetid odor, and, therefore, compromises the quality of life of the patient. In addition, it carries a non-negligible risk of carcinogenicity. This is the reason why a large literature exists, mostly by stomatologists, but there is a lack of strong evidence supporting the efficacy of any therapy for OLP, with the possible exception for calcineurin inhibitors. In OLP, topical corticosteroids are the first line of therapy, a choice which has been recommended by several studies (Cribier et al. 1998). The second line is represented by calcineurin inhibitors, which have replaced topical cyclosporine A. A number of other treatments, including biologics, require further rigorous studies.

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Lichen Simplex Chronicus

54

Mary Gantcheva and Valentina Broshtilova

Key Points

- Lichen simplex chronicus (LSC) is an acquired, severely itching chronic dermatosis with circumscribed lichenified lesions, which are due to skin rubbing and scratching.
- The key point of therapy is to introduce an individualised therapy regimen according to the patient's age, pre-existing diseases, medications, quality and intensity of pruritus.
- Explanation of the basic itch-scratch mechanisms and their relationship to the disease course is extremely helpful, because the patient realises his key role in the induction of the pathological process.
- General pruritus-relieving measures are simple and helpful approaches for long-term application that should be recommended to the patients. These measures include wet and cold wraps and application of lotio alba, a short-time localised heat.
- Systemic therapy aims to relieve itch. New therapeutic modalities such as opioid agonists and antagonists, gabapentin and leukotriene antagonists are being administered together with conventional antipruritic drugs to reduce itching and improve quality of life of patients.
- Topical therapy is introduced on a long-term basis due to its anti-inflammatory, antiseptic and antipruritic properties. Different topical modalities are used according to the stage of the disease.

Definition and Epidemiology

Lichen simplex chronicus (LSC) is an acquired, severely itching chronic dermatosis of circumscribed lichenified lesions, which are due to rubbing and scratching of previously normal looking skin. It follows a self-perpetuating scratch-itch cycle, which begins with rubbing and scratching of the skin to form areas of thickened, leathery, brownish lesions. Often there is no known predisposing skin disorder and underlying cause of the

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_54, © Springer-Verlag Berlin Heidelberg 2015

development of the lichenification. However, itch may be associated with chronic eczema, atopic dermatitis, psoriasis, or other pre-existing skin conditions, as well as nervousness, anxiety, depression or any other psychological disorders. It is common in children, who chronically scratch insect bites or other areas, especially in mentally retarded individuals with chronic repetitive movements.

Variants in clinic morphology, size and location have led to several clinical variants, which affect the population worldwide. LSC is particularly common in Orientals and is comparatively rare in black people. Women are predominantly affected with the peak incidence between 30 and 50 years.

LSC frequency demonstrates a high burden and an impaired quality of life. As a consequence of the diversity of possible underlying diseases, no single therapy concept can be recommended. Each form of LSC has to be considered individually. There is a significant lack of randomised controlled trials that can be explained by the diversity and complexity of LSC symptoms, multifactorial aetiologies and the lack of well-defined outcome measures. However, new therapies for improved medical care have been suggested.

Basic Concepts of Pathogenesis

Lichenification may occur secondary to many pruritic dermatoses, and some authors suggest that LSC is a minimal variation of atopic eczema in adults with a personal or family history of atopic disorders. Others suppose that the occurrence of the disease is related to internal disorders such as gastrointestinal or liver cholecystopathies, diabetes mellitus or constipation. Lichenification also develops in the course of other irritant dermatoses or complicates persistent skin lesions of many types, such as chronic contact dermatitis, seborrhoeic and stasis dermatitis, lichen planus, pruritus ani et vulvae and rarely psoriasis.

Pruritus seems to be the cause and not just a symptom of LSC. It is the main factor for the development of the lichenification and probably results from mediator release or proteolytic enzyme activity. Nervous stress and psychovegetative disorders unlock an unconscious habit of rubbing and repeated scratching, which lead to thickening of the skin with accentuation of the skin markings. Sometimes nodular lesions appear as a consequence of prolonged rubbing. The increase in neuropeptides, calcitonin gene-related peptide and substance P immunoreactive nerve fibres can be related to prolongation and refractive course of LSC with secondary formation of nodular lesions. Other patients (e.g. black people) develop papular and follicular lichenification. Presumably, there is a native predisposition to the development of lichenification and its persistence.

LSC is classified, based on the presumptive aetiology, into (I) “dermatological”, (II) “systemic”, (III) “neurological”, (IV) “various”, including “somatoform”. The latter LSC variant should be defined as lichenification where psychiatric and psychosomatic factors play a critical role in the initiation, intensity, aggravation or persistence of the lesions.

Clinical Presentation

Pruritus is severe and paroxysmal and usually occurs at night. It is often out of proportion to the extent of the objective changes. The original lesion is usually isolated and a three-zone structure could be distinguished: central, infiltration and flat lichenification; middle, closely set lichenoid papules; and peripheral, slight thickening and pigmentation. There are different forms of lichenification with their own features depending on the localisation and duration. In early lesions the two external zones may be absent. In some cases leucoderma can be seen accompanied by vitiligo-like macules and depigmented area of infiltrated plaques. Rarely, LSC is presented with isolated lichenoid papules without central lichenification.

Almost every skin area may be affected, but the most common locations are those that are conveniently reached: the nape of the neck, scalp, extensor aspect of forearm, sacrum, inner thighs,

lower legs and ankles, vulva, pubis and scrotum (Fig. 54.1).

Lichen nuchae occurs on the back of the neck (Fig. 54.2) particularly in women under emotional stress or in patients with atopic dermatitis. This area is easily reached and patients may scratch it intensively. In both cases the disease is characterised by scaly psoriasiform plaques that are frequently impetiginised.

Nodular neurodermatitis of the scalp presents with pruritic and excoriated papules. The epidermal thickening of the scalp in this situation is enough to form nodules.

Giant lichenification of Pautrier presents with warty, cribriform plaques. Usually it affects the genitocrural region. The pruritus is persistent for many years. Sharply demarcated patches of verrucoid hyperplasia can be elevated above the surrounding surface, and tumour-like plaques may be formed.

The clinical evidence of "pebbly" lichenification is presented by plaques of coalescing smooth papules or discrete small nodules resembling lichen planus. They could also be seen in patients with atopic dermatitis, photodermatitis and seborrhoeic dermatitis.

The course of LSC is chronic and the lesions persist indefinitely depending on individual variation.

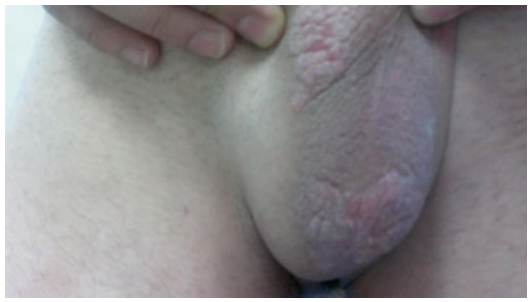

Fig. 54.1 Circumscribed lichenified lesions on the skin of the scrotum in a man with lichen simplex chronicus

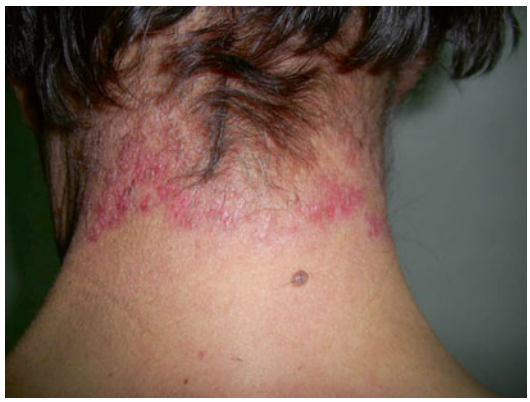

Fig. 54.2 Lichen simplex chronicus on the back of the neck

Diagnosis

A patient's history should always include all current and recent medications, infusions and blood transfusions. Severe pruritus can lead to considerable psychological distress. This should not be underestimated by the physician and should be addressed directly. Examination of patients includes a thorough inspection of the entire skin including mucous membranes, scalp, hair, nails and anogenital region. The distribution of primary and secondary skin lesions should be recorded together with skin signs of systemic disease. General physical examination should include palpation of the liver, kidneys, spleen and lymph nodes. A skin biopsy specimen shows some variations with site and duration. Hyperkeratosis and acanthosis are constant. The rete ridges are lengthened. Sometimes spongiosis is present and small areas of parakeratosis are seen. Hyperplasia is everywhere.

Differential Diagnosis

- Atopic dermatitis: onset at childhood, presence of atopic stigmata, symmetrical lichenified lesions of predilection, positive radioallergosorbent test (RAST) or skin prick tests, elevated serum immunoglobulin E (IgE)
- Nummular eczema: absence of lichenified plaques
- Psoriasis: usually no itch, presence of psoriatic lesions elsewhere, thick adherent white scales and positive clinical symptoms, distinct histology on skin biopsy

- Lichenified chronic eczema: presence of more inflammatory changes, distinct histology on skin biopsy
- Hypertrophic lichen planus: involvement of the mucosa in about 50 % of patients, Wickham's striae
- Lichen amyloidosis: infiltrated itchy papules with typical ripple appearance, no plaque formation, symmetrical distribution, histology verification
- Prurigo nodularis Hyde: single nodules on normal skin
- Tinea (dermatophyte infection): microbiology, typical Wood's light features
- Contact dermatitis: patient's history, usually symmetric involvement, positive patch testing
- Drug reactions (gold, trimethoprim sulphamethoxazole diflunisal, bupivacaine, quanidine, quinacrine): history of drug intake
- Cutaneous T-cell lymphoma: distinct histology and immunohistochemistry.
- Stasis dermatitis: skin lesions on the lower legs in the presence of chronic venous insufficiency

General Principles of Treatment

An individualised therapeutic regimen according to the patient's age, pre-existing diseases, medications, quality and intensity of pruritus should be established. Elderly patients, pregnant women and children need special attention. As the care of LSC patients often extends over a long period, frustration regarding the failure of past therapies and general psychological stress frequently occurs. Some patients need a psychiatric consultation and in such cases psychotherapy is recommended. These are usually individuals who feel themselves emotionally distributed or have functional complaints. The diagnostic procedures and therapy should be discussed with the patient in order to achieve best possible compliance.

Patients should be given treatment for any underlying stress. The lesions worsen during periods of fatigue and emotional tension and improve with relaxation. In most cases the rubbing and scratching exist as a reflexive and unconscious habit. Explanation of the itch-scratch mechanism and its relationship to the disease course could be helpful.

Pruritus-Relieving Measures

There are simple and helpful measures such as wet and cold wraps and application of lotio alba. Application of short-time localised heat has shown promising itch-relieving results in case reports and an experimental study. Cool to tepid baths are another commonly used method of reducing itching. During active treatment, patients must avoid washing the involved areas with soaps and detergents and should have their nails cut.

Topical Treatments

(a) *Glucocorticosteroids.* External therapy without steroid treatment is not conceivable, although there are side effects associated with them. High-potency glucocorticosteroids tend to relieve the itching and infiltration of the lesions. Very potent topical steroids as a local application and under occlusive dressings are recommended for a short time. If the lesion is located in the genital area, it is preferable to use mild-potency steroids. Intralesional applications of triamcinolone acetonide (crystalline suspension – 10 mg/mL, 1: 4 dilution in 1 % local anaesthetic) should be tried in small lesions. Care must be taken to avoid the risks of atrophy and depigmentation. Injection should not be made into excoriated or infected lesions.

(b) *Tar.* The anti-inflammatory property of tar and tar products is well known. Liquor carbonis detergents or pure coal tar could be prescribed for a few days. It is better if combined with emollients because tar dries the skin. Photosensitisation, contact dermatitis and folliculitis may also occur as side effects. Combined therapy is well tolerated, including steroids and tar with or without salicylic acid.

(c) *Urea.* Urea preparations have been applied with great success in LSC therapy, follow-up and prophylaxis. Efficacy is based on its properties to increase the water-binding capacity of the corneal layer, on its keratoplastic abilities, anti-pruriginous effect and proliferation-suppressing action. The combination of hydrocortisone and urea may prove useful in the treatment of LSC.

(d) *Doxepin.* Topical application of 5 % doxepin cream has significant antipruritic activity in patients suffering from LSC. Doxepin cream provides pruritus relief with transient and mild adverse effects, such as stinging at the side of application.

(e) *Others*

Local anaesthetics. Local anaesthetics act via different groups of skin receptors. They can be used for pain, dysaesthesia and pruritus. Benzocaine, lidocaine, pramoxine as well as a mixture of prilocaine and lidocaine are widely used topically but have only a short-term effect. Intralesional application has also been used in persistent and therapy-resistant cases.

Capsaicin. Topical application has significant antipruritic activity with long-term effect. It is easy to use and highly effective. Only a few side effects have been described such as stinging and drowsiness at the side of application.

Cannabinoid receptor agonists. Since 2003 topical cannabinoid receptor agonists are used as antipruritic and analgesic substances for localised pruritic lesions.

Tacrolimus and pimecrolimus. The effects of tacrolimus and pimecrolimus on pruritus are mediated both through their immunological and neuronal properties. They can be used on a long-term basis for coping with the inflammation in LSC. Patients should be aware that transient irritation and burning at the site of application can appear.

Zinc, menthol and camphor. Although zinc oxide, menthol and camphor have been used in dermatology for over 100 years, due to their anti-inflammatory, antiseptic and antipruritic properties, their efficacy and safety are not proven in double-blind placebo-controlled study. However, prescriptions in creams, liniments, lotions, ointments and pastes are widely used and favoured in coping localised forms of pruritus, especially in children.

Mast cell inhibitors. Pruritus in atopic dermatitis responds to topical sodium cromoglycate and may exert favourable effect in LSC.

Topical Treatments at a Glance

- General pruritus-relieving methods are highly effective in coping with itch and discomfort in LSC.
- Topical corticosteroids are main stones of therapy. They may be applied alone or in combination with other agents to exert more favourable effect.
- Emerging topical regimens include local anaesthetics, capsaicin, cannabinoid receptor agonists and macrolide immunomodulators. Unfortunately, most can cause irritation and burning sensation at the site of application and often have only a short-term effect.
- No fixed-dose combination topical formulations for LSC exist. The therapeutic regimen should be strictly individualised and referred to the patient's general psychological condition.

Systemic Treatments

(a) *Antihistamines.* Antihistamines are the most widely used systemic antipruritic drugs in dermatology. First-generation antihistamines, such as chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine and promethazine, bind not only to H1-receptors but also to muscarinic, α-adrenergic, dopamine or serotonin receptors, thus exerting a central sedative effect. Therefore, their use is nowadays restricted and reserved only for cases with self-accentuation and obsession-compulsion syndromes. Second-generation antihistamines like cetirizine, levocetirizine, loratadine, desloratadine, ebastine, fexofenadine and rupafine have minimal activity on non-histaminic receptors, little sedative effect and a longer duration of action compared to

the first generation. Higher doses of second-generation antihistamines enhance their activity and may also be beneficial. Antihistamines are widely used as first-line drugs in patients with symptomatic LSC due to systemic diseases such as chronic renal failure, cholestasis, haematopoietic diseases and thyroid disorders.

(b) *Glucocorticosteroids.* There are no studies investigating the efficacy of the exclusive use of systemic glucocorticosteroids in LSC. Thus, systemic glucocorticosteroids should not be considered a therapeutic option and should not be prescribed in LSC cases. Systemic corticosteroids can be used as short-term treatment in severe cases for no more than 2 weeks.

(c) *Opioid receptor agonists and antagonists.* Experimental and clinical observations have demonstrated that pruritus can be evoked or intensified by endogenous or exogenous μ-opioids. This phenomenon can be explained by activation of spinal opioid receptors, mainly μ-opioid receptors. Therefore, μ-opioid antagonists may inhibit pruritus. The opposite is true for k-opioids. Their binding to μ-opioid receptors leads to inhibition of pruritus. Nalmefene, naloxone and naltrexone have exhibited high antipruritic potency and can be used in LSC therapy. High state of precaution is needed on administration of these drugs due to their broad side-effect profile.

(d) *Gabapentin and pregabalin.* Gabapentin is an antiepileptic drug also used in neuropathic disorders causing pain or pruritus. The mechanisms of action of the 1-aminomethyl-cyclohexane acetic acid, which is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), remain unclear. It is used in postherpetic neuralgia, especially with paroxysmal pain or pruritus. Anecdotal indications are brachioradial pruritus and cutaneous T-cell lymphoma. Off-label use of gabapentin and pregabalin can be recommended in some cases of LSC.

(e) *Antidepressants.* Psychoemotional factors are known to modulate the "itch threshold". Under certain circumstances, they can trigger or enhance LSC. Itch is a strong stressor and can elicit psychiatric disease and psychological distress. Depressive disorders are present in some patients with LSC. Consequently, depressive symptoms should be treated in these patients, and some antidepressants may also exert an effect on pruritus through their pharmacological action on serotonin and histamine.

(f) *Leukotriene receptor antagonists.* Leukotriene receptor antagonists (e.g. montelukast, zafirlukast) influence the pathogenesis of pruritus. They have been used in combination with antihistamines as antipruritic therapy. They may be considered, but due to the lack of evidence, cannot be recommended in the treatment of LSA.

(g) *Cyclosporin A.* Pruritus in atopic dermatitis and prurigo nodularis responds to treatment with cyclosporin A. It should have beneficial effect on LSC lesions as well. However, no controlled double-blind studies exist.

(h) *Aprepitant.* Substance P has a dominant role in pruritus induction in the skin. Via binding to the neurokinin 1 receptor (NKR1) on keratinocytes, blood vessels and mast cells, substance P is increased in skin lesions with nerve fibre hyperplasia. Presumably, inhibition of the corresponding receptor should cope with the itch sensation and relieves the LSC symptoms. There are only anecdotal reports on the beneficial effect of aprepitant in cases of cutaneous T-cell lymphoma, solid tumours and drug-induced pruritus. It may be considered a second-line option in therapy of refractory cases with persistent pruritus.

Systemic Treatments at a Glance

- Second-generation antihistamines are recommended as first choice for the treatment of long-lasting LSC, refractory to topical modalities.
- Oral medications should always be combined with topical itch-relieving modalities and general antipruritic measures.
- The beneficial effect of oral LSC therapy is not proven in double-blind placebo-controlled studies, and this lack of evidence

restricts the therapeutic choice to individualised approach of patient's systemic involvement and pre-existing conditions.
- Highly refractory LSC cases may require a short-term therapy of different class medication groups.

Alternative and Experimental Treatments

Alternatively, topical photochemotherapy (PUVA) three times weekly (3–5 J/cm/sq.m) is recommended to 20 therapeutic sessions per course.

Bulgarian dermatologists have been pioneers in the successful treatment of LSC using high-mountain climatotherapy. Itching is reduced by a cooling off in the atmosphere at 2,000 m above sea level. Pathologically changed reactivity of the organism modifies to a state of hyposensibilisation. The beneficial effects of high-mountain climatotherapy are based on the relative cleanliness of the air, the abundance of ultraviolet radiation and the low partial pressure of O2, stimulating the hormonal activity of adrenal glands.

- Acupuncture is also helpful in the relief of pruritus and could be recommended on a follow-up basis.

Guidelines for LSC Treatment

The treatment choice should be individualised and should take into account the age and medical history, the course and severity of the disease, the underlying systemic conditions and the impact of the dermatological problem on the quality of life of the patient. Topical regimens should be used as first-line therapy. Mild-to-moderate topical corticosteroids are found to have highest efficacy. The potent corticosteroid medications, even under occlusive dressings, should be used only in refractory cases.

Combined topical regimens are not fixed and depend on physician's own judgement, routine and skilfulness. The individual patient's characteristics and pre-existing conditions should always be taken into consideration.

Systemic drugs should be used only on a short-term basis in patients with systemic involvement and a protracted disease course.

Alternative therapeutic options such as high-mountain climatotherapy, acupuncture and topical photochemotherapy may provide safe and beneficial option in the combined therapeutic regimen.

An algorithm of treatment according to LSC clinical forms is suggested:

Cutaneous findings	Pre-existing dermatosis	No underlying skin condition
	Treatment of the main clinical entity	Topical corticosteroids
	Leukotriene antagonists in atopic patients	Tacrolimus and pimecrolimus
	Zink, menthol, camphor	Combination of topical preparations with oral antihistamines in refractory cases
	Mild corticosteroid tars	
	Tars in psoriasis and chronic eczemas	
Systemic	Depending on the underlying disease	
	Usually requires topical and systemic therapy	
	Opioid receptor antagonists in patients with chronic liver or kidney failure and cancers	
Neurological	Antidepressants	
	Gabapentin	
	Psychodynamic treatment options	
Various	Topical capsaicin	
	Doxepin	
	Mild-to-moderate corticosteroids	
	Alternative regimens, e.g. acupuncture, high-mountain climatotherapy	

Future Perspectives

Future perspectives include various psychodynamic techniques, new preparations for itch relief and combined regimens of alternative curative methods such as thalassotherapy, high-mountain therapy, traditional Chinese medicine approaches and orthomolecular treatment with natural substances, enzymes and vitamins. New electrophysiological, ultrasound, cavitation and synergic methods of reflexotherapy should also be taken into consideration.

Double-blind placebo-controlled trials on the efficacy of newly introduced antipruritic drugs are needed to provide control and introduce the principles of good medicine practice in the everyday care of patients with LSC and general itch.

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Lupus Erythematosus

55

Annegret Kuhn and Aysche Landmann

Key Points

- Therapeutic agents are applied off-label for patients with cutaneous lupus erythematosus (CLE), mainly based on the experience of experts.
- Topical corticosteroids are the mainstay of treatment for all different subtypes of the disease, but they are of limited value because of their well-known side effects, such as skin atrophy and telangiectasia.
- A safe and effective alternative topical treatment for CLE are the calcineurin inhibitors tacrolimus and pimecrolimus.
- Irrespective of the subtype of the disease, antimalarials, such as hydroxychloroquine or chloroquine, are the first-line systemic treatment for disfiguring and widespread skin manifestations.
- Systemic steroids can be used additionally in patients with highly acute and severe skin lesions but should be time limited due to the common side effects, such as osteoporosis.
- In contrast to immunosuppressive agents, such as azathioprine, cyclophosphamide, and cyclosporine, methotrexate has received more attention in the therapeutic management of skin manifestations of the disease.
- Further second-line treatment includes retinoids, dapsone, and mycophenolate mofetil. Other agents, such as rituximab and ustekinumab, have been used in single cases of therapy-refractory CLE and need to be evaluated in randomized controlled trials.

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Definition and Epidemiology

The inflammatory autoimmune disease lupus erythematosus (LE) encompasses different clinical entities, reaching from a primarily cutaneous form (cutaneous lupus erythematosus, CLE) to a severe systemic disease (systemic lupus erythematosus, SLE). Only a small number of patients with CLE subsequently develop a systemic organ manifestation; however, cutaneous lesions can

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_55, © Springer-Verlag Berlin Heidelberg 2015

appear in 73–85 % of patients with SLE and may occur at any stage of the disease (Kuhn et al. 2009). In 1982, the American College of Rheumatology (ACR) developed a set of criteria for the classification of SLE that provides some degree of uniformity in classifying the patient population (Tan et al. 1982). However, the ACR criteria are of limited value to distinguish CLE from SLE as 4 of the 11 criteria are dermatological criteria; therefore, patients with primarily skin manifestations may be classified as SLE based on mucocutaneous lesions (Albrecht et al. 2004). Recently, the Systemic Lupus International Collaborating Clinics (SLICC) revised and validated these criteria in order to improve clinical relevance, meet stringent methodology requirements, and incorporate new knowledge regarding the immunology of SLE (Petri et al. 2012).

The classification of the cutaneous lesions into LE-specific and LE-nonspecific manifestations based on histological criteria of skin biopsy specimens was initially proposed by Gilliam in 1972 (Gilliam 1977). For example, vascular skin changes, such as urticarial vasculitis and livedo reticularis, are defined as LE-nonspecific skin lesions, which are mostly associated with active SLE, reflecting potentially systemic organ manifestations and serious complications (Costner et al. 2003). In contrast, the LE-specific skin lesions present the different subtypes of CLE, which are classified by the "Duesseldorf Classification 2004" (Kuhn and Ruzicka 2004); this classification subdivides the skin manifestations into acute CLE (ACLE); subacute CLE (SCLE); chronic CLE (CCLE), including discoid lupus erythematosus (DLE) as the most common form of CLE; and intermittent CLE (ICLE) (Table 55.1).

Up to date, no drugs have been approved specifically for the treatment of CLE, although several agents are licensed for systemic organ manifestations, such as lupus nephritis, or other immunological diseases. This is mainly due to the fact that only single randomized, controlled trials have been performed in CLE. According to the Cochrane Database of Systematic Reviews, two randomized, controlled trials are available for DLE (Jessop et al. 2009). Further randomized, controlled trials for other CLE subtypes were performed in the past years, i.e., comparing tacrolimus ointment with clobetasol propionate or the vehicle (Tzung et al. 2007; Kuhn et al. 2011a). Thus, topical and systemic agents in CLE are applied "off-label," mainly based on the experience of experts. In 2011, the novel monoclonal antibody belimumab, a B lymphocyte stimulator-specific inhibitor (Manzi et al. 2012), was approved for SLE based on two phase III trials (Furie et al. 2011; Navarra et al. 2011). This agent showed significant improvement for mucocutaneous manifestations, evaluated by the SLE Responder Index (SRI), but further prospective studies using a validated skin score are necessary to assess its efficacy in the different subtypes of CLE. In this article, recent information on therapeutic options and strategies for the treatment of skin manifestations of the disease is summarized (Table 55.2).

Table 55.1 Dusseldorf classification of cutaneous lupus erythematosus

Acute cutaneous lupus erythematosus (ACLE)
Localized form
Generalized form
Subacute cutaneous lupus erythematosus (SCLE)
Annular form
Papulosquamous form
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Localized form
Disseminated form
Chilblain lupus erythematosus (CHLE)
Lupus erythematosus profundus/panniculitis (LEP)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET)

Topical Treatments

Topical Corticosteroids

Topical corticosteroids show a high efficacy in the treatment of localized skin lesions in CLE and SLE; therefore, class I to class IV corticosteroids

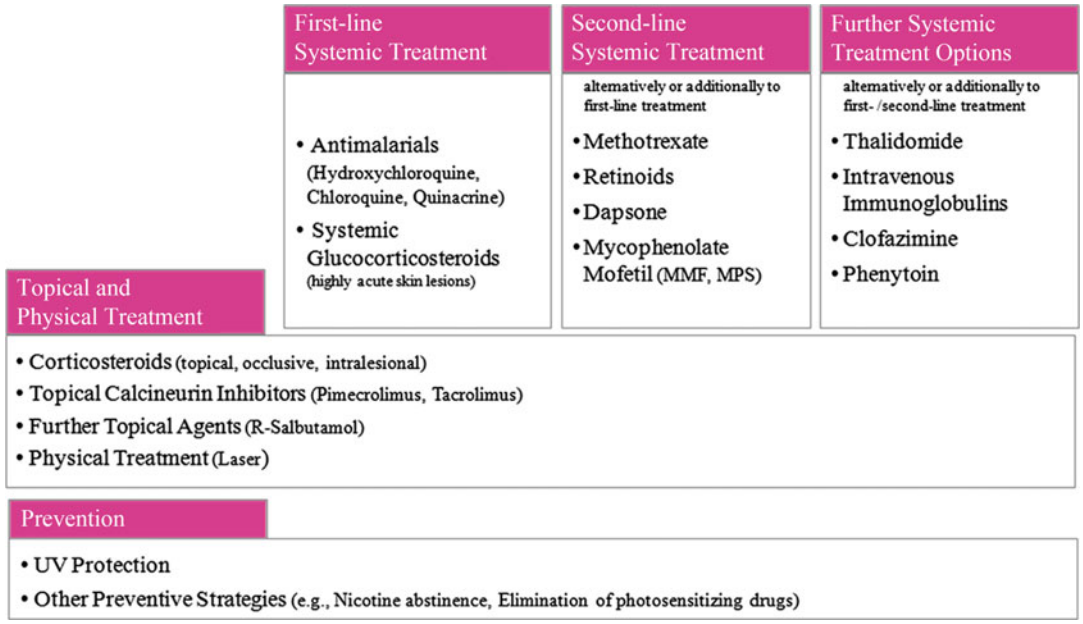

Table 55.2 Therapeutic Options of Cutaneous Lupus Erythematosus

are the mainstay of treatment in all disease subtypes. One randomized, controlled, 12-week crossover study exists, which compares 0.05 % fluocinonide, a potent corticosteroid cream, with 1 % hydrocortisone, a low-potency corticosteroid cream, in 78 patients with DLE (Jessop et al. 2009; Roenigk et al. 1980). This trial showed an improvement of skin lesions in 27 % of patients using fluocinonide and in 10 % of patients using hydrocortisone. However, corticosteroids are of limited value in the long-term topical treatment of facial and widespread skin lesions due to the well-known side effects, such as skin atrophy and telangiectasia (Kuhn et al. 2011b). Therefore, topical corticosteroids should be applied time limited and preferably intermittent. To increase penetration and efficacy of corticosteroids, occlusive techniques, such as plastic food wrap and adhesive gas-permeable surgical dressings, may be applied. Intralesional injection of corticosteroids (triamcinolone acetonide 5–10 mg/ml) has also proved very effective in skin lesions of localized DLE, but the risk of subcutaneous atrophy has to be considered (McCauliffe 2001).

Topical Calcineurin Inhibitors

The calcineurin inhibitors tacrolimus and pimecrolimus are approved for the topical treatment of moderate to severe atopic dermatitis in children and adults. Recently, various case series and reports have also shown topical calcineurin inhibitors to be effective for skin manifestations in CLE and SLE (Sardy et al. 2009; Wollina and Hansel 2008; Tzellos and Kouvelas 2008; Sticherling 2011). In a randomized, double-blind, bilateral comparison study, tacrolimus 0.1 % ointment was compared with 0.05 % clobetasol propionate in 18 patients with facial CLE lesions (Tzung et al. 2007). To improve the penetration of the agents into the skin, microdermabrasion was performed once weekly. Both agents were found to be efficient, but in contrast to clobetasol propionate, tacrolimus ointment showed no side effects, such as skin telangiectasia. In a retrospective study, Madan et al. (2010) assessed the efficacy of a specially formulated preparation of tacrolimus 0.3 % in clobetasol propionate 0.05 % ointment in 13 therapy-refractory CLE patients. Eleven of the patients demonstrated a better response to the

combined preparation compared to five patients who applied tacrolimus 0.1 % ointment as monotherapy. However, the combined preparation showed telangiectasia and acne in two patients. A multicenter, randomized, double-blind, vehicle-controlled trial demonstrated that tacrolimus 0.1 % ointment has a significantly higher efficacy in 30 patients with different CLE subtypes compared to the vehicle (Kuhn et al. 2011a). A high degree of improvement was observed in patients with LET, SCLE, and ACLE, who applied tacrolimus 0.1 % ointment, whereas patients with DLE showed the lowest response rate. Another group performed an open-label and uncontrolled study evaluating the efficacy of pimecrolimus 1 % cream in 11 patients with different subtypes of CLE (Kreuter et al. 2004). The agent was applied twice daily for 3 weeks (overnight occlusion with hydrocolloid dressings) and improvement was observed in all patients. In ten patients with DLE, who were treated with pimecrolimus 1 % cream twice daily for 8 weeks, similar results were obtained (Tlacuilo-Parra et al. 2005). In a further randomized double-blind pilot study, the efficacy of pimecrolimus 1 % cream was compared with topical betamethasone 17-valerate 0.1 % cream in ten patients with moderate to severe DLE of the face, and significant improvement was seen in both groups (Barikbin et al. 2009). Topical calcineurin inhibitors appears to be quite safe, with no potential of skin atrophy, and the most common adverse effect being a transient sensation of burning at the site of application (Czarnecka-Operacz and Jenerowicz 2012). In CLE, tacrolimus ointment and pimecrolimus cream are recommended particularly in atrophy-prone areas such as the face; however, randomized controlled phase III trials need to be performed.

R-Salbutamol

In 2005, a pilot study described the beneficial use of R-salbutamol 0.5 % cream in four SCLE and five DLE patients (Wulf and Ullman 2007). Consecutively, a multicenter, double-blind, randomized, placebo-controlled phase II trial was performed in 37 patients with DLE, and R-salbutamol 0.5 % cream was applied twice daily for 8 weeks (Jemec et al. 2009). Scaling/hypertrophy, pain, itching, and global patient assessment showed a significantly better result in the R-salbutamol-treated patients compared with the placebo-treated group. However, phase III trials still need to be performed to approve the efficacy of R-salbutamol in CLE.

Physical Therapy

Due to the possible induction of Koebner phenomenon, laser therapy, cryotherapy, and dermabrasion should only be used in CLE, especially in persistent DLE lesions, after risk–benefit analysis and evaluation of other possible therapeutic options (Kuhn et al. 2000; Ueki 2005). In single case reports, the use of argon laser (telangiectatic DLE) and carbon dioxide (CO_2) laser (disfiguring DLE) was reported to be successful (Kuhn et al. 2000; Nurnberg et al. 1996; Henderson and Odom 1986; Walker and Harland 2000). The pulsed dye laser was also applied in patients with different subtypes of CLE, resulting in clearance or significant improvement of active disease (Raulin et al. 1999; Erceg et al. 2009; Truchuelo et al. 2012; Diez et al. 2011).

Systemic Treatments

Antimalarials

The first-line treatment for widespread and disfiguring skin manifestations in CLE and SLE are antimalarials, including hydroxychloroquine (HCQ), chloroquine (CQ), and quinacrine (synonym: mepacrine) (Kuhn et al. 2011b). Antimalarials should be considered if (1) local therapy is ineffective or relapses occur soon after cessation of topical therapy, (2) lesions are disfiguring and mutilating, or (3) the extent of the lesions is too large for topical therapy, and (4) no contraindications exist (Kuhn et al. 2010a). In addition, treatment with antimalarials is associated with higher rates of remission and fewer relapses in SLE patients. Therefore,

antimalarials are recommended as standard treatment in all patients with a systemic manifestation of the disease (Bertsias et al. 2008). In the mid-twentieth century, large case series with a total of 771 DLE patients reported impressive improvement with quinacrine in 73–85 % of the patients (Dubois 1978; Wallace 1989). However, quinacrine was slowly replaced by HCQ and CQ due to their more convenient side effect profile, although the occurrence of irreversible retinopathy also limited the use of CQ and HCQ. This unwanted effect is primarily related to an excessive daily dosage but can mostly be prevented by adhering the maximal daily dosage of 3.5–4.0 mg for CQ and 6.0–6.5 mg for HCQ per kg adjusted to the ideal body weight (calculation for daily routine: males, body length in cm – 100 – 10 %; females, body length in cm – 100 – 15 %). Ophthalmological examinations are recommended before and during treatment (fundoscopy, visual field testing, testing of color vision, Amsler grid test) (Kuhn et al. 2009). A daily oral dose of 250 mg CQ or 400 mg HCQ leads to therapeutic plasma concentrations not before 3 weeks after start of treatment due to the long plasma half-life time. Initial higher doses, such as 2×250 mg/day CQ or HCQ up to 1,200 mg/day for 4 weeks, however, often cause unspecific side effects (nausea or gastrointestinal symptoms) (Munster et al. 2002). Therefore, higher dosages should only be given for a short period of time.

As quinacrine works synergistically with HCQ and CQ and does not further increase the risk of a retinopathy, a combination therapy with either agent may be effective in patients not responding to HCQ or CQ treatment. Several studies and case reports describe a high efficacy of a combination therapy in patients with DLE, SCLE, and lupus erythematosus profundus (LEP) (Chung and Hann 1997; Feldmann et al. 1994; von Schmiedeberg et al. 2000; Lipsker et al. 1995; Chang et al. 2011). In a recent prospective longitudinal cohort study, 128 patients with CLE were analyzed to evaluate the response to antimalarial agents. The results of the study demonstrated that a combination of HCQ with quinacrine shows good response in patients for whom HCQ monotherapy fails (Chang et al. 2011). However, oral doses of 100 mg/day quinacrine (one tablet) should not be exceeded and be reduced after achieving a good response (after 3–6 months). In case of adverse reactions, the daily dose can be tapered to 25–50 mg (Wallace 1989).

Up to date, only single randomized, controlled trials have been performed evaluating the efficacy of antimalarials (Kuhn et al. 2014) in patients with CLE. For example, a study comparing the efficacy of HCQ with acitretin (Ruzicka et al. 1992) has shown that overall improvement was observed in 50 % of patients when treated with HCQ and 46 % of patients treated with acitretin, but more side effects were seen in patients who applied acitretin. However, large case series studies suggest that smoking interferes with the efficacy of antimalarials and some mechanisms by which smoking may alter the antimalarial metabolism have been proposed (Kreuter et al. 2009). It has been suggested that nicotine inhibits CQ uptake in cultured cells and blocks the accumulation of antimalarials within lysosomes (Polet 1985). In contrast, recent studies assessing the efficacy of HCQ and/or CQ in CLE patients and smoking indicate that nicotine does not have any significant influence on the response to antimalarials (Wahie et al. 2011). Therefore, prospective studies are required to determine whether the efficacy of antimalarials is influenced by smoking (Dutz and Werth 2011).

Systemic Corticosteroids

The application of systemic corticosteroids is indicated in CLE patients with highly acute and severe skin lesions but only as a short-term treatment due to their well-known side effects, such as osteoporosis and type II diabetes. As described for patients with SCLE (Goldberg and Lidsky 1984), the usual dose of systemic corticosteroids is 0.5–1 mg/kg body weight/day orally over 2–4 weeks followed by tapering of the dose or 3-day intravenous (i.v.) pulse therapy.

Methotrexate (MTX)

The folic acid analog MTX has been primarily administered in patients with refractory SCLE (Kuhn et al. 2002; Boehm et al. 1998; Wenzel et al. 2005) and DLE (Wenzel et al. 2005; Boehm et al. 1998; Bottomley and Goodfield 1995; Goldstein and Carey 1994). A retrospective analysis of 12 patients with different subtypes of CLE assessed the efficacy of MTX in doses of 10–25 mg per week applied orally or i.v. (Boehm et al. 1998). Six of these patients showed complete remission, four partial remission, and two patients did not respond; five of the ten responding patients presented with a long-term remission. A further study including 43 patients with therapy-refractory disease confirmed this beneficial effect of MTX in CLE (Wenzel et al. 2005). Skin lesions of 98 % of patients improved with low-dose MTX, administered either orally or. i.v., and patients with SCLE and localized DLE showed a better improvement than disseminated DLE. In a follow-up study, MTX was applied subcutaneously (s.c.) in 15 of the 43 CLE patients and showed good acceptance by the patients due to easier and self-administered injection; the efficacy of the agent was comparable to the i.v. application (Huber et al. 2006). In addition to the recommended dose of 7.5–25 mg MTX once weekly, folic acid supplementation should be given up to 5 days a week, excluding the day of MTX application, to prevent gastrointestinal side effects (Kuhn et al. 2011c).

Retinoids

In 1985, Ruzicka et al. (1985) first applied etretinate (50 mg daily) in 19 patients with localized and disseminated DLE, SCLE, and one SLE patient with skin manifestations in an open prospective trial. A complete or almost complete clearing of the skin lesions was observed in 11 patients, and a moderate response or treatment failure was seen in 8 patients. In the following years, etretinate has been replaced by its major metabolite acitretin due to its shorter half-life and better safety profile. The efficacy of acitretin was evaluated in 20 patients with CLE; complete clearing or marked improvement could be observed in 75 % of the patients (Ruzicka et al. 1988). Moreover, acitretin (50 mg/day) was compared with HCQ (400 mg/day) in a randomized, double-blind, multicenter, controlled trial with 28 and 30 patients, respectively (Ruzicka et al. 1992). Both agents showed a similar good efficacy (acitretin 46 % and HCQ 50 %). Furthermore, one case report described the successful treatment of hyperkeratotic/verrucous refractory DLE on hands, feet, and legs with acitretin (Al-Mutairi et al. 2005). Treatment of DLE and SCLE with isotretinoin, a further compound of the retinoid family, was published in approximately 50 patients with an efficacy of up to 86.9 % (Newton et al. 1986; Vena et al. 1989; Furner 1990; Shornick et al. 1991; Richardson and Cohen 2000). The recommended dose for acitretin and isotretinoin in CLE is 0.2–1.0 mg/kg body weight/day (Bacman et al. 2004). Due to their relatively innocuous side effects, acitretin and isotretinoin are listed as "second-line" substances for CLE in the American Academy of Dermatology guidelines (Drake et al. 1996). Because of their high teratogenicity, effective contraception is highly important during and after treatment with retinoids (isotretinoin, 1 month; acitretin, 2 years).

In 2008, the vitamin A derivative alitretinoin has been approved for use in severe chronic hand eczema unresponsive to treatment with potent topical corticosteroids (Garnock-Jones and Perry 2009). Recently, a case report on three patients with different subtypes of CLE who received alitretinoin demonstrated a high efficacy of 30 mg alitretinoin in the treatment of the disease (Kuhn et al. 2012). Further studies are necessary to confirm the efficacy and evaluate the safety profile of alitretinoin in patients with different subtypes of CLE.

Dapsone

In the literature, dapsone has been described to be effective in several subtypes of CLE, urticarial vasculitis, oral ulcerations, and bullous rash of

SLE (Bacman et al. 2004; Ludgate and Greig 2008). In 1981, Ruzicka and Goerz (1981) reported on dapsone treatment in four patients with DLE and three patients with SLE, resulting in clearance of discoid lesions, oral ulcerations in DLE, and urticarial vasculitis in SLE, whereas widespread macular–papular eruptions of SLE and disseminated DLE did not respond to this agent. In two further studies, dapsone was applied in 44 patients with DLE and showed a clinical response in 24 patients, with an excellent result in eight of the patients (Coburn and Shuster 1982; Lindskov and Reymann 1986). Single case reports of successful treatment with dapsone in SCLE and LEP have also been described in the literature (Bohm et al. 1998; McCormack et al. 1984; Fenton and Black 1986; Holtman et al. 1990; Ujiie et al. 2006; Yamada et al. 1989). A recent case report on one patient with vesico-bullous SCLE, who received a combination of HCQ and dapsone, described a clinical improvement of skin lesions after 3 weeks of treatment and a clearance on continuous treatment (Pinto-Almeida et al. 2012). As the formation of new skin lesions already stopped after 5 days of treatment, the prompt clinical efficacy might have been due to dapsone. In CLE, dapsone is recommended in doses ranging from 25 to 150 (maximum 200) mg/day; however, the lowest effective dose should be applied to minimize possible side effects, such as hemolysis and methemoglobinemia (Duna and Cash 1995).

Mycophenolate Mofetil (MMF) and Mycophenolate Sodium (EC-MPS)

In single case reports of patients with CLE, such as SCLE, DLE, and chilblain lupus erythematosus (CHLE), the efficacy of the immunosuppressive drug MMF has been reported (Boehm and Bieber 2001; Goyal and Nousari 2001; Schanz et al. 2002; Cetkovska and Pizinger 2006). For example, a complete remission within 3 months of starting MMF was achieved in four patients with various manifestations of refractory CLE and smoldering systemic involvement (Hanjani and Nousari 2002). In contrast, MMF was not efficient in five of seven patients with various LE-specific and nonspecific skin diseases in the context of SLE, such as vasculitis and urticarial rash (Pisoni et al. 2005). MMF is recommended in doses of 2–3 g per day; the common dose of 2 g MMF is best tolerated and hematological side effects are rare. In a non-randomized, open-pilot study, the enteric-coated form of MMF (EC-MPS) was applied in ten patients with active therapy-refractory SCLE, showing a significant improvement of the cutaneous manifestations (Kreuter et al. 2007).

Thalidomide and Lenalidomide

Due to the immunomodulatory and anti-inflammatory characteristics of thalidomide, successful treatment in a high number of cases has been reported in particular in patients with DLE. First-case series with thalidomide were published in 1983 (Knop et al. 1983). High initial doses of 400 mg/day and a maintenance dose of 50–100 mg/day of thalidomide were applied in 60 patients with DLE. In 90 % of the patients, a complete or marked response was observed; however, although most patients relapsed after stopping thalidomide, the cutaneous manifestations were not as severe as prior to treatment. However, peripheral polyneuropathy appeared in 25 % of the patients. In a retrospective study with 48 CLE and SLE patients overall clinical response rate of 81 % has been shown in a retrospective study with 48 CLE and SLE patients (Cuadrado et al. 2005). Different dosages (100 mg/day, 50 mg/day, and 50 mg/day on alternate days) were applied; interestingly, there was no clear dose-dependent effect of thalidomide. Skin lesions relapsed in 67 % of 39 patients after discontinuation of thalidomide. In 13 (27 %) of the 48 patients, evidence of polyneuropathy (EMG abnormalities or symptoms) was observed, which were irreversible in a high number of patients. In four further studies, approximately 160 patients with CLE, such as DLE, LEP, and SCLE, as well as SLE with cutaneous manifestations were treated with thalidomide, confirming the efficacy of this drug (Briani et al. 2004; Kyriakis et al. 2000; Coelho et al. 2005; Cortes-Hernandez et al. 2012). In the recent prospective

study by Cortes-Hernandez et al. (2012), complete response to treatment with thalidomide (100 mg/day) was observed in 85 % of the CLE patients, but clinical relapse was frequent (70 %) and usually occurred 5 months after withdrawal or reduction of thalidomide. Patients with SCLE showed a long-term remission of skin lesions even after treatment discontinuation, whereas DLE tended to relapse and required a long-term maintenance dose of thalidomide. In addition to the teratogenic effect and the strict precautions for the use of this drug in women of childbearing potential, these studies confirmed the high relapse rate, the well-known side effects and, most importantly, the high risk of potential irreversible polyneuropathy. Therefore, due to high incidence of polyneuropathy, thalidomide should only be used to treat severe therapy-refractory cases of CLE.

Lenalidomide is a structural derivative of thalidomide with more immunomodulatory effects and lower risk of polyneuropathy (Braunstein et al. 2012). In 2009, two patients with refractory disseminated DLE were treated with lenalidomide (Shah et al. 2009). One patient showed good clinical response at a dosage of 10 mg per day, while no improvement was seen in the second patient; however, this patient received only 5 mg lenalidomide per day. Recently, five patients with refractory DLE or SCLE were treated with 5 mg lenalidomide daily, and in four patients, clinical improvement of skin lesions was observed (Braunstein et al. 2012). Even though lenalidomide showed a good efficacy, one patient developed new-onset proteinuria and an exacerbation of arthralgias. In addition, the same strict precautions as for thalidomide have to be applied for lenalidomide in women of childbearing potential (appropriate contraception), although the risk of polyneuropathy seems to be lower for lenalidomide. Therefore, further studies are required to assess the benefit–risk balance of lenalidomide in the treatment of patients with CLE.

Intravenous Immunoglobulins (IVIG)

Several case reports have shown a good response to IVIG in therapy-refractory patients with SCLE (Genereau et al. 1999; Kreuter et al. 2005; Lampropoulos et al. 2007), and a complete resolution was seen in most of the 17 patients with different subtypes of CLE (DLE, SCLE, bullous SLE) reported by Goodfield et al. (2004) and Piette et al. (1995). In addition, a recent case report demonstrated a good efficacy in a patient with LEP, who had not responded to any other previous treatment (Espirito Santo et al. 2010). However, this efficacy could not be confirmed in five patients with malar rash and oral ulcers in the context of SLE and two patients with SCLE, which were also treated with IVIG (De Pita et al. 1997). The SCLE lesions worsened and the cutaneous manifestations in the SLE patients did not show any response, even though some clinical and immunological parameters improved. Adverse reactions of IVIG include headache but also urticarial rash, cutaneous vasculitis, proteinuria, acute renal failure, deep venous thrombosis, embolia, myocardial infarction, stroke, and anaphylactic reactions. Additional clinical trials need to be performed in order to investigate the efficacy of this promising but highly expensive therapy in CLE.

Clofazimine

In 1974, clofazimine, an antibacterial substance for the treatment of leprosy, was applied in 26 refractory patients with DLE, and a remission of skin lesions was observed in 65 % of the patients (Mackey and Barnes 1974). A further randomized, comparative trial was performed in 33 SLE patients with active CLE lesions (ACLE, SCLE, and localized disseminated DLE) (Bezerra et al. 2005). The results of this study suggested that clofazimine has a similar efficacy as CQ in controlling cutaneous manifestations of SLE, but further studies are necessary to assess the efficacy of this agent in different subtypes of CLE and SLE.

Phenytoin

Despite promising data from earlier studies, treatment with phenytoin (93 DLE, excellent response in about 90 %) (Rodriguez-Castellanos et al.

1995) is historic and should only be used in therapy-refractory patients as a last alternative treatment due to the wide spectrum of side effects.

Azathioprine, Cyclophosphamide, and Cyclosporin

Immunosuppressive drugs, such as azathioprine, cyclophosphamide, and cyclosporine, are not recommended for CLE and skin manifestations in SLE, as poor efficacy in the treatment of cutaneous disease has been reported (Kuhn et al. 2009). However, these drugs are frequently used as basic or additional therapy in patients with systemic organ manifestations.

Biologicals

It is well known that TNF-alpha blockade leads to the formation of antinuclear antibodies including anti-dsDNA antibodies (Charles et al. 2000; Louis et al. 2003). Furthermore, induction of CLE subtypes (SCLE and DLE-like eruption, CHLE) and worsening of SCLE through infliximab have been reported (High et al. 2005; Vabre-Latre et al. 2005; Stratigos et al. 2004; Richez et al. 2005). However, other biologicals, such as ustekinumab, rituximab, and belimumab, are promising agents in the treatment of CLE.

Ustekinumab

Ustekinumab is a human monoclonal antibody against interleukin-12 and interleukin-23, registered for the treatment of psoriasis (Leonardi et al. 2008). Recently, three case reports on therapy-refractory patients with CLE, which were treated with ustekinumab have been published, describing a good efficacy of this agent. Winchester et al. (2012) described a patient with severe psoriasis and hypertrophic DLE, who received three doses of 45 mg and one dose of 90 mg ustekinumab i.v. within 16 weeks, resulting in a marked improvement of the skin lesions. In one patient with severe DLE and overlap to CHLE, ustekinumab was administered in four doses of 45 mg i.v., respectively, within 34 weeks (Dahl et al. 2013). The erythema on the face, scalp, and fingertips improved, and the ulcers on the fingertips healed, while the erythema on the toes remained unchanged. In a further case report, the efficacy of this agent was confirmed in a patient with SCLE treated with ustekinumab (De Souza et al. 2011). In none of the reported patients, any side effects were observed, suggesting that this agent may be an alternative treatment for CLE; however, randomized controlled studies are required to assess the efficacy and safety of ustekinumab in patients with the disease.

Rituximab

The chimeric monoclonal anti-CD20 antibody rituximab has been applied successfully in adults and children for refractory SLE, usually in combination with corticosteroids, immunosuppressives, antimalarials, or a combination of these agents (Garcia-Carrasco et al. 2009). In a case report by Risselada and Kallenberg (2006), two patients with SLE and cutaneous manifestations, such as urticarial vasculitis and diffuse generalized rash with painful erythema on hands and feet, were treated with $2 \times 1{,}000$ mg rituximab i.v. in combination with 100 mg methylprednisolone i.v. at an interval of 2 weeks. In both patients, skin manifestations cleared completely and persistently. A further recent case report described a 48-year-old patient with refractory SCLE in which rituximab (375 mg/m^2 i.v.) was administered weekly for 4 weeks, in addition to HCQ (600 mg daily) and topical clobetasol propionate 0.05 % (Kieu et al. 2009). The skin lesions improved after 16 weeks but recurred after 11 months of follow-up, and rituximab treatment was repeated with maintenance therapy every 8 weeks for 2 years, resulting in an ongoing disease remission. In a recent single-center, retrospective study, 14 patients with consecutive SLE, 1 patient with CCLE, and 2 patients with SCLE with recalcitrant skin involvement were treated with 2× rituximab 1 g and 1× cyclophosphamide 750 mg (Hofmann et al. 2013). Six months after B-cell depletion therapy, 9 of 17 (53 %) patients showed a complete or partial remission; however, relapses occurred in 12 patients. The results of this study demonstrate that B-cell depletion

therapy based on rituximab is well tolerated and may be effective in CLE, but further randomized, controlled trials are required to further assess the efficacy of this agent.

Belimumab

Belimumab, the first of a new class of immunomodulators with a novel mechanism of action, was approved for SLE in 2011 based on two phase III studies (Furie et al. 2011; Navarra et al. 2011). SLE therapy was assessed by the SLE Responder Index (SRI) at week 52 and belimumab was used in 1 and 10 mg/kg versus placebo. Belimumab plus standard SLE therapy showed a significantly higher efficacy than placebo plus standard therapy, also for mucocutaneous manifestations. In addition, a post hoc analysis was performed in these 1,684 autoantibody-positive SLE patients, and SLE disease activity was assessed by the "Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index" (SELENA-SLEDAI) and the "British Isles Lupus Assessment Group" score (BILAG) (Manzi et al. 2012). A validated skin activity and damage score, such as the Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI) (Kuhn et al. 2010b), was not applied to assess improvement of skin manifestations in SLE. Therefore, it is difficult to evaluate the positive results on mucocutaneous manifestations with regard to the different CLE subtypes. Future prospective studies using a validated skin score are required to assess the efficacy of belimumab on mucocutaneous manifestations of the disease.

Conclusion

Several agents are approved for the treatment of SLE, including the novel anti-BLyS monoclonal antibody belimumab. However, no drugs have been licensed specifically for the treatment of CLE. Thus, "off-label" topical and systemic agents are applied to skin manifestations of the disease, mainly based on expert opinions. Corticosteroids are the first-line topical treatment for patients with CLE, but they are of limited value because of their well-known side effects, such as skin atrophy and telangiectasia. In recent years, topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, have been shown to be efficient in various CLE subtypes and are recommended particularly in atrophy-prone areas such as the face. Antimalarials, e.g., HCQ or CQ, are the mainstay of treatment for disfiguring and widespread skin manifestations, irrespective of the subtype of the disease. Both agents can be combined with quinacrine in refractory CLE, and systemic steroids can be added in acute exacerbations of the disease for short periods of time. In contrast to immunosuppressive agents, such as azathioprine, cyclophosphamide, and cyclosporine, methotrexate has received more attention in the treatment of cutaneous manifestations of the disease. Further second-line treatment includes retinoids, dapsone, and MMF/EC-MPS. Due to severe side effects or high costs, other agents, such as thalidomide or high-dose IVIG, respectively, are reserved for severe recalcitrant CLE. In addition to belimumab, other biologics, such as rituximab, have been evaluated to treat SLE in clinical trials and have also been shown to be efficient in single cases of CLE. In conclusion, several treatment options exist for patients with skin manifestations of the disease, but only single agents are supported by evidence from randomized, controlled trials.

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Lyme Borreliosis

56

Jana Hercogová

Key Points

- Lyme borreliosis is an inflammatory disease caused by the spirochaete *Borrelia burgdorferi* which is transmitted by tick (mainly of the genus *Ixodes*).
- It is an anthropozoonosis which manifests itself as a multisystem disorder of the skin and other organs (joints, nerves, heart, eye, etc.).
- Cutaneous manifestations of Lyme borreliosis include erythema migrans, borrelial lymphocytoma and acrodermatitis chronica atrophicans.
- The diagnosis of Lyme borreliosis is based on the history of tick exposure, the characteristic clinical picture and confirmation of *B. burgdorferi* infection by serological tests
- Antibiotic therapy should be started as soon as possible after the diagnosis has been made. Borreliae are sensitive to four groups of antibiotics—penicillins, cephalosporins (third generation and cefuroxime axetil), tetracyclines and macrolides. The drugs of choice for oral treatment of Lyme borreliosis are doxycycline and amoxicillin and for parenteral treatment ceftriaxone, cefotaxime and penicillin G.

Definition and Epidemiology

Lyme borreliosis is an inflammatory disease caused by the spirochaete *Borrelia burgdorferi* which is transmitted by tick (mainly of the genus *Ixodes*). It is an anthropozoonosis which manifests itself as a multisystem disorder of the skin and other organs (joints, nerves, heart, eye, etc.).

Lyme borreliosis is the most common vector-borne disease in Europe and the USA. Ticks of the genus *Ixodes* are the vectors that transmit the infection to mammals in endemic areas—in the North American and Euro-Asian continents. In Europe, Austria, Slovenia, Sweden and the Czech Republic belong to the most endemic areas (incidence could raises to 100 cases per 100,000 inhabitants). *B. burgdorferi* has been isolated from patients worldwide. Cutaneous involvement

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_56, © Springer-Verlag Berlin Heidelberg 2015

is the most frequent manifestation of the disease: it represents 60–80 % of all reported cases. Concerning cutaneous symptoms, erythema migrans is the most prevalent (approximately 85 %), followed by acrodermatitis chronica atrophicans (10 %) and borrelial lymphocytoma (5 %). Concrete cutaneous manifestations affect different age groups—erythema migrans is mainly present in middle-aged adults (30–50 years), borrelial lymphocytoma is typical for children and acrodermatitis is a disease of the elderly.

Basic Concepts of Pathogenesis

The aetiological agent, *B. burgdorferi* sensu lato, has been subdivided into three genospecies causing the human disease: *B. burgdorferi* sensu stricto, *B. afzelii* and *B. garinii*. Strains of all three species have been isolated from patients in Europe, whereas only the first species is involved in the USA. Some studies show that *B. afzelii* represents a dominant human skin isolate in Europe. Antigenic differences of three genospecies may explain the variability of clinical manifestations in patients with Lyme borreliosis. Genetic analysis of *B. garinii* OspA serotype 4 strains is correlated with the development of neuroborreliosis. *B. afzelii* OspA serotype 2 closely correlates with the development of acrodermatitis chronica atrophicans.

After the tick bite, borreliae spread in the dermis causing cutaneous symptom of the early localized stage (erythema migrans and borrelial lymphocytoma). Antibody immune response could be demonstrated in 3–4 weeks in the IgM class and in 4–6 weeks in the IgG class. Haematogenic spread of borreliae follows weeks to months after the tick bite and can manifest itself as the early disseminated stage of the disease. The development of the chronic stage is a subject of ongoing studies. The question is whether the symptoms are a result of the host immune response against organism or even against tissue autoantigens. T-cell-mediated immunity might be responsible for inducing and exacerbating cardiac and joint symptoms. T-cell-mediated immunopathology may result from the antigenic specificity of T cell, the activation of a specific T-cell subset or ability of persisting antibodies to induce hypersensitive auto-reactive T cells in the joints and the heart. Auto-reactive B-lymphocytes as well as significantly raised concentrations of IgA rheumatoid factor were proven in the serum of patients with the chronic stage of Lyme borreliosis; production of these antibodies may be a result of B-cell auto-reactivity.

Clinical Presentation

Cutaneous manifestations of Lyme borreliosis include erythema migrans, borrelial lymphocytoma and acrodermatitis chronic atrophicans; morphoea and its initial stage, lichen sclerosus et atrophicus, are considered to be polyaetiological entities in which borreliae (*B. afzelii* and *B. garinii*) were isolated from morphoea lesions. Extracutaneous manifestations are variable (Table 56.1).

Erythema migrans is an early localized form of Lyme borreliosis. It appears 3–30 days after the tick bite and is defined as a red patch, bigger than 4 cm in diameter at the site of the tick bite which spreads centrifugally and can reach several decimetres in diameter. Three main clinical types are

Table 56.1 Clinical manifestations of Lyme borreliosis

Early stage
Localized infection
Erythema migrans (annular, macular, concentric)
Borrelial lymphocytoma (papular, infiltrative)
Disseminated infection
Multiple erythemata migrantia
“Flu-like” symptoms
Meningitis, manigoradiculoneuritis
Endocarditis, myocarditis, pericarditis
Arthritis, tenosynovitis
Hepatitis, keratitis, conjunctivitis
Chronic stage
Acrodermatitis chronica atrophicans (macular, telangiectatic, fibrotic, atrophic)
Chronic encephalitis, encephalomyelitis, polyneuritis
Chronic arthritis

known: (a) homogenous (a red, sharply demarcated patch without a central clearing), (b) annular (a red, sharply demarcated patch with a central clearing) and (c) iris-like (concentric annular patches). From time to time, also multiple or bullous types could be present. A central reddish macule, representing the site of the tick bite, may be apparent in any of these three clinical types.

Erythema migrans can be present anywhere on the body surface, but the lower extremities are the most frequent sites. In children, the head and neck are also usually affected.

Borrelial lymphocytoma is a bluish-red papule, nodule or plaque, 1–3 cm in diameter, localized on the ear lobe. The areola mammae, scrotum and nose are other typical sites.

Acrodermatitis chronica atrophicans starts as an inflammatory stage which evolves into an atrophic stage. Firstly, bluish-red, not sharply demarcated patch(es) or plaque(s) appear on the dorsal aspect of the foot or hand. Predilection sites include the skin above the bony prominences (on the lower extremities, the ankle, lateral aspects of the foot, fingers and knee and on the upper extremities, fingers and elbow). Lesions usually spread from distal to proximal sites, including the trunk and face. Four clinical types of the lesions can be differentiated: (a) erythematous lesions (bluish-red patches, plaques in cases of swelling), (b) telangiectatic lesions (telangiectasias predominately, red patches), (c) fibrous lesions (firm, bluish-red of skin-coloured nodules, mainly above the elbow, ulna or small joints of the hand) and (d) atrophic lesions (thin skin with wrinkles, prominent vessels).

Diagnosis

The diagnosis of Lyme borreliosis is based on the history of tick exposure, the characteristic clinical picture and confirmation of *B. burgdorferi* infection by serological tests (with the exception of early pathognomonic cutaneous manifestations of the disease, e.g. annular erythema migrans and borrelial lymphocytoma which is localized on the ear lobe and is present in children). Histopathological examination should be performed in acrodermatitis chronic atrophicans patients and in those where the diagnosis is not clear from a clinical point of view.

Direct proof of borrelial infection includes isolation (allowing the demonstration of live *B. burgdorferi*, e.g. in the skin, synovial fluid, myocardium) and histopathological detection of the microorganisms in the tissue by a modified Dieterle's stain or a modified Steiner's method, electron microscopy, DNA hybridization and polymerase chain reaction (nested PCR and quantitative PCR). PCR testing of cutaneous lesions is helpful to confirm the diagnosis in clinically atypical cases.

Indirect methods include enzyme-linked immunosorbent assay (ELISA) and immunoblotting. Two-step serological testing is recommended in which a serum specimen with a positive test result by the ELISA is further tested with immunoblotting. The standardization of an immunoblotting method for the diagnosis of Lyme borreliosis would require agreement on the strains used for antigen preparation. This approach would not be possible in Europe due to different local prevalences of genospecies of *B. burgdorferi* sensu lato and also to heterogeneity within those strains. To date, none of the serological tests should be termed as a "screening" test. Special attention should be given to patients in whom serological tests could be false positive (other spirochetal infections, autoimmune disorders) and/or false negative (immunocompromised patients).

Histopathological examination of the erythema migrans lesion shows superficial perivascular dermatitis, composed of lymphocytic infiltrate with plasma cells and eosinophils. Borrelial lymphocytoma is a pseudolymphoma; lymphocytes are top heavy, without nuclear atypia, and plasma cells can be present. Acrodermatitis chronica atrophicans shows superficial perivascular or lichenoid dermatitis, lymphocytic infiltrate with plasma cells, epidermal atrophy, dilated vessels in the upper part of the dermis and orthohyperkeratosis. Later on, degeneration of elastic and collagen fibres, as well as gland adnexae, could follow.

Differential Diagnosis

Erythema migrans should be differentiated from erysipelas, superficial tinea, fixed drug eruption, discoid cutaneous lupus erythematodes, granuloma annulare, morphoea and contact dermatitis.

Borrelial lymphocytoma could be similar to histiocytoma, keloid, angioma, Kaposi's sarcoma, granuloma faciale, granuloma annulare, sarcoidosis and lupus erythematodes. In all cases, histopathological examination is helpful. Malignant lymphoma can be distinguished by immunohistochemical examination.

Acrodermatitis chronica atrophicans can mimic circulatory insufficiency, perniones, morphoea and dermatomyositis; fibrotic papules and nodules are considered to be rheumatic nodules or gouty tophi.

General Principles of Treatment

Antibiotic therapy should be started as soon as possible after the diagnosis has been made. Some studies demonstrate that even an appropriate antibiotic regimen may not always eradicate the spirochete. On the one hand, the treatment of disseminated Lyme borreliosis for 3 months may not be sufficient: the spirochetes can remain in serum, skin and other tissues, and clinical relapses can occur. However, it remains unresolved whether the prognosis of patients with disseminated Lyme borreliosis could be improved by longer initial treatment. On the other hand, the outcomes of most persons diagnosed as having Lyme borreliosis who are treated with antimicrobial agents are excellent. Extracutaneous manifestations of Lyme borreliosis are described after any antibiotic regimen in up to 10 % patients. Recently, treatment trials for post-Lyme disease symptoms were revised, and authors did not find any data supporting the benefit of retreatment of the patients who had been treated with antibiotics previously.

Cutaneous manifestations disappear after the therapy, but immediate disappearance of borrelial lymphocytoma and acrodermatitis chronica atrophicans during antibiotic therapy is exceptional. Those lesions begin to fade and lose the swelling, but resolution can take up to 6 months. The degenerative changes in acrodermatitis are not reversible. No significant differences were found in the outcome of erythema migrans after 1 year in patients whose immune system was impaired compared to previously healthy individuals.

The immunological response after antibiotic therapy appears to be abrogated, so levels of antiborrelial antibodies cannot be used as proof of successful therapy. Furthermore, the antibody titre development after therapy is unpredictable and variable, and it is largely uncorrelated with the clinical course. It was also shown that even after the proper antibiotic therapy, *B. burgdorferi* DNA could persist up to 6 months.

Recommended Therapies

Borreliae are sensitive to four groups of antibiotics—penicillins, cephalosporins (third generation and cefuroxime axetil), tetracyclines and macrolides. The drugs of choice for oral treatment of Lyme borreliosis are doxycycline and amoxicillin and for parenteral treatment ceftriaxone, cefotaxime and penicillin G. Ceftriaxone is primarily used as a treatment for patients with extracutaneous (joint, neurological, cardiac) and multiple cutaneous manifestations. If the coinfection with ehrlichiosis is suspected, doxycycline is the drug of choice. Doxycycline is also preferred in cases of penicillin-cephalosporin allergy since erythromycin has inferior efficacy. Children with solitary erythema migrans could be treated with phenoxymethyl penicillin and cefuroxime axetil; however, drug-related side effects were more frequently observed with cefuroxime axetil. Minocycline causes teeth discoloration even in young adults and discoloration of the skin, nails, sclera and conjunctivae. Vertigo, ataxia and dizziness have been described during minocycline therapy. These symptoms are a major disadvantage, in particular for patients with neurological symptoms, as in Lyme disease.

Recommended therapies for uncomplicated erythema migrans include oral doxycycline

200 mg daily (divided into two doses every 12 h) or amoxicillin 3 g daily (divided into three doses every 8 h) for 15 days. If any general signs or symptoms (subfebrilia, malaise, fatigue, arthralgias, myalgias, meningism, conjunctivitis, etc.) are present even if for 1 day, the duration of antibiotic therapy should be 20 days. In case of penicillin of tetracycline allergy, azithromycin is prescribed (500 mg daily p. o. for 10 days and for 15 days in the presence of general signs or symptoms).

Borrelial lymphocytoma is treated with the same antibiotic regimen; only the duration of therapy is at minimum 20 days. Acrodermatitis chronica atrophicans patients are given the same oral antibiotics for 25–30 days, but in the presence of any extracutaneous manifestations, parenteral therapy is needed—ceftriaxone 2 g i. v. daily in one dose of penicillin G i. v. 20 million units daily (divided into 4 doses of 5 million units every 6 h) for 15 days followed by oral antibiotic (as in the early stage) for the next 15 days.

Special attention should be given to pregnant women with Lyme borreliosis. Penicillins, macrolides and ceftriaxone are used, but antibiotic administration depends on the time of tick bite; if the tick bite is suspected during the trimester, then parenteral antibiotics are used. On the other hand, if the tick bite occurs later in pregnancy and the patient has no extracutaneous symptoms or signs, oral antibiotics are sufficient for therapy.

Prevention

Prevention of Lyme borreliosis includes avoiding exposure to tick bites by limiting outdoor activities in endemic areas, using tick repellents containing diethyltoluamide (DEET) 10–35 % or picaridin 20 %, tucking in clothing and frequent skin inspection for early detection and correct removal of ticks. Persons who have undergone tick removal should be monitored up to 30 days for signs and symptoms.

Antibiotic prophylaxis has not been shown to be effective in reducing the risk of acquiring Lyme borreliosis. Some authors recommend local antibiotics after the tick bite; the other did not confirm the efficacy of topical antibiotics in preventing dissemination of the disease.

Vaccination trials showed that a single recombinant outer surface protein A (OspA) appears to be safe and immunogenic in man. A single antigen OspA vaccine in not effective in Eurasia, where more heterogeneous species of borrelia and more variable OspA are present. In Eurasia, compared to the USA, a vaccine must be effective against all subgroups of the borrelia spirochaete. Some protective immunity against borrelia infection in laboratory animals was demonstrated by some other *B. burgdorferi* proteins, e.g. OspB and OspC.

Recently, it was shown by the study from Northeastern US patients that those treated for early Lyme disease develop protective immunity that is strain specific and lasts for at least 6 years. Repeated serologic testing is of very limited value for assessing therapy efficacy and therefore not recommended in the follow-up of dermatoborrelioses patients.

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Lymphogranuloma Venereum

57

Henry John Christiaan de Vries

Abbreviations

B.i.d.	Bis in die/two times a day
C	*Chlamydia*
LGV	Lymphogranuloma venereum
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
Q.i.d.	Quater in die/four times a day
STI	Sexually transmitted infection

Key Points

- Lymphogranuloma venereum (LGV) is a sexually transmitted infection (STI) caused by *C. trachomatis* genovar L (that primarily involves the lymphatics of the anogenital region).
- Left untreated, LGV can lead to irreversible lymph oedema and fibrotic sequelae.
- The disease is endemic in the tropical regions of Africa, Asia and South America.
- In 2004, it was found endemic in the Western world among men who have sex with men (MSM) with high-risk sexual behaviour.
- The standard algorithm to diagnose LGV is to first exclude *C. trachomatis* infection in suspected individuals via a commercially available routine nucleic acid amplification test (NAAT). In case this routine test is positive, genovar L has to be confirmed via an "in house" *C. trachomatis* genovar-specific *C. trachomatis* NAAT.
- Apart from HIV and STI screening, HCV testing should be offered to all LGV patients.
- The goal of therapy is to eradicate the pathogen.
- Late sequelae do not respond to antibiotic treatment and need to be managed surgically.
- Subjects who have had sexual contact with an LGV patient should be examined, tested for chlamydial infection and promptly treated.
- To exclude reinfections, STI screening during a follow-up visit 3 months after an LGV diagnosis should be offered.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_57, © Springer-Verlag Berlin Heidelberg 2015

Definition and Epidemiology

Lymphogranuloma venereum (LGV) has been renamed several times in the past and was known as tropical bubo, climatic bubo, poradenitis inguinalis, Durand-Nicolas-Favre disease, lymphopathia venereum and the fourth, fifth or sixth diseases. However, the name LGV is currently the standard name and should be distinguished from granuloma inguinale, a bacterial STI caused by *Klebsiella granulomatis*.

The causative agent of LGV is *Chlamydia trachomatis* genovar L. Worldwide, LGV is thought to account for 2–10 % of genito-ulcerative diseases in tropical climate areas such as India and Africa. In Europe, North America and Australia, LGV is endemic mainly among HIV coinfected men who have sex with men (MSM, homo- and bisexual men) and is for the large part caused by genovar L2b. Heterosexual transmission of this MSM-associated L2b strain has been described.

The degree of infectiousness and the reservoir of disease have not been accurately defined, but heterosexual transmission has been attributed largely to asymptomatic female carriers, and in the MSM population, asymptomatic rectal infection and/or penile infection is the likely source of onward transmission.

Basic Concepts of Pathogenesis

Chlamydia trachomatis types L1, L2 and L3 are the causative pathogens. Additional variants have been described such as L2b, the strain currently found in MSM. Genovar L strains are invasive organisms that disseminate via underlying connective tissue and spread to regional lymph nodes. As a result, most LGV infections cause (systemic) symptoms in contrast to infections with *C. trachomatis* genovars A–K that remain confined to the mucosa and are asymptomatic in many cases. The incubation period of LGV is 1–4 weeks.

Clinical Presentation

Depending on the site of inoculation, LGV can cause inguinal disease (usually after inoculation of the genitalia) or the anorectal syndrome (usually after inoculation via the rectum). The disease course usually follows three separate stages (Table 57.1).

Table 57.1 Clinical spectrum of lymphogranuloma venereum

Manifestations	Complications
Primary stage transient papule, pustule, herpetiform ulcer, nodular ulceration, non-specific urethritis, balanitis or balanoposthitis, bubonulus, cervicitis, salpingitis, parametritis	Phimosis, labial oedema, infertility
Secondary stage (inguinal syndrome) severe proctitis, bubo formation, inguinal multilocular abscess, groove sign of Greenblatt	Sinus tracts, frozen pelvis, infertility, systemic arthritis, pneumonia, hepatitis, perihepatitis, spondylitis, ocular inflammatory disease
Tertiary stage (genito-anorectal syndrome) genital syndrome, anorectal syndrome, proctitis, proctocolitis	Genital elephantiasis, ramrod or saxophone penis, esthiomene, vaginal stenosis, urethral strictures, fistulae (rectovaginal, urethrovaginal, vulval), rectal strictures, stenosis, abscess formation (perirectal, ischiorectal, supralevator), rectal adenocarcinoma, lymphorrhoids
Urethro-genito-perineal syndrome	Papillary genital growths, perineal sinus
Ocular manifestations mixed papillary-follicular conjunctivitis, episcleritis, corneal ulcers, iritis, iridocyclitis	Iritis, iridocyclitis
Cutaneous manifestations id eruption – transient generalised exanthemata, papules, pustules, nodules, urticaria, scarlatiniform eruption, erythema multiforme, erythema annulare centrifugum, erythema nodosum, photoallergic dermatitis	
Others LGV tonsillitis, pharyngitis, cholecystitis	

Adapted from de Vries et al. 2012

In the current LGV epidemic among MSM, proctitis is the primary manifestation of infection, usually presenting within a few weeks of sexual contact. It is characterised by severe symptoms of painful anorectal ulcers (Fig. 57.1) and bloody and/or purulent anal discharge. Tenesmus and

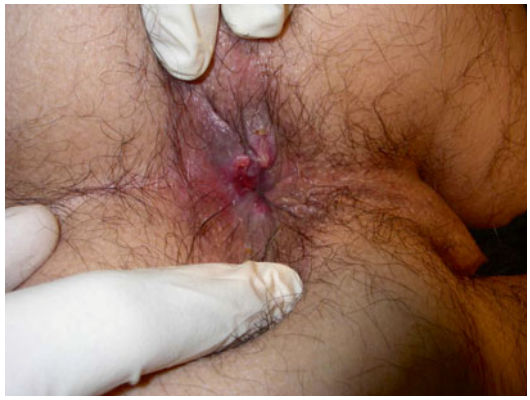

Fig. 57.1 Anorectal lymphogranuloma venereum (LGV) with perianal ulceration

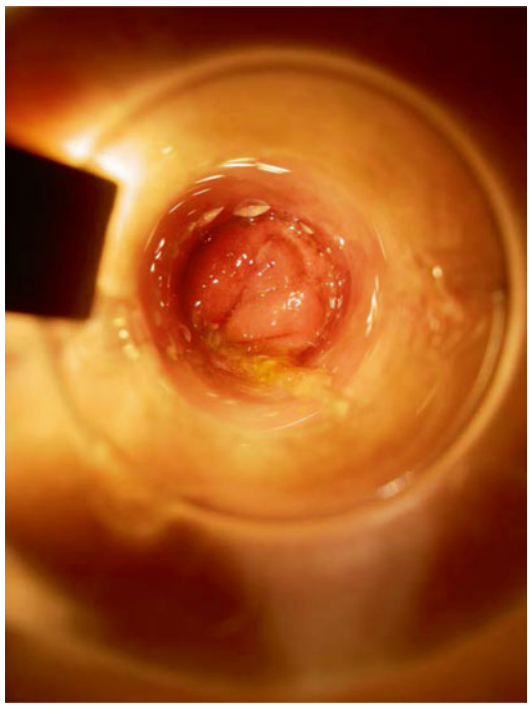

Fig. 57.2 Anorectal lymphogranuloma venereum (LGV) with discharge, mucosal inflammation and oedema (same patient as in Fig. 57.1)

constipation are also seen due to the mucosal and perirectal oedema. Anoscopic examination may reveal a granular or haemorrhagic proctitis with purulent exudate, mucosal ulceration and tumorous masses (Fig. 57.2). LGV proctitis is usually not accompanied by inguinal lymphadenopathy; but diagnostic imaging techniques may demonstrate pelvic node involvement. There is a debate about the proportion of asymptomatic LGV cases among MSM. In UK cohorts, almost all LGV infections appear to be symptomatic, in contrast to Dutch studies where a significant proportion of asymptomatic infections have been detected.

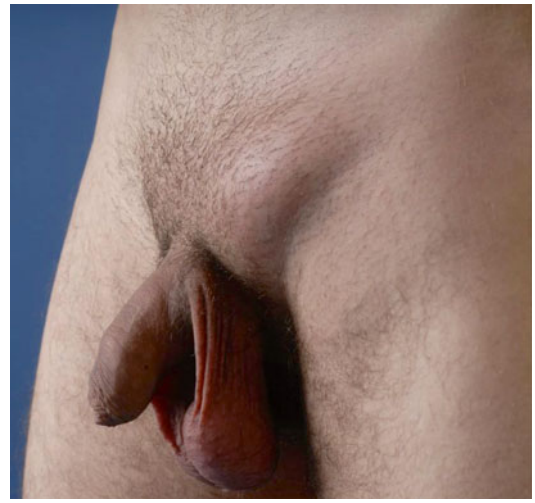

Fig. 57.3 Inguinal lymphogranuloma venereum (LGV) with a bubo in the groin area

The primary lesions are small painless papules or pustules that may erode to form a herpetiform ulcer. They usually heal within 1 week and often go unnoticed. In the secondary stage 2–6 weeks after onset of primary lesion, painful inflamed inguinal and/or femoral lymph nodes, usually one sided, arise (Fig. 57.3). These "buboes" may become fluctuant and rupture in every third patient (Fig. 57.4). Inguinofemoral lymphadenopathy is mainly seen when the inoculation site is located on the external genitalia, which is the case in many male patients. In contrast, women more often have primary involvement of the rectum, upper vagina, cervix or posterior urethra; as these regions drain to the deep iliac or perirectal nodes, inguinofemoral lymphadenopathy is not seen. The resultant intra-abdominal or retroperitoneal lymphadenopathy may lead to symptoms of lower abdominal pain or low back pain. Constitutional symptoms, such as low-grade fever, chills, malaise, myalgias and arthralgias, may present during the second stage of disease. A rare presentation is the pharyngeal syndrome affecting the mouth and throat. Cervical lymphadenopathy and buboes can occur.

The third stage of disease in LGV is often called the "anogenitorectal syndrome" and is more

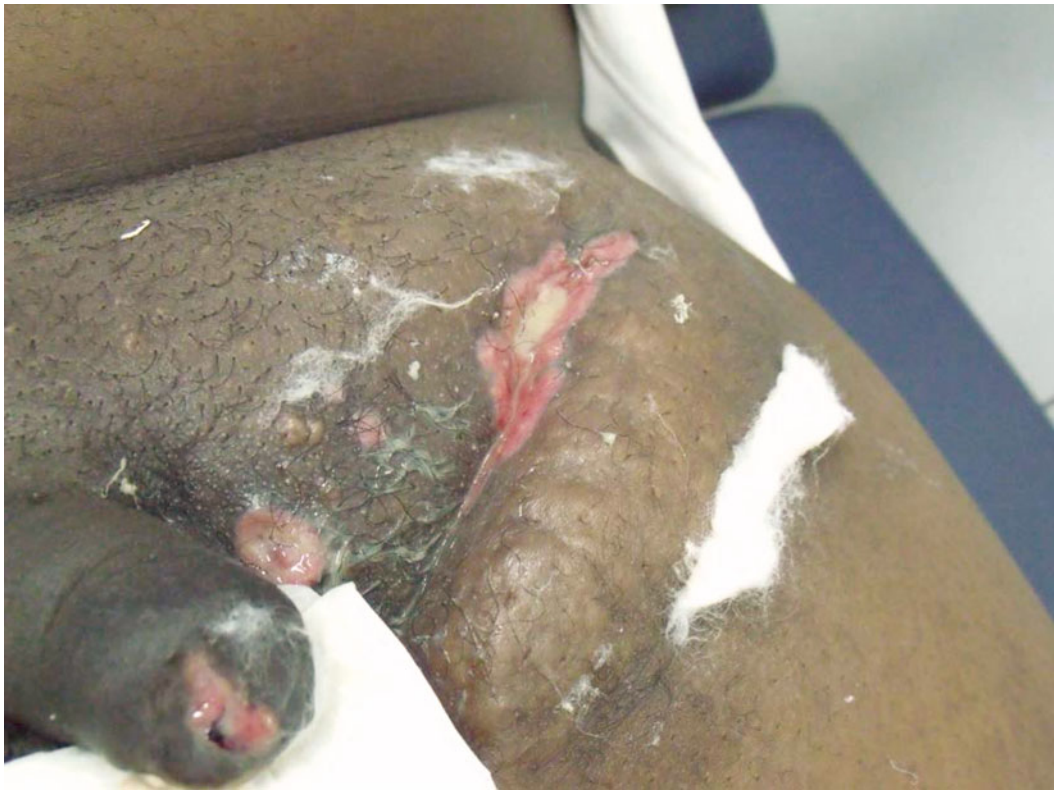

Fig. 57.4 Late-stage inguinal lymphogranuloma venereum (LGV) with fistulae (From Dr. R. Hu, Dermatological Service, Paramaribo, Suriname)

often present in women. Patients initially develop proctocolitis followed by perirectal abscess, fistulas, strictures and stenosis of the rectum, possibly leading to "lymphorrhoids" (haemorrhoid-like swellings of obstructed rectal lymphatic tissue). Without treatment, chronic progressive lymphangitis leads to chronic oedema and sclerosing fibrosis, resulting in strictures and fistulas of the involved region, which can ultimately lead to elephantiasis, esthiomene (the chronic ulcerative disease of the external female genitalia) and the frozen pelvis syndrome. If left untreated, LGV proctitis can lead to rectal strictures, with subsequent sequelae of soiling, pain, constipation and the possible development of megacolon.

Differential Diagnosis

LGV proctitis can mimic chronic inflammatory bowel diseases like Crohn's disease, both clinically and in the pathological substrate. It is therefore often misdiagnosed by gastroenterologists confronted with MSM presenting with proctitis symptoms. The clinical and histologic picture of early LGV proctocolitis is similar to that seen in inflammatory bowel disease and LGV proctitis has been mistaken for Crohn's disease. This has led to delay in the correct diagnosis and suboptimal treatment.

Since LGV is characterised by a diversity of presentations (depending on the inoculation site and the different stages of disease evolution), it is extremely difficult to establish a definitive diagnosis by clinical examination alone. As a result, it can be a challenge to differentiate LGV from other dermatological and sexually transmitted diseases (Table 57.2).

The clinician often misses the primary inoculation site. If present, it may simulate genital herpes, primary syphilis, chancroid or traumatic ulceration and bacterial, candidal or traumatic balanoposthitis. A mucopurulent urethritis noted in a few instances of LGV is often mistaken for non-specific urethritis or gonorrhoea.

Table 57.2 Differential diagnosis of lymphogranuloma venereum (adapted from de Vries et al. 2012)

Primary stage
Genital herpes
Primary syphilis
Chancroid
Granuloma inguinale
Traumatic ulcer
Secondary stage (inguinal syndrome)
Chancroid
Syphilis
Genital herpes
Plague
Tularaemia
Tuberculosis
Cat-scratch disease
Septic lymphadenitis
Hodgkin's disease
Incarcerated inguinal hernia
Psoas abscess
Tertiary stage
Genital elephantiasis
Filariasis
Tuberculosis
Fungal infection
Parasitic infection
Toxaemia of pregnancy
Anorectal syndrome
Inflammatory bowel disease (esp. Crohn's disease)
Rectal stricture
Malignancy
Trauma
Actinomycosis
Tuberculosis
Schistosomiasis

The second stage of LGV manifests as regional lymphadenitis and perilymphangitis with bubo formation and is often confused with buboes caused by chancroid, syphilis, genital herpes, plague, tularaemia, tuberculous lymphadenitis, cat-scratch disease, septic lymphadenitis, Hodgkin's disease, incarcerated inguinal hernia or psoas abscess.

In the tertiary stage, genital elephantiasis may mimic filariasis, tuberculosis, fungal or parasitic infection, granuloma inguinale (pseudo-elephantiasis) or transient vulvar elephantiasis with toxaemia of pregnancy. The rectal strictures of LGV may resemble those caused by trauma, actinomycosis, tuberculosis, schistosomiasis or adenocarcinoma of the rectum.

General Principles of Treatment

Systemic antibiotic therapy is the cornerstone in the treatment of LGV infection. Despite a paucity of robust evidence regarding the efficacy of therapy for any rectal chlamydial infections (LGV or non-LGV), 3 weeks of oral doxycycline 100 mg twice daily to treat LGV is recommended (Centers for Disease Control and Prevention (CDC) 2004; Clinical Effectiveness Group of the British Association for Sexual Health and HIV (CEG/BASHH) 2006; Workowski et al. 2010). Doxycycline is contraindicated in pregnancy and breastfeeding.

Early and prompt treatment is essential to prevent ongoing transmission, serious complications and mutilating sequelae. The low incidence of the disease, its complex presentation and the natural history marked by spontaneous remissions and exacerbations have precluded any rigorous evaluation of management. Nevertheless, sporadic trials in the treatment of LGV have shown successful use of tetracyclines (especially doxycycline) and erythromycin. Early and prompt antibiotic treatment shortens the duration of buboes, ulcers, sinuses and rectal discharges. Prolonged treatment (at least for 3 weeks) is the norm and more than one course of therapy or alternating some of the antibiotics may be necessary for chronic cases. The vast majority of recent MSM case reports have observed complete responses to 3-week doxycycline therapy; shorter courses may not eradicate the organism. It has been shown that L biovar *C. trachomatis* RNA can persist for up to 16 days in LGV proctitis patients treated with doxycycline.

The following antibiotic chemotherapy recommendations have been made for uncomplicated LGV infections:

- Doxycycline, 100 mg orally b.i.d. × 21 days, or erythromycin, 500 mg orally q.i.d. × 21 days, or azithromycin, 1 g orally once weekly × 21 days (Workowski et al. 2010).
- Doxycycline, 100 mg orally b.i.d. × 14 days, or erythromycin, 500 mg orally, q.i.d. × 14 days, or tetracycline, 500 mg orally, q.i.d. × 14 days, or sulphadiazine, 1 g orally q.i.d. × 14 days (WHO 2003).
- For pregnant and lactating women or children below 8 years, erythromycin stearate is

prescribed (Banor et al. 1953). In children, the dose is 7.5–12.5 mg/kg/dose q.i.d. for 14 days.

Other mentioned antibiotic modalities which have been successfully used in treating acute bubonic LGV and LGV proctocolitis are minocycline, 300 mg orally initially, followed by 200 mg b.i.d. for 10 days. Azithromycin regimens have been suggested but the dosage and duration of therapy are not known.

Surgical Treatment

Fluctuant buboes are aspirated through the surrounding unaffected skin with a wide-bore needle and not incised. Perianal and perirectal abscesses must be surgically drained. Rectal strictures are dilated either manually or with elastic bougies at weekly intervals. When the stricture is impassable, a preparatory ileocolostomy followed by proctocolectomy is a justifiable procedure. Chronic intractable ulcerative lesions of the rectum may be treated by suitable single-stage surgical procedures, such as full skin cover by direct flaps, myocutaneous flaps or sliding flaps (floating island). A urethral stricture can be dilated with Lister's or Clutton's bougies.

The chronic manifestations of tertiary LGV such as rectovaginal fistulae, genital elephantiasis, vulvar growths, esthiomene or rectal strictures and stenosis do not respond to antibiotic therapy and require surgical intervention and plastic reconstruction. Polypoid excrescences of the vulva, pedunculated tumours or elephantiasic vulvae require local excision and partial or total vulvectomy.

Management of Patients with Proctitis

It is recommended to screen all MSM who report receptive anal sexual practices in the previous 6 months for anorectal *C. trachomatis* infection with a commercially available nucleic acid amplification test (NAAT). Subsequently, MSM with anorectal *C. trachomatis* infection are then screened for LGV proctitis using a genovar L-specific "in house" developed NAAT. In the recent MSM LGV epidemic, incident cases of both HIV and hepatitis C have been observed, and serological testing should be offered for both infections after appropriate window periods have elapsed according to relevant local guidelines. The prevalence of HIV among LGV cases ranges from 67 to 100 % in 13 descriptive studies (Rönn and Ward 2011). Tests for STI, including HIV (if not already known HIV positive), hepatitis B and hepatitis C should be offered before starting therapy.

Given the high incidence of STIs in MSM with proctitis complaints, the CDC recommends presumptive therapy in MSM with a high index of suspicion (Workowski et al. 2010) rather than waiting for positive cultures that can take more than a week to return (Box 57.1). Delay in treatment can lead to potential complications and "lost to follow-up" infections.

Box 57.1. Proctitis Syndromic Treatment Guidelines for High-Risk Individuals with Anal Complaints (Adapted from de Vries et al. 2013)

Syndromic treatment of a symptomatic proctitis or confirmed non-LGV *C. trachomatis* proctitis:

- Doxycycline 100 mg p.o., 2d.d. 7 days

Syndromic treatment of a suspected *N. gonorrhoea* proctitis (e.g. based on Gram-negative intracellular diplococci) or confirmed *N. gonorrhoea* proctitis:

- Ceftriaxone 500 mg i.m. single dose

PLUS

- Doxycycline 100 mg p.o., 2d.d. for 7 days

Syndromic treatment of LGV proctitis or confirmed LGV proctitis:

- Doxycycline 100 mg p.o., 2d.d. for 21 days

OR

- Erythromycin 500 mg p.o., 4d.d. for 21 days

Follow-Up

Patients are followed up clinically until signs and symptoms resolve. This may occur within 3–6 weeks. All patients diagnosed with LGV should be followed up at the end of treatment, to ensure resolution of symptoms and signs of infection, to check that adequate partner notification has been completed, to address any patient concerns and to arrange suitable follow-up testing for syphilis and blood-borne viruses including hepatitis B and C and HIV.

Doxycycline failure in LGV has been reported in 3 out of 75 treated patients (Rodríguez-Domínguez et al. 2014). If the recommended 21-day course of doxycycline is completed, a test of cure for LGV seems indicated only in those with persistent complaints. It should be noted that doxycycline can also cause gastrointestinal symptoms like mucous discharge and diarrhoea. A routine microbiological test of cure is usually not done.

Partner Management

It is essential that sex partner notification be initiated when the diagnosis is made. Partners who have had sexual contact with an LGV patient, should be promptly treated for LGV according to the above-mentioned therapy advice. STI testing should be offered to all sexual contacts within the last 3 months (or in case of symptomatic patients within 30 days before the onset of the patient's symptoms). Moreover, empiric antibiotic therapy should be recommended to partners, until STI has been excluded in the partner.

Prevention

Patients diagnosed with LGV should be counselled regarding prevention of other STIs including HIV and hepatitis C. Moreover, regular sexual health screening including HIV testing should be offered, condom use should be demonstrated and promoted, hepatitis A and B vaccination for MSM offered, and patients at risk of HIV infection should be advised of the availability of post-exposure prophylaxis for HIV. In particular, HIV-positive MSM should be made aware of recent trends in hepatitis C epidemiology and warned of the risks of unprotected anal sex, serosorting, recreational drug use and mucosally traumatic sexual practices such as fisting. Enema use prior to receptive anal sex should be discouraged since it is associated with rectal chlamydial infections and especially LGV proctitis. Although sharing of equipment was rare, it is prudent to advise against sharing any such equipment and to wash equipment thoroughly after use.

Sexual contacts must be traced and promptly treated. Patients on antibiotic therapy should be monitored for recurring symptoms over a period of 6 months following antibiotic treatment. Doctors and other health care workers must observe proper safeguards such as wearing gloves when touching infected sites or handling soiled dressings or other contaminated items. Health-seeking behaviour and health education of those at risk should be encouraged.

Future Perspectives

In the ongoing LGV epidemic, there is a need for better and cheaper screening tools to detect cases in larger groups of individuals at risk. This is of importance to prevent complications in the individual patient and to halt transmission in the community. Physicians should consider LGV in case MSM present with inguinal lymphadenopathy, genital ulceration or proctitis complaints. If chronic inflammatory bowel syndromes like Crohn's disease are considered, especially in MSM, LGV proctitis should always be excluded. Shorter antibiotic courses than the present ones of 21 days are needed to increase patient compliance to the treatment but require large controlled clinical trials. Lastly, a deeper understanding of the microbial and immunological background of LGV infection in relation to HIV could shed light on the considerable number of asymptomatic LGV cases found.

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Primary Cutaneous Lymphomas

58

Wolfgang Bauer and Robert Knobler

Abbreviations

CR	Complete response
EORTC	European Organisation for Research and Treatment of Cancer
ISCL	International Society for Cutaneous Lymphomas
OR	Overall response
ORR	Overall response rate
R-CHOP	Rituximab cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone
R-COP	Rituximab cyclophosphamide, vincristine, prednisolone
TCR	T-cell receptor gene rearrangement

Key Points

- Primary cutaneous lymphomas are most often T-cell lymphomas.
- Most of these lymphomas have an indolent clinical course.
- The most common cutaneous lymphoma is mycosis fungoides.
- Up to now no curative treatment is available.
- Apart from the rare cases with aggressive clinical behavior, therapy should follow the principle of primum nil nocere.

Definition and Epidemiology

Lymphoid neoplasms can affect the skin either secondarily as manifestations of disseminated nodal lymphomas or primarily without evidence of further organ involvement at the time of diagnosis. This chapter will only deal with the latter. The skin is the second most common site of manifestation of extranodal non-Hodgkin's lymphomas (NHL, after the gastrointestinal tract), with an estimated incidence of approximately 1:100,000 inhabitants per year. The distinction between primary cutaneous and disseminated nodal NHL is obligatory due to the specific cellular pathobiology of these lymphomas, their clinical course, resulting treatment options, and prognosis.

Primary cutaneous T- and B-cell lymphomas (CTCL and CBCL) are classified based on clinical, histological, immunohistochemical, and molecular features (Table 58.1). Accordingly, treatment options vary between different types of cutaneous lymphomas and will be discussed separately.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_58, © Springer-Verlag Berlin Heidelberg 2015

Table 58.1 WHO-EORTC classification of cutaneous lymphomas (2005)

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides (MF)
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome (SS)
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large-cell lymphoma (PCALCL)
Lymphomatoid papulosis (LyP)
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous γδ T-cell lymphoma (provisional)
Primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Relative frequencies and survival of the different entities are depicted in Table 58.2. Mycosis fungoides (MF) and its variants represent the most common cutaneous lymphoma with an indolent course, whereas Sézary syndrome is the most common aggressive CTCL.

Diagnosis and Staging of Cutaneous Lymphomas

A skin biopsy (if necessary multiple biopsies) with histological analysis and immunophenotyping forms the basis of the diagnosis. A complete

Table 58.2 Relative frequencies and disease-specific 5-year survival of primary cutaneous lymphomas (Trautinger 2011)

WHO-EORTC classification	Frequency (%)	Disease-specific 5-year survival (%)
Cutaneous T-cell lymphomas		
Indolent clinical behavior		
Mycosis fungoides (MF)	44	88
Folliculotropic MF	4	80
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
Primary cutaneous anaplastic large-cell lymphoma (PCALCL)	8	95
Lymphomatoid papulosis (LyP)	12	100
Subcutaneous panniculitis-like T-cell lymphoma	1	82
Primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma	2	75
Aggressive clinical behavior		
Sézary syndrome (SS)	3	24
Extranodal NK-/T-cell lymphoma, nasal type	<1	NR
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma	<1	18
Cutaneous γδ T-cell lymphoma	<1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified	2	16
Cutaneous B-cell lymphomas		
Indolent clinical behavior		
Primary cutaneous marginal zone B-cell lymphoma	7	99
Primary cutaneous follicle center lymphoma	11	95
Intermediate clinical behavior		
Primary cutaneous diffuse large B-cell lymphoma, leg type	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	<1	50
Intravascular large B-cell lymphoma	<1	65

physical examination including inspection of the entire skin and palpation of all lymph nodes together with the identification of any organomegaly should be performed. Imaging studies and laboratory analysis of blood, enlarged lymph nodes, and/or bone marrow biopsy should be performed according to the type of lymphoma and for accurate staging.

For staging of cutaneous lymphomas, the TNM classification as suggested by the ISCL-EORTC (2007) should be used. MF and Sézary syndrome share a distinct staging system which also has some prognostic relevance (Tables 58.3 and 58.4), in contrast to all other forms of cutaneous lymphomas (Table 58.5). More details on diagnosis and staging examinations are provided in the discussion of the specific entities.

Table 58.3 ISCL/EORTC revised classification of MF and Sézary syndrome (ISCL/EORTC 2007)

TNMB stages	
T: skin	
T1	Patches, papules, plaques <10 % of skin surface
	T1a: patches only
	T1b: plaque ± patch
T2	Patches, papules, plaques >10 % of skin surface
	T2a: patches only
	T2b: plaque ± patch
T3	One or more tumors (≥1 cm)
T4	Confluence of erythema ≥80 % body surface area
N: lymph nodes	
N0	No clinically abnormal peripheral lymph nodes
N1	Clinically abnormal peripheral nodes: histopathology NCI LN0-2
	N1a: clone negative
	N1b: clone positive
N2	Clinically abnormal peripheral lymph nodes: histopathology NCI LN3
	N2a: clone negative
	N2b: clone positive
N3	Clinically abnormal peripheral lymph nodes: histopathology NCI LN4; clone positive or negative
NX	Clinically abnormal peripheral lymph nodes: no histological confirmation
M: visceral organs	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation)
B: blood	
B0	Absence of significant blood involvement: ≤5 % atypical lymphocytes
	B0a: clone negative
	B0b: clone positive
B1	Low blood tumor burden: ≥5 % atypical lymphocytes
	B1a: clone negative
	B2b: clone positive
B2	High blood tumor burden: ≥1,000/μl atypical cells with positive clone

Clinical Endpoints in Evaluating Response to Treatment

To determine the response of a patient to any given therapy, it is desirable to follow objective criteria. Up to the present, unfortunately these have only been clearly defined for MF and Sézary syndrome. They take into account the response in the skin (modified severity-weighted assessment tool, mSWAT), lymph nodes, viscera, and blood. These individual factors are used to define a global response score (complete remission, partial remission, stable disease, progressive disease). In assessing response to treatment in other forms of cutaneous lymphomas, it is advisable to follow the same basic principles.

General Principles of Treatment

Treatment strategies have to consider the precise diagnosis, tumor stage, and preceding treatments. Due to the chronic course of many of the most common types of cutaneous lymphomas, a general principle is to choose a therapeutic regimen with the least associated toxicity. In case of indolent and early-stage cutaneous lymphomas, therapy directed only against the manifestation on the skin is often sufficient to manage and control the disease. In more advanced stages, systemic therapies complement topical ones.

Table 58.4 TNM staging of MF and Sézary syndrome (ISCL/EORTC 2007)

	T	N	M	B	
IA	1	0	0	0, 1	Early stage
IB	2	0	0	0, 1	
IIA	1, 2	1, 2	0	0, 1	
IIB	3	0–2	0	0, 1	Advanced stage
IIIA	4	0–2	0	0	
IIIB	4	0–2	0	1	
IVA_1	1–4	0–2	0	2	
IVA_2	1–4	3	0	0–2	
IVB	1–4	0–3	1	0–2	

Table 58.5 TNM classification system for primary cutaneous lymphomas other than MF and Sézary syndrome (ISCL/EORTC 2007)

T: skin	
T1	Solitary skin involvement
	T1a: solitary lesion <5 cm diameter
	T1b: solitary lesion >5 cm diameter
T2	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions
	T2a: all-disease-encompassing in <15 cm diameter circular area
	T2b: all-disease-encompassing in >15 and <30 cm diameter circular area
	T2c: all-disease-encompassing in >30 cm diameter circular area
T3	Generalized skin involvement
	T3a: multiple lesions involving 2 noncontiguous body regions
	T3b: multiple lesions involving ≥3 body regions
N: lymph nodes	
N0	No clinical or pathological lymph node involvement
N1	Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2	Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3	Involvement of central lymph nodes
M: visceral organs	
M0	No evidence of extracutaneous non-lymph node disease
M1	Extracutaneous non-lymph node disease present

It is emphasized that whenever possible, patients with cutaneous lymphomas should be treated in specialized centers allowing access to best clinical practice and new therapeutic options in clinical trials.

In the following we will discuss the most common variants of cutaneous lymphomas.

Treatments of CTCL

Mycosis Fungoides (MF)

MF is the most common variant of cutaneous T-cell lymphoma and typically affects older adults. In most cases it is an indolent lymphoma slowly evolving from patches to plaques and finally tumors on the skin (Fig. 58.1). In late stages lymph nodes and visceral organs can be involved.

Histopathologically the lesions are characterized by infiltrating atypical epidermotropic $CD4^+$ T cells, which might show a characteristic loss of certain pan T-cell surface molecules (CD2, CD5). Rare cases of $CD8^+$ $CD4^-$ lymphomas are described and do not show a different clinical course. A transformation to a diffuse large-cell lymphoma (CD30 positive or negative) might occur and is associated with a worse prognosis.

Among the many variants, it is important to highlight folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin due to their distinct clinicopathological manifestation. In folliculotropic MF, atypical lymphocytes infiltrate the hair follicles and lead to mucinous degeneration of the follicles and hence alopecia especially in the head and neck area. This manifestation is associated with a worse prognosis than classical MF. In pagetoid reticulosis, localized neoplastic T cells proliferate exclusively intraepidermally. In granulomatous slack skin, circumscribed areas of lax skin develop due to a granulomatous infiltrate of neoplastic T cells admixed with macrophages and giant cells, which lead to a destruction of elastic fibers. It shows a predilection of axillae and groins. The latter two variants of MF are not associated with a different clinical prognosis than classical MF.

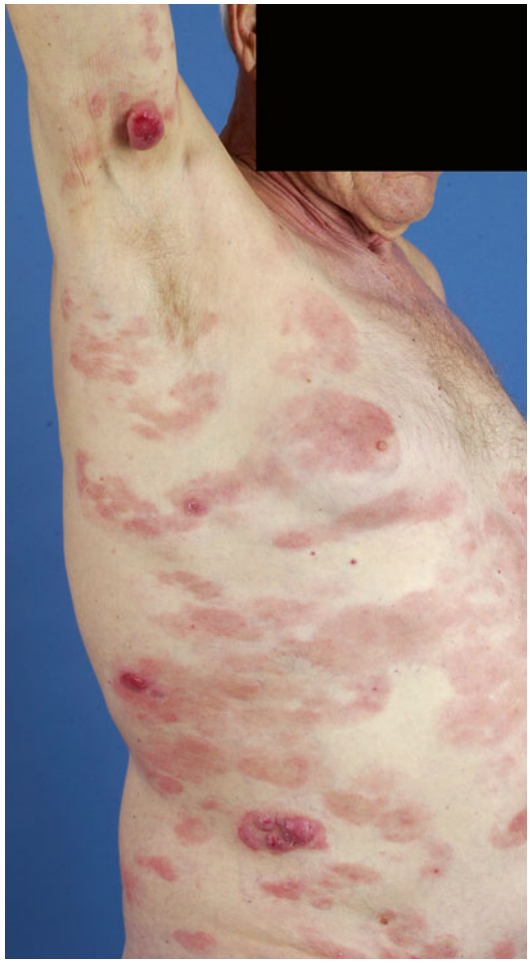

Fig. 58.1 Patient with mycosis fungoides stage IIB disease showing patches, plaques, and tumors

Diagnosis and staging of MF are outlined above (see also Table 58.3). In addition, the determination of TCR gene rearrangement from skin samples can be helpful in corroborating the diagnosis. A complete blood cell count with manual differential, LDH, liver function tests, the analysis for abnormal lymphocytes (ideally by flow cytometry together with manual count of abnormal lymphocytes), and molecular identification of T-cell clones in the blood should be performed.

Therapy

Up to the present, mycosis fungoides is still considered an incurable disease. Nevertheless patients with early-stage disease can survive for a considerable long period of time (see also Table 58.2), and the outcome is not generally altered by use of early aggressive therapy. Indeed, patients with stage IA disease have a near-normal life expectancy; it is therefore considered legitimate to follow a "watch-and-wait" strategy treating only large or cosmetically annoying lesions, provided a careful monitoring of the disease is maintained.

In general, early-stage MF (IA–IIA) is thus treated with skin-directed therapies (Table 58.6) including topical steroids, PUVA (psoralen + UVA), and topical cytotoxic agents. UVB-311 nm should only be used in patients with patches. PUVA is usually administered two to four times per week until skin lesions have cleared. OR is very high reaching up to 95 %; CR can be achieved in approximately 58–83 % depending on the tumor stage.

Radiotherapy is very effective for thicker plaques, and patients with early localized disease or pagetoid reticulosis might even remain disease-free for very long times. In refractory patients second-line options include retinoids (bexarotene, acitretin), interferon (IFN)-α (alpha), low-dose methotrexate (up to 25 mg/week), or combinations of PUVA and IFN-α (alpha) or bexarotene.

Bexarotene is still the only retinoid exclusively available for the treatment of cutaneous lymphomas. In contrast to other retinoids, it was developed to bind specifically to the retinoid X receptors, thereby mediating effects on cell differentiation and apoptosis. It is approved in Europe for the treatment of advanced-stage CTCL in adult patients refractory to at least one systemic treatment. The usual daily dosage is 300 mg/m^2 and treatment can be continued indefinitely provided clinical response. Reported ORR is up to 45 %. The most common side effects are hypertriglyceridemia, hypercholesterolemia, and central hypothyroidism requiring careful

Table 58.6 Treatment recommendations for MF and Sézary syndrome

Stage	First line	Second line
Early stage	Watch and wait	Oral retinoid (bexarotene, acitretin)
	Topical steroids	IFN-α
	PUVA	Low-dose MTX
	UVB-311 nm (only for patches)	PUVA + IFN-α
	Local radiotherapy (≥30 Gy)	PUVA + bexarotene
	Topical NH2	TSEB
	Topical BCNU	Novel agents (clinical trials)
Late stage		
Tumor stage (IIB)	Radiotherapy	Bexarotene
	PUVA ± IFN-α	HDAC inhibitors
	PUVA ± retinoid	Denileukin diftitox
	Retinoid + IFN-α	Gemcitabine
	TSEB	Doxorubicin
Stage III–IV + Sézary syndrome	ECP	Bexarotene
	IFN-α	MTX
	PUVA + IFN-α	Denileukin diftitox
		HDAC inhibitors
		Alemtuzumab
		Chemotherapy: cladribine, fludarabine, cyclophosphamide CHOP-polychemotherapy
		Allogeneic stem cell transplantation

NH2 nitrogen mustard, *BCNU* carmustine, *MTX* methotrexate, *TSEB* total skin electron beam therapy, *HDAC* histone deacetylase inhibitors, *ECP* extracorporeal photopheresis

monitoring, treatment with lipid-lowering agents (gemfibrozil is contraindicated) and thyroid hormone, and dose modification in individual cases.

OR of IFN-α (alpha) monotherapy is reported to be 70 % with CR seen in up to 35 % of patients. Efficacy has been demonstrated regardless of tumor stage but is higher in early stages. Generally, three million units of IFN-α (alpha) three times a week are recommended; higher doses do not necessarily seem to provide an additional effect. The most common side effects of this treatment include fatigue, flu-like symptoms, and leukopenia, requiring careful monitoring. The combination treatment of IFN-α (alpha) with retinoids is regarded inferior to the combination with PUVA.

Total skin electron beam therapy is an excellent option for widespread disease or for patients no longer responding to other skin-directed therapies.

Patients developing one or a low number of tumors (stage IIB) also profit from local radiotherapy. PUVA in combination with retinoids or IFN-α (alpha), denileukin diftitox, and an HDAC inhibitor (histone deacetylase inhibitor) are all considered before treating these patients with systemic chemotherapy.

Treatment of patients with stage III–IV disease follows the same principles as in Sézary syndrome. Erythrodermic patients with B0–B1 blood involvement in particular seem to profit from extracorporeal photopheresis (ECP). In this apheresis-based treatment, leukocytes are separated from the rest of a patient's blood, exposed to 8-methoxypsoralen, irradiated with UVA, and then returned to the patient. Treatment is usually very well tolerated with only very few patients experiencing mild transient hypotension or mild anemia/thrombocytopenia. Initial treatment is performed every 2–4 weeks; subsequently treatment intervals can be extended to once every 4–8 weeks. Response to treatment can occur late and it is recommended to treat for at least 6 months for final evaluation of a response. OR

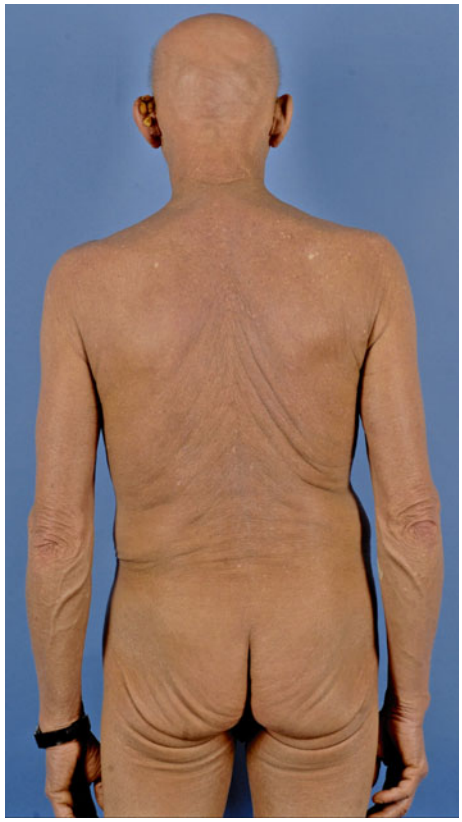

Fig. 58.2 Erythrodermic patient with Sézary syndrome

varies and has been observed in up to 80 %, CR in up to 30 % of patients (Table 58.6).

Single- or multiagent chemotherapy is only indicated in patients with massive lymph node (N3) or visceral involvement. Many different regimens have been tried; unfortunately response duration is most often very short. For single-agent treatment, gemcitabine and pegylated liposomal doxorubicin have resulted in OR of up to 75 and 88 %, respectively. Multiagent regimens are often based on cyclophosphamide, doxorubicin, vincristine, and prednisone and have shown similar response rates.

It should be mentioned that data on maintenance therapies in CTCL are lacking. Due to great experience and relative good long-term safety, oral retinoids, IFN-α (alpha), and ECP are excellent candidates for such a treatment modality. In fact patients responding to initial treatment with ECP are recommended to continue treatment with progressive extension of treatment intervals up to 8 weeks.

Sézary Syndrome (SS)

Although rare, SS is the most common variant of an aggressive CTCL with an estimated 5-year survival rate of about 24 % and a median survival between 2 and 4 years. It is characterized by the triad of erythroderma (Fig. 58.2), lymphadenopathy, and atypical tumor cells in peripheral blood. These cells have enlarged and indented nuclei (cerebriform) and can either be identified morphologically or by flow cytometry. They are usually $CD3^+4^+$ T cells that can show loss of markers such as CD2, CD3, CD4, CD7, or CD26 and lead to a shift in the CD4/CD8 ratio (required for diagnosis $\geq$10). The determination of a clonal TCR gene rearrangement in peripheral blood is another prerequisite for the diagnosis.

Specific histologic changes in the skin can be similar to those observed in MF but are missing in up to one third of all cases. Staging examinations are the same as in MF.

Therapy

Since Sézary syndrome is a systemic disease by definition, skin-directed therapies are not sufficient for the treatment. Topical steroids or PUVA can nevertheless be useful in alleviating erythroderma and pruritus. Extracorporeal photopheresis (ECP) plays an important role as a first-line therapy with a reported overall response rate of 30–80 % although response to treatment may take up to 6 months. It can be used alone or in combination with other systemic agents including IFN-α (alpha) or bexarotene. Alternatively PUVA in combination with bexarotene and/or IFN-α (alpha) is recommended. Second-line therapies include prolonged treatment with low-dose chlorambucil and systemic steroids, low-dose methotrexate, denileukin diftitox, HDAC inhibitors, TSEB, and alemtuzumab. In younger patients, bone marrow transplantation or conventional chemotherapy (e.g., single-agent chemotherapy with gemcitabine, fludarabine, cladribine, or pentostatin) can be considered.

Primary Cutaneous CD30+ Lymphoproliferative Disorders

These are the second most common types of CTCL and encompass two main diseases: lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma (PCALCL). These tumors are histologically characterized by large pleomorphic and anaplastic tumor cells that share the expression of CD30 and have a very good prognosis in common. LyP and PCALCL are believed to represent two ends of a spectrum of diseases. Histology alone might not be sufficient for the diagnosis in some cases so that the clinical course decides about definitive diagnosis and choice of treatment. Treatment recommendations are summarized in Table 58.7.

Lymphomatoid Papulosis (LyP)

Chronic recurrent eruptions of self-healing papules and nodules with histological features of cutaneous lymphoma characterize this disease. Although LyP does not present a risk to survival itself, it is associated with other cutaneous or nodal lymphomas (MF, ALCL, M. Hodgkin) in up to 25 % of cases. This aspect has to be given special attention during follow-up of patients.

Due to the intrinsic benign nature of this disease, the main concept to follow when treating patients should be primum non nocere.

None of the reported therapies for LyP has been shown to alter the course of the disease or prevent secondary lymphomas. Therefore a watch-and-wait strategy is a possible first-line approach. PUVA and low-dose methotrexate (5–25 mg/week) show very good response rates, but after cessation of therapy, relapses occur fast and frequently. Hence maintenance therapy is sometimes needed. In these cases special care should be given to limit side effects including risk for nonmelanoma skin cancer or liver fibrosis. Very large and persisting lesions can be removed surgically or irradiated; however, non-regressing lesions should be monitored for progression to PCALCL.

Cutaneous Anaplastic Large-Cell Lymphoma (PCALCL)

PCALCL presents with solitary or localized, rarely multifocal rapidly growing, and ulcerating nodules and tumors. As in LyP, the skin lesions can show partial or complete regression in up to 44 % of patients and frequently relapse. Extracutaneous manifestation can be observed in about 10 % of cases, mainly involving local lymph nodes.

First-line therapy in solitary or localized lesions is surgical excision or radiotherapy. Relapses occur in about 40 % of cases and need not be treated differently. Multifocal cutaneous lesions can be treated with low-dose methotrexate. In cases with extracutaneous dissemination or rapidly progressive cutaneous lesions, doxorubicin-based multiagent chemotherapy is indicated.

Table 58.7 Treatment recommendations for CD30+ lymphoproliferative diseases

	Solitary lesions	Multiple lesions	Extracutaneous spread
LyP			
	Observation	Observation	
	Phototherapy	Phototherapy	
	Topical steroids	Methotrexate	
		Topical steroids	
		Alternatives: retinoids, INF-α	
PCALCL			
	Excision	Methotrexate	Single-/multiagent chemotherapy
	Radiotherapy	Alternatives: retinoids, IFN-α	

Treatments of CBCL

The three main types of CBCL are primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT), which can be stratified according to their clinical behavior in indolent (PCMZL and PCFCL) and aggressive (PCLBCL, LT).

If a cutaneous B-cell lymphoma is clinically suspected, a representative biopsy, ideally an excisional biopsy, should be obtained. Diagnosis is based on histologic and immunohistologic factors; a detection of clonal IgH gene rearrangements based on the BIOMED-2 protocol can be helpful in selected cases. In addition to the general staging principles mentioned above, the following parameters should be obtained: serum electrophoresis, flow cytometry of peripheral blood, *Borrelia* serology and *Borrelia* PCR from tissue sections in endemic areas, and a bone marrow biopsy in cases of PCLBCL (optional for PCMZL and PCFCL, although in the latter the authors recommend a bone marrow biopsy because of prognostic relevance). Imaging studies should include a CT scan (with or without a positron emission tomography) of at least the chest, abdomen, and pelvis and extending to all other body areas affected.

Treatment recommendations according to EORTC and ISCL are summarized in Table 58.8.

Primary Cutaneous Marginal Zone B-Cell Lymphoma (PCMZL)

PCMZL presents with solitary or multiple papules, plaques, or nodules preferentially on the extremities. In endemic areas it can be associated with *Borrelia burgdorferi* infection. Only in rare cases the disease will spread to extracutaneous sites but recurrence on the skin happens frequently. Histopathologically dermal infiltrates composed of small B cells, including marginal zone cells, lymphoplasmacytoid cells, and plasma cells predominate.

Therapy

Patients with solitary or only a few scattered lesions can be treated with local radiotherapy or excision. Due to the indolent course, it is also possible to follow a wait-and-see strategy under close monitoring of the patient. In such cases only symptomatic skin lesions are treated.

When patients present with extensive skin lesions, chlorambucil is still a widely used option. Alternatively rituximab intralesionally or intravenously can be used. In cases that show an association with *B. burgdorferi* infection, intravenous application of cephalosporins might represent a treatment alternative.

Primary Cutaneous Follicle Center Lymphoma (PCFCL)

PCFCL typically manifests itself with solitary or grouped papules and nodules on the head or trunk. The cellular infiltrate is composed of neoplastic follicle center cells that show a follicular, follicular and diffuse, or diffuse infiltration of the dermis. In 5–10 % extracutaneous dissemination is observed. After preliminary successful therapy, cutaneous relapses occur in up to 20 % of all cases.

Therapy

Solitary or localized diseases are preferentially treated with radiotherapy ($\geq$30 Gy) whereby the radiation field is extended to include a safety margin of clinically uninvolved skin of at least 1.5 cm. Small lesions can also be removed surgically.

Analogous to PCMZL, a wait-and-see strategy with active treatment only of symptomatic lesions or radiotherapy can be considered for patients with few scattered lesions.

In the case of disseminated skin lesions, systemic rituximab is considered first-line therapy. Combination chemotherapy (R-COP, R-CHOP) should only be considered in patients with progressive disease or in patients developing extracutaneous disease. Special consideration should be given to patients developing PCFCL on the legs since these tumors seem to clinically behave like PCLBCL, LT and should therefore be treated accordingly.

Table 58.8 Treatment recommendations for CBCL (EORTC/ISCL 2008)

Disease type and extent	First-line therapy	Alternative therapies
PCMZL		
Solitary/localized	Local radiotherapy	IFN-α i.l.
	Excision	Rituximab i.l.
	Antibiotics[a]	i.l. steroids
Multifocal	Wait and see	IFN-α i.l.
	Local radiotherapy	Rituximab i.l.
	Chlorambucil	Topical or i.l. steroids
	Rituximab i.v.	
	Antibiotics[a]	
PCFCL		
Solitary/localized	Local radiotherapy	IFN-α i.l.
	Excision	Rituximab i.l.
Multifocal	Wait and see	R-CVP/CHOP[b]
	Local radiotherapy	
	Rituximab i.v.	
PCLBCL, LT		
Solitary/localized	R-CHOP ± IFRT	Local radiotherapy
		Rituximab i.v.
Multifocal	R-CHOP	Rituximab i.v.

IFRT involved field radiotherapy, *i.l.* intralesional, *i.v.* intravenous
[a]In case of *B. burgdorferi* infection
[b]For patients developing extracutaneous disease or exceptional cases

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCLBCL, LT)

PCLBCL, LT typically presents with tumors on the legs, rarely at other sites, in elderly patients. Histopathologically they are characterized by diffuse infiltrates predominated by centroblasts and immunoblasts. The disease frequently relapses on the skin and can present with extracutaneous dissemination, which explains the worse prognosis than seen in other CBCL.

Therapy

Because of the similar clinical behavior, this tumor should be treated like systemic DLBCL. R-CHOP with or without involved field radiotherapy is considered first-line therapy. In patients not able to tolerate the toxicities of systemic chemotherapy, radiotherapy alone with or without rituximab or rituximab only can be considered.

Alternative and Experimental Therapies in Cutaneous Lymphomas

Continuous strive for better treatment of patients with (cutaneous) lymphomas leads to constant development of new therapeutic options. Patients who fail to respond to recommended drugs should therefore always be evaluated for new agents in clinical trials. In the following we sum up some of the agents newly available or in clinical testing.

Mechlorethamine (Nitrogen Mustard, HN2)

Nitrogen mustard is a cytotoxic agent acting by alkylating DNA and the consecutive formation of interstrand cross-links. When applied topically to the skin, additional immunomodulatory effects might contribute to its effects. In the past, topical HN2 has been used with success for the treatment of early-stage MF; lack of availability has limited its use. Recently the FDA approved the first

commercially available preformulated mechlorethamine gel (Valchlor®, 0.016 % gel) for stage IA and IB MF in the USA, and hopes are that the European Medicines Agency will approve its use throughout Europe. It is usually applied once a day for several weeks until lesions are cleared, followed by a maintenance treatment once or twice a week for several months. Overall response rates are up to 83 % with complete responses seen in up to 50 % of all patients. The main side effects are hypersensitivity or toxic reactions; the risk of developing nonmelanoma skin cancers seems to be small when used as a monotherapy.

Topical Imiquimod

Preliminary reports have shown efficacy of topically applied imiquimod cream in patients with MF, but controlled studies are lacking.

Retinoids

Retinoids have been a mainstay in the treatment of CTCL. Tazarotene is a novel synthetic retinoid that is applied as a 0.1 % gel. Preliminary reports have shown some efficacy in early MF.

Pralatrexate

This new antifolate shows higher affinity for tumor cells than methotrexate and is the first drug approved specifically for the treatment of peripheral T-cell lymphomas. In a phase II study, response rate in CTCL was 45 %.

Histone Deacetylase Inhibitors (HDACi)

Vorinostat has been approved for the treatment of relapsed, refractory CTCL in the USA but not in Europe. This has encouraged research in other HDACi like romidepsin, panobinostat, or belinostat.

Lenalidomide

Lenalidomide is an immunomodulatory drug derived from thalidomide in order to reduce known side effects such as peripheral polyneuropathy. It is used successfully in the treatment of multiple myeloma but also in many other NHLs and in Hodgkin's disease. It has been shown to be effective in refractory CTCL with an ORR of 28 % and, pending confirming studies, could become an option for maintenance therapy.

Monoclonal Antibodies

Alemtuzumab (anti-CD52 antibody) has been used in refractory cases of CTCL with ORR of up to 40 %. Nevertheless its use is limited by considerable immunosuppression. Experimental results have explained better response rates in Sézary syndrome than in MF. Its availability for this indication is questionable.

Zanolimumab (anti-CD4 antibody) has shown promising results in phase II studies and is evaluated in combination treatments.

Brentuximab vedotin is an anti-CD30 antibody coupled to the antimitotic agent monomethyl auristatin E (MMAE). It is approved for the treatment of relapsed or refractory Hodgkin's lymphoma and relapsed or refractory systemic anaplastic large-cell lymphoma. Hopes are high that this drug might be a future therapeutic option in patients with $CD30^+$ CTCL.

Another antibody-drug conjugate is ibritumomab tiuxetan, in which an anti-CD20 antibody is coupled via a chelator to yttrium-90 or indium-111. This drug is approved for the treatment of refractory or relapsed follicular lymphoma and might present a future treatment option in CBCL.

Other emergent monoclonal antibodies include new CD20 antibodies like ofatumumab, the anti-CD23 antibody lumiliximab, or the anti-CD40 antibody dacetuzumab for the treatment of PCLBCL.

Allogeneic Stem Cell Transplantation

In young patients with advanced MF or Sézary syndrome, with poor projected survival and multiple prior therapies, allogeneic stem cell transplantation might represent a future treatment option. In studies performed so far, it was possible to achieve a long-term disease control in 50–70 % of treated patients.

Conclusion

In the last decade, the field of cutaneous lymphomas has experienced significant advances associated with a better understanding of lymphocyte and lymphoma biology. The new combined WHO-EORTC classification has

paved the way for new diagnostic, staging, and therapeutic guidelines for most of the individual lymphoma subtypes and, even more, defined for the first time clinical endpoints and response criteria (MF and Sézary syndrome). This should lead to a standardization of future clinical trials and thereby to an improvement of treatment options in diseases that for the most part show an indolent clinical course but are not curable at present.

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Mastocytosis

59

Arnold P. Oranje and Dirk Van Gysel

Definition

Mastocytosis is a disease of mast cells, as stated by the European Competence Network of Mastocytosis (ECNM), based on monoclonal proliferation – at least – in adults. The disease is generally characterized by the presence of abnormally dense infiltrations of mast cells in the dermis or other organs. Mastocytosis belongs to the Orphan diseases and is listed as such in the Orphanet database (Table 59.1) (Figs. 59.1 and 59.2).

History

Mastocytosis was first described by Nettleship and Tay as a "Rare form of Urticaria" in the British Medical Journal in 1869. The name mastocytosis was proposed in 1939. Recently, the knowledge on mastocytosis as Orphan disease has increased dramatically. The first consensus classification was proposed by Metcalfe in 1991. Many cellular, molecular and biochemical defects in mastocytosis were elucidated later and mastocytosis is currently considered as monoclonal (= neoplastic) in nature, although some think that the disease in childhood may be reactive. In 2001 and later in 2007, the WHO defined the criteria and the classification of mastocytosis (Valent 2006). Mastocytosis as such is defined as

Table 59.1 Mastocytosis clinical presentations and therapy – modalities based on symptomatology

Mastocytoma	Therapy usually not necessary
	Reassurance
	Sometimes corticosteroid (moderate potent) under occlusion/wet-wrap dressing
Cutaneous mastocytosis (CM)	Therapy usually not necessary
	Oral antihistamines, oral sodium cromoglycate
Bullous mastocytosis	Especially in first two years of life (CM and DCM); symptomatic therapy, in severe cases metabolic dysregulation making intensive care necessary
Diffuse cutaneous mastocytosis (DCM)	See bullous mastocytosis, in rare cases experimental therapy
Telangiectasia macularis perstans	Probably does not exist but is residual cutaneous mastocytosis. Therapy indicated for telangiectasia and will consist of pulse dye laser

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_59, © Springer-Verlag Berlin Heidelberg 2015

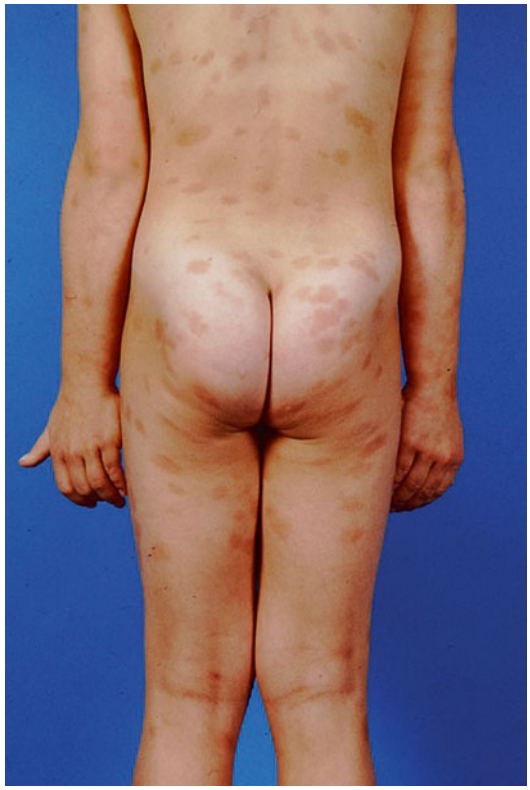

Fig. 59.1 Cutaneous mastocytosis. Childhood big-spot expression

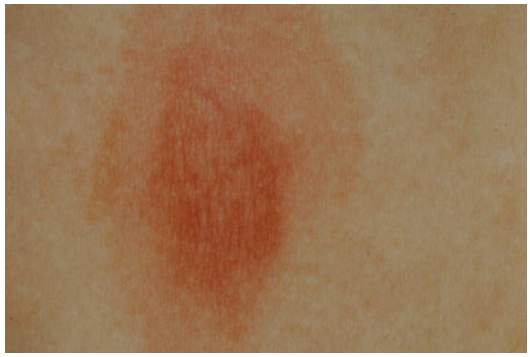

Fig. 59.2 Positive sign of Darier in mastocytoma

a clonal haematopoietic disease. Recently, Hartmann proposed another classification (see later) and Escribano underlined that the WHO classification cannot be used in children because often a bone marrow examination is not performed.

Classification and Epidemiology

Mastocytosis covers a wide spectrum of proliferative mast cell diseases. The disease is a primary abnormal proliferative accumulation of mast cells.

Mast cell infiltrates occur almost primarily in the skin but may be present anywhere in the body. In particular, as a second organ, the bones may be involved.

The most accepted classification dates from 2007 (WHO classification) and is as follows:

1. Cutaneous mastocytosis (common in children)
2. Indolent systemic mastocytosis (also in children)
3. Systemic mastocytosis (with an AHNMD)
4. Aggressive systemic disease
5. Mast cell leukaemia (MCL)
6. Mast cell sarcoma
7. Extracutaneous mastocytoma

Recently, proposed: Polymorph and monomorph cutaneous mastocytosis, mastocytoma and systemic mastocytosis. Rogier Heide and Arnold Oranje earlier proposed terms such as childhood-type (big-spot) and adult-type (small-spot) mastocytosis, mastocytoma, diffuse cutaneous mastocytosis and systemic mastocytosis. This is in complete agreement with the WHO classification.

The prevalence of mastocytosis remains unknown. The disease may start at any age but starts in the first years of life in the majority of cases. Between 10 and 20 % of the adult mastocytosis starts in childhood. Familial cases have been described but are not common. The majority of the patients with mastocytosis do have a normal life prognosis. In children, mastocytosis may go into complete remission in more than 60 % of the cases during, shortly before or shortly after puberty. Adult mastocytosis starts in childhood in 10–20 % of the cases.

Basic Concepts of Pathogenesis

Mastocytosis represents a hyperplastic response to an abnormal stimulus and can be considered as a monoclonal proliferative disorder. The prognosis

is much better in the majority of the cases, especially the big-spot variants as described earlier in children.

Basic research is focused on mutations in the proto-oncogene receptor c-kit. Childhood mastocytosis is less frequently associated with c-kit mutations or with other c-kit mutations than that in adults (Verzijl et al. 2007).

Clinical Presentation

We generally distinguish cutaneous mastocytosis (CM) and systemic mastocytosis (SM). For classifications, see earlier in the text.

Maculopapular cutaneous mastocytosis (MCM) is a form of cutaneous mastocytosis (CM) characterized by the presence of multiple hyperpigmented macules, papules, nodules or plaques. It is the most common form of CM (accounting for up to 90 % of cases). This disease is most commonly reported among the Caucasian population and affects both sexes, almost equally. The majority of the patients present in infancy or childhood, but the onset may also occur in adulthood. As lesions vary in aspect, several subvariants were described in the past (plaque form, typical form, telangiectatic form and nodular form) but are all now grouped under the same entity. We distinguish big-spot (childhood-type) and small-spot (adult-type) mastocytosis as described earlier.

Cutaneous mastocytoma is a form of cutaneous mastocytosis (CM) generally characterized by the presence of a solitary or multiple hyperpigmented macules, plaques or nodules associated with an abnormal accumulation of mast cells in the skin. Mastocytomas are the second most frequent form of CM in children accounting for 10 % of the cases. Patients generally present during infancy, with most presenting in the first 3 months of life. This variant is only very rarely observed in adults. Mastocytomas usually appear as oval lesions with red-brown, pink or yellow pigmentation. The diameter varies from around 1 to 4 cm and the surface may be smooth or have a "peau d'orange" appearance.

Diffuse cutaneous mastocytosis (DCM) is a rare form of cutaneous mastocytosis characterized by a generalized erythroderma, various degrees of blistering and skin with a "peau d'orange" appearance. At least two DCM variants are recognized, one with extreme blistering (bullous) and one with infiltrations (pseudoxanthomatous). It accounts for less than 3 % of all the cases of CM and almost exclusively presents initially at birth or during infancy. The majority of patients present with a generalized erythroderma with a reddish to brown-orange discolouration and extensive bullae. The blisters may become haemorrhagic, may be grouped or linear and are usually located on the trunk, the extremities or the scalp. The bullous lesions typically resolve by the age of 3–5 years. A small number of patients have been reported with yellow-orange infiltrated and xanthogranuloma-like lesions. Over time, the skin becomes thickened and has a doughy consistency.

The course and the prognosis of childhood mastocytosis are often milder than that of adult-onset mastocytosis. The best prognosis has been observed in big-spot disease and is excellent in cutaneous mastocytoma. Nonetheless, more than 10 % of the adult mastocytosis starts in childhood.

Diagnosis

The diagnosis of mastocytosis can often be readily made by the clinical history and the visible skin lesions and their distribution. Rubbing or trauma of the affected skin results in a wheal with flare (Darier's sign) in more than 90 % of the patients. A biopsy for histopathological examination is indicated in almost all cases to verify the diagnosis.

Measurement of the released mediators can be used to support the diagnosis and help to identify possible systemic cases. The serum Tryptase level has become the golden standard in mastocytosis. However, an elevated serum Tryptase level in children does not directly indicate systemic mastocytosis with certainty. Follow-up in mastocytoma and noncomplicated maculopapular

mastocytosis with normal serum Tryptase levels without complaints is unnecessary (to be published).

Bone marrow examination in children is not indicated unless it has consequences. Further evaluation in such manner should be reserved only for those children with persisting high serum Tryptase levels after the age of 5 years.

Bone marrow should be examined if there is evidence of haematemesis, melaena and severe bone pain and bone involvement, abnormal haematological values such as unexplained anaemia and leucopenia and the presence of mast cells in the peripheral blood. Children should always be examined in such cases by a dermatologist in cooperation with a paediatrician. Both should also have a special interest in mastocytosis.

In adults, an elevated serum Tryptase level of 20 μmol/l or higher indicates thorough investigations by a specialized internal physician.

Screening for systemic involvement should include a complete blood cell count. Unexplained anaemia, leucopenia, leucocytosis and/or thrombocytopenia indicate bone marrow involvement and make a bone marrow examination necessary. An early osteoporosis should also be evaluated. Other complaints such as abdominal pain may require other investigations such as ultrasound or magnetic resonance examinations.

Differential Diagnosis

Differential diagnosis includes lentigines, freckles, histiocytosis, café-au-lait freckling, juvenile xanthogranuloma and post-inflammatory pigmentations. All of these require histopathological examination.

General Principles of Treatment

Treatment is not indicated in most cutaneous variants and noncomplicated cases without complaints and/or systemic involvement. In cases with complaints or suspicion of systemic involvement, multidisciplinary approach is indicated. A team will at least include a dermatologist and an internal physician (adults) and a paediatrician (children). The therapy consists of reassuring the patient and his/her family in the majority of the cases.

Treatment is directed at alleviation of symptoms because a more pathophysiological approach to mast cell hyperplasia is unavailable. As most variants of the disease usually run a benign course, therapy can often be limited to reassurance and avoidance of factors known to stimulate mast cell degranulation. Further treatment must be tailored to the symptom complex of the individual patient (Heide et al. 2008).

Limited lesions may be treated with topicals with or without occlusion; topical corticosteroids and pimecrolimus cream are effective as reported by for corticosteroids and Correia (2010) and Ma (2010) for the calcineurin inhibitor. Treatment of bullae is supportive and consists of local care and prevention of infection.

Pruritus, urtication and flushing respond to H1-receptor antagonists. Positive results of rupatadine have also been reported (Siebenhaar and Fortsch 2013).

H1-receptor antagonists (e.g. hydroxyzine maximum 2 mg/kg daily in three doses; cetirizine 10–20 mg daily for children aged 2–6 years and 5 mg twice daily for those older than 6 years, as in adults; rupatadine 20 mg daily for 4 weeks) can control symptoms such as pruritus, urtication and flushing (Siebenhaar and Fortsch 2013). The addition of an H2-receptor antagonist (e.g. cimetidine 20 mg/kg daily in three doses, ranitidine 4 mg/kg daily in two doses) may be warranted in children who exhibit gastrointestinal symptoms of hyperacidity or ulceration, although this is controversial. Patients with diarrhoea may benefit from treatment with an H2-receptor antagonist, with or without disodium cromoglycate (a stabilizer of mast cell membranes) orally 100 mg four times daily. Another mast cell stabilizer, ketotifen 1 mg/kg twice daily, has been demonstrated to reduce whealing and pruritus in patients with maculopapular cutaneous mastocytosis, although a more recent controlled comparison with hydroxyzine in paediatric cutaneous mastocytosis showed no advantage. Patients with significant malabsorption may need oral predni-

sone treatment at a dose of 1–2 mg/kg daily at the start, slowly tapering off (stress dose = 2 mg/kg daily). However, it includes a real danger of accentuating concomitant bone disease that is caused by the mast cells in the marrow.

Patients with diarrhoea may benefit from treatment with disodium cromoglycate (a stabilizer of mast cell membranes) orally 100 mg three to four times daily.

Ultraviolet A (UVA) or UVA combined with oral psoralens (PUVA) may be used in adolescents and adults for skin manifestations that are resistant to more standard therapy.

One may consider therapy with imatinib mesylate in more complicated systemic cases (Droogendijk and Kluin-Nelemans 2006). Most other therapies are experimental. Research is directed at drugs that target the mutations of the KIT receptor (Fuller 2012).

Cytoreductive agents should be avoided if possible in patients with indolent SM, where the disease cause is nonprogressive. For aggressive systemic mastocytosis, interferon-α therapy (Hauswirth and Simonitsch-Klupp 2004; Butterfield 2005) and cladribine (Kluin-Nelemans and Oldhoff 2003) are the first-line drugs of choice with response rates of approximately 50 %.

The expression of kit in neoplastic mast cells (MCs) has led to the development of targeted therapies (El-Agamy 2012; Fuller 2012) using tyrosine kinase inhibitors (TKI) like STI571 (such as the earlier-mentioned imatinib) (Akin and Metcalfe 2004; Droogendijk and Kluin-Nelemans 2006). Unfortunately, the c-kitD816V mutation is associated with relative resistance against STI571. However, TKIs with activity against c-kitD816V-positive cells have recently been developed, and some of them (dasatinib, nilotinib/AMN107, PKC412) have already been tested in phase I/II trials. Although both dasatinib and PKC412 display remarkable in vitro activity against c-kitD816V, the preliminary results from human clinical trials in adults have not been as impressive (Gotlib and George 2007; Rondoni and Paolini 2007). In addition, non-TKI-kit signalling inhibitors (e.g. geldanamycin, rapamycin) or monoclonal antibodies directed against neoplastic MCs may evolve as future therapeutic options (Sotlar 2007).

Anaesthesia and Mastocytosis: Risk of Anaphylaxis

There is controversy on the risk of anaesthesia in children with mastocytosis. Recently, Carter et al. (2008) examined peri-anaesthetic records of 22 patients with paediatric mastocytosis and conducted a literature review of the anaesthetic experience in paediatric mastocytosis. They concluded that deviations from routine anaesthesia techniques were not necessarily warranted. However, an understanding of the anaesthetic implications of the disease and meticulous preparation to treat possible adverse events were advised.

As all patients with mastocytosis are at risk for unprovoked anaphylaxis (Silva and Carvalho 2008), we still recommend preventive measures in complicated cases with elevated serum Tryptase levels (Heide et al. 2008) at narcosis in children with large or unknown disease burden, in children with a history of anaphylaxis, those with bullous skin lesions or diffuse CM and those with SM or with high serum Tryptase levels.

Prognosis

The prognosis has been mentioned already in different paragraphs. In children, about two-thirds of the cases will regress, particularly those with big-spot disease and with solitary or multiple mastocytomas. Mastocytoma is very rarely observed in adults so that they clear almost completely before puberty. Most mastocytosis patients can live a normal life. However, a minority of the cases do have major complaints and in most extreme forms is life threatening.

Conclusions

Mastocytosis is not a disabling disease and the life expectancy is normal.

However, it is wrong to tell the parents that they do not have to worry and that the disease will disappear. It does not happen in one-third of the cases.

Anaphylaxis is a threat only in a minority of the cases when EpiPen prophylaxis should be prescribed. Children with mastocytosis, bullous disease, high serum Tryptase levels and/or a history of anaphylaxis should be equipped with an epinephrine auto-injector (Simons and Gu 2002) and be prepared (very important) together with the parents for this self-medication.

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Melanoma

60

Dimitrios Papakostas and Alexander J. Stratigos

Key Points

- Malignant melanoma shows a steady incidence increase by 3–7 % in fair-skinned Caucasian populations over the past four to five decades.
- Early recognition and diagnosis of thinner melanomas has resulted in the stabilization of mortality with improved 5-year survival rates in most countries.
- Phenotype (I–II), intermittent sun exposure, and genetic predisposition are key risk factors.
- The majority of sporadic melanomas associated with intermittent sun exposure are characterized by BRAF or NRAS mutations.
- Suspicious or atypical melanocytic lesions should be excised with a 2 mm safety margin deep to the subcutaneous fat.
- Sentinel lymph node biopsy (SLNB) is a diagnostic tool for the determination of stage, prognosis, and need for adjuvant therapy.
- Surgical excision is the primary treatment of melanoma, remains the mainstay in the treatment of locoregional metastasis, and has an increasing role in the treatment of limited disseminated disease.
- High-risk melanoma patients should be offered the option of adjuvant therapy after surgical excision of the primary tumor with the goal of reducing the risk of relapse and achieving a cure.
- Metastatic disease can be managed by systemic therapy, surgery, radiotherapy, or best supportive care. Until the emergence of novel targeted treatments in recent years, no drug demonstrated any substantial impact on survival improvement.
- Novel inhibitors of signal transduction such as the BRAF inhibitors vemurafenib and dabrafenib and immunomodulating monoclonal antibodies such as the CTLA-4 blocking autoantibody ipilimumab have revolutionized the treatment of metastatic melanoma.
- Follow-up of melanoma patients for a time period of up to 10 years aims to the early detection and treatment of recurrences and to an improved progression free and overall survival.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_60, © Springer-Verlag Berlin Heidelberg 2015

Definition and Epidemiology

Melanoma is a malignant melanocytic tumor developing in most cases from epidermal melanocytes. In 5 % of cases, primary extracutaneous manifestation with involvement of the eye (conjunctiva and iris), the meninges, and the mucosa may occur. After an initial horizontal or radial growth phase marked by pagetoid spread of malignant melanocytes within the epidermis and infiltration of the papillary dermis, a vertical growth phase with infiltration of the deeper dermis and subcutaneous fat follows. The vertical growth phase may lead to lymphogenic (intransit/lymph node metastasis) and/or hemotogenic spread (distant metastasis). Sixty percent of the metastases can be traced in the regional lymph nodes. Disease progression with involvement of the lung, the central nervous system (CNS), the bones, and the liver results to a poor prognosis and frustrating survival rates. Melanoma accounts for 5 % of all skin malignancies, but it is responsible for 85 % of the deaths by skin cancer.

A steady incidence increase of 3–7 % in fair-skinned Caucasian populations over the past four to five decades has utterly transformed the epidemiology and the socioeconomic impact of this previously infrequent skin malignancy. No other human malignancy with the exception of non-melanoma skin cancer (NMSC) has shown such a high yearly incidence increase. Indeed, the lifetime risk has risen from 1:1,500 in the 1920s in the USA to 1: 50 in 2010. In non-Caucasian populations, melanoma remains a rarity. Australia is the country with the highest incidence worldwide, with up to 60 new cases per 100,000 inhabitants per year compared to 20 new cases per 100.000 inhabitants per year in Germany. Despite the observed incidence increase over the last decades, early recognition and diagnosis of thinner melanomas in central and northwestern Europe, the USA, and Australia have been associated with stabilization of mortality and improved 5-year survival rates (>80 %), outranked only by prostate, thyroid, and testicular cancer. On the other hand, the disproportionate burden of thicker advanced melanomas due to late diagnosis in the elderly patients (>65 years), especially men, explains the mortality increase in this age group. Although the incidence peaks in elderly populations, melanoma can still affect younger adolescents and even children. Melanoma is rather rare in children, accounting for just 1 % of all new melanoma cases. Yet it is still the most common skin malignancy in this age group and usually associated with a poor prognosis.

Pathogenesis

Melanoma is a heterogeneous malignancy with a complex etiology. Phenotype, sun exposure, and genetic predisposition are principal risk factors in a complex etiological interaction with each other that explains the diversity of clinical manifestations and the epidemiology of the disease.

The consistent increase in incidence over the last decades could be attributed to the altered recreational habits in western industrial countries resulting to an increased sun exposure due to sun tanning on the beach or even indoor tanning. Indeed, melanoma preferably affects fair-skinned individuals of phenotype I or II who present with multiple lentigines and fair skin, hair, and eyes. There is a higher incidence in lower altitudes and among immigrant populations to areas of high ambient ultraviolet radiation. Furthermore, there is an association with sun-induced skin damage, actinic keratoses, and NMSC. Intermittent sun exposure due to recreational habits stimulates a high proliferative activity of melanocytes resulting potentially in the development of multiple melanocytic nevi and melanomas, particularly on truncal locations where most sporadic cases occur. Instead, chronic sun exposure allows a proper adjustment of the melanocytes at a low level of proliferative activity and is more commonly associated with actinic keratoses, NMSC, and melanoma on head and neck locations. The relative risk for malignant melanoma correlates to the number of common melanocytic and atypical/dysplastic nevi. However, only 30 % of all melanomas will develop on a preexisting

melanocytic nevus. Nevus-associated melanoma develops preferably on congenital nevi (60 %). Congenital melanocytic nevi are associated with a 0.7 % lifetime risk for melanoma, a risk that increases (2–3 %) in the case of giant congenital nevi (>20 cm in diameter). Clinically atypical or dysplastic nevi present with morphological asymmetry, are larger than 0.5 cm in diameter, have blurred and/or irregular borders, and contrary to common belief are rather common in general population (10 %). Although the relative risk of malignant transformation of the individual atypical nevus remains limited, multiple atypical or dysplastic nevi, especially in the setting of the dysplastic nevus syndrome and familial melanoma, are associated with an increased risk of melanoma and should be screened routinely.

Lately, the identification of molecular signatures or mutations based on anatomic location and sun exposure patterns has shed light on the molecular basis of melanoma. The majority of sporadic melanomas associated with intermittent sun exposure are characterized by BRAF/NRAS mutations, compared to cyclin-D1 and c-KIT alterations which are seen in tumors on chronically sun-damaged skin or c-KIT alterations in tumors located in areas without exposure, e.g., mucosal melanoma. About 50 % of sporadic cutaneous melanomas are BRAF mutated and 15–30 % have NRAS mutations, both of which are mutually exclusive. BRAF and NRAS are essential effectors of the MAPK/ERK kinase signaling cascade. Mutations result to an unregulated activation of this kinase cascade and uncontrolled tumor proliferation.

In familial melanoma (10 % of cases), germline CDKN2A and CDK4 mutations can be identified. Both genes play an essential role in cell cycle control and apoptosis regulation and are being currently considered as high-risk genes for melanoma, compared to low-risk genes such as TYR, TYRP1, and M1CR. The latter present as common variations or polymorphisms among the general population with a high frequency (>1 %) and are indicative for a lower lifetime risk compared to that conferred by high-risk genes.

Clinical and Histological Characteristics

The classical clinicopathological classification of melanoma in different subtypes, i.e., superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM), covers about 90–95 % of all melanoma cases. In some cases (5 %), extracutaneous manifestations in the eyes, mucosa, or even the meninges may occur and can be associated with late diagnosis and poor prognosis. Rare variants of cutaneous melanoma such as the amelanotic, the desmoplastic, and the mucosal type as well as the melanoma in childhood should be also considered due to the challenging differential diagnosis and the importance of an early recognition and treatment.

Histologically melanoma presents as an asymmetrical melanocytic lesion with pagetoid spread of atypical melanocytes, heterogeneous in size and morphology, throughout the epidermis. Atypical melanocytes may form confluent nests, while infiltrating the dermis and extending down to the adnexa. There is no maturation of melanocytes in the deeper layers of the dermis. Mitoses and signs of regression may be also observed. Staining for HMB45 and Melan-A is helpful for better distinguishing cells of melanocytic lineage. S100 has a very high sensitivity for melanoma but is also widely expressed in a variety of spindle cell tumors. Tumor thickness in the dermis is measured in mm, formerly known as Breslow index, currently described as AJCC depth.

Superficial spreading melanoma is the most frequent type (60 %). It is located in areas of intermittent sun exposure such as the back of males or the legs of females. It starts as a superficially spreading asymmetric macule with blurred or irregular borders (horizontal phase), followed by secondary nodular growth (vertical phase) (Fig. 60.1).

Nodular melanoma is the second most common melanoma type (10–20 %). This type shows an aggressive biological behavior due to the rapid vertical growth phase without prior horizontal phase. It presents as a rapidly growing darkly

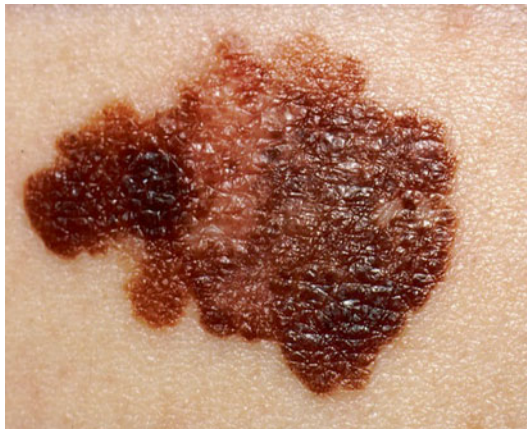

Fig. 60.1 Superficial spreading melanoma (SSM)

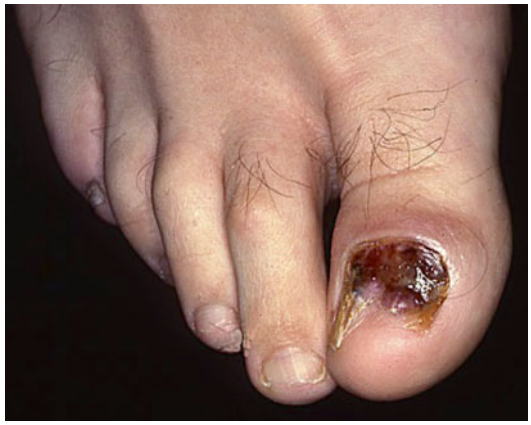

Fig. 60.2 Melanoma of the nail

pigmented nodule, although less pigmented and nonpigmented variants also exist.

Lentigo maligna melanoma can be spotted on areas of chronic sun exposure such as the face, the ears, the shoulders, and the extremities, preferably in elderly patients (60–70 years). LMM can develop on the ground of a preexisting atypical pigmented macule (lentigo maligna, in situ melanoma) accounting for about 10 % of all melanoma cases.

Acral lentiginous melanoma is a rather uncommon variant of melanoma (5 %), mostly on the palms and soles of elderly patients. In case of melanonychia, subungual melanoma should be always included in the differential consideration (Fig. 60.2).

Rare Melanoma Variants

Amelanotic melanomas account for 2 % of all melanomas. They lack the melanoma warning signs, particularly due to the absence of pigmentation and presence of reddish plaques or nodules, making the differential diagnosis from basal cell carcinoma or pyogenic granuloma a rather challenging quest.

Desmoplastic melanoma develops as a slowly enlarging area of thickened skin, resembling a scar, most commonly on exposed areas of the head and neck (>50 %). They are usually skin colored but may be pigmented as well, and they usually lack the classic recognition signs of melanoma often resulting in a late diagnosis. Proper histological diagnosis is a difficult task, since there is no or little spread of malignant cells within the epidermis. Instead, atypical spindle cells separated by a fibrous stroma are found within the dermis or subcutaneous fat.

Uveal melanoma preferably affects middle-aged patients with fair skin and is marked by GNAQ and GNA11 mutations. The choroid is the most common site of tumor development. Blurred vision, floaters, flashing lights, and shadows are usual visual symptoms reported by some patients, although others may have no symptoms at all. Late diagnosis is associated in most cases with poor prognosis.

Mucosal melanoma accounts for less than 5 % of melanoma cases. The majority of mucosal melanomas begin in the head and neck region, the anorectal region, and the female genital tract. Rare locations of primary mucosal manifestation include the esophagus, the gallbladder, the bowel, the conjunctiva, and the urethra. Mutations of the c-KIT gene are found in mucosal melanomas which are typically BRAF negative. There is no relation to UV exposure and no obvious identifiable risk factors.

Melanoma in childhood may be very rare, accounting for 1 % of all melanomas. There is no association with excessive sun exposure, and it usually arises within a giant congenital melanocytic nevus of >20–40 cm diameter. It is more often amelanotic (flesh colored, pink, or red), nodular, hemorrhagic, and ulcerated. Prognosis is usually poor.

Diagnosis

Melanoma usually presents as a melanin-rich lesion changing in size, shape, or color within weeks or months, or as a preexisting nevus with distinct clinical characteristics compared to other nevi ("ugly duckling" sign) without any history of change, or as a new nevus with atypical appearance and/or rapid change in size. The differential diagnosis may prove challenging, and the list of differential diagnosis includes a large number of melanocytic and nonmelanocytic tumors, such as lentigo, melanocytic nevi, seborrheic warts, pigmented basal cell carcinoma, angiokeratoma, dermatofibroma, and hemangioma, or even hematoma should be taken into diagnostic consideration.

For an early diagnosis, clinical examination and use of the ABCDE algorithm (*A*symmetry of a melanocytic lesion with irregular or blurred *B*orders, different *C*olors and *D*iameter >0.5 cm, *E*volving in time) may prove very useful: Dermoscopy, an in vivo noninvasive diagnostic magnification of skin lesions, can substantially improve the clinical diagnostic sensitivity in the hands of experienced dermatologists. An atypical melanin network, pseudopods in the periphery of an atypical melanocytic lesion, black dots (atypical melanocytes in the stratum corneum), regression structures, blue-whitish veil (orthohyperkeratosis), and gray veil (melanophages in the dermis) are suggestive for melanoma. Suspicious melanocytic lesions should be totally excised with a 2 mm conservative margin deep to the subcutaneous fat in order to remove the entire lesion and obtain adequate material for a proper histological diagnosis. Wider margins should be avoided upon primary excision in order to permit accurate lymphatic mapping at a second stage, if needed.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) is a diagnostic tool for the determination of stage, prognosis, and the need for adjuvant therapy. Its impact on overall prognosis is unclear. It is performed in tumors thicker than 1.0 mm or even thinner (<1 mm) in the presence of additional risk factors such as ulceration, mitoses rate ≥1, or extensive regression. Other factors may play a role in the decision to perform SLNB such as the patients' medical background, age, and comorbidities.

Tumor Classification

The American Joint Commission on Cancer (AJCC) lately (2009) revised the staging system for cutaneous melanoma based on the TNM tumor classification. A multivariate analysis of 30,947 stage I, II, III and 7,972 stage IV melanoma patients from the AJCC patient database was conducted. T defines features of primary tumor (Table 60.1), N of regional disease (Table 60.2), and M of extra-regional disease

Table 60.1 AJCC 2009 TNM staging categories: T

Tis	Melanoma in situ	
T1a	Thickness ≤1 mm	Without ulceration and mitoses/mm2 < 1
T1b	Thickness ≤1 mm	With ulceration and/or mitoses/m2 ≥ 1
T2a	Thickness 1.01–2 mm	Without ulceration
T2b	Thickness 1.01–2 mm	Ulcerated
T3a	Thickness 2.01–4 mm	Without ulceration
T3b	Thickness 2.01–4 mm	Ulcerated
T4a	Thickness >4 mm	Without ulceration
T4b	Thickness >4 mm	Ulcerated

Table 60.2 AJCC TNM staging categories: N

N0	No evidence of lymph node metastasis
N1	1 metastatic lymph node
	(a) Micrometastasis
	(b) Macrometastasis
N2	2–3 metastatic lymph nodes
	(a) Micrometastasis
	(b) Macrometastasis
	(c) In-transit metastasis/satellite metastases without metastatic lymph nodes
N3	4 or more metastatic lymph nodes or matted nodes or in-transit metastasis/satellite metastases with metastatic lymph nodes

(Table 60.3). The T category is defined by tumor thickness and ulceration (T1–T4). Tumors thinner than 1.0 mm are upgraded in the presence of ulceration and dermal mitoses (≥1). The N category is defined by the number of metastatic lymph nodes, the observed micro- or macrometastases, and the presence of satellite or in-transit metastases. Finally, the M category is defined by distant metastases in the presence of normal or elevated LDH (Table 60.4).

Approximately 84 % of melanoma patients are diagnosed with local disease, 9 % with regional disease, 4 % with distant disease, and 4 % remain unstaged. Prognosis by means of survival rates depends on stage and ranges from a remarkable 98.3 % 5-year survival for patients with localized disease to 62.4 % for patients with regional disease and 16 % for patients with disseminated disease.

Table 60.3 AJCC TNM staging categories: M

M0	No evidence of extra-regional metastases
M1a	Extra-regional cutaneous-subcutaneous or lymph node metastases
	Normal LDH levels
M1b	Extra-regional lung metastases
	Normal LDH levels
M1c	Any other extra-regional metastasis with normal LDH levels
	or
	Any extra-regional metastasis with elevated LDH levels

Table 60.4 AJCC 2009: stage groupings

Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a	M0
	T1-4a	N2a	
IIIB	T1-4b	N1a, N2a	M0
	T1-4a	N1-2b, N2c	
IIIC	T1-4b	N1-2b, N2c	M0
	Any T	N3	
IV	Any T	Any N	M1

Initial Staging Workup

Baseline imaging should be generally recommended for stages ≥ IIC. Cross-sectional imaging methods like CT, PET/CT, and MRI are preferably recommended. For stages up to IIB, imaging could be considered only for evaluation of specific signs and symptoms. Whole-body CT and cranial MRI are not advised as a standard diagnostic procedure in asymptomatic low-risk patients with the diagnosis of primary melanoma. Lymph node ultrasound and the serologic marker S100 should be recommended in stages ≥ IB. Serum LDH has no prognostic validity upon primary diagnosis of melanoma and should be reserved for patients with stage IV melanomas.

Molecular Pathology Workup

High-risk patients in stages IIIB and above should be screened for BRAF, NRAS, and c-KIT, which are now commercially available. Novel targeted treatments have opened new therapeutic horizons and could be offered in case of inoperability and/or metastatic disease. About 50 % of all primary melanomas carry BRAF mutations and about 5 % of all mucosal or acral melanomas are positive for c-KIT mutations. NRAS mutations can be also found in 15 % of all melanomas. BRAF mutations are present throughout different phases of melanoma progression. If a biopsy of a metastatic lesion is not available, the most recent surgical sample, e.g., a positive lymph node or even the primary tumor, may be adequate.

General Principles of Treatment

Surgical Treatment

Surgical excision is the standard of care in the treatment of melanoma (Fig. 60.3). When melanoma is excised with intent to cure, a radical

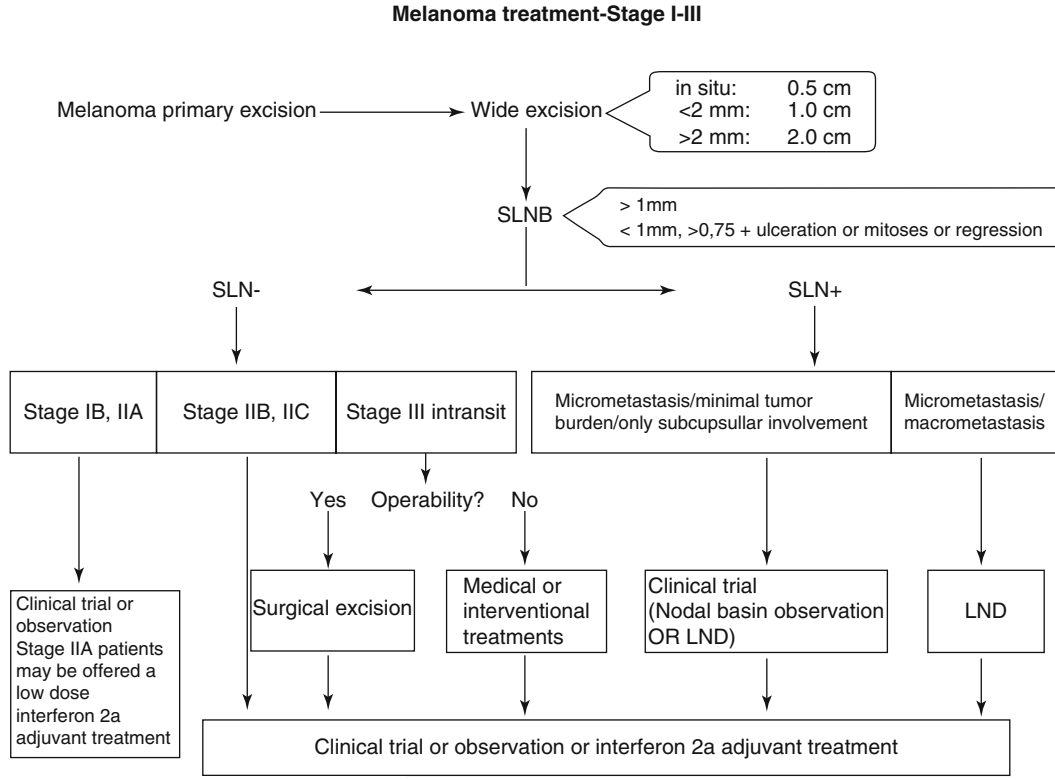

Fig. 60.3 Melanoma treatment: stages I–III

wide excision with adapted safety margins should be performed after the diagnostic primary excision in order to prevent local recurrences. Surgery remains the mainstay in the treatment of locoregional metastases and can be offered in a setting of interdisciplinary approach in case of limited disseminated disease or as a last palliative resort to improve patients' quality of life.

Wide Excision

A 5 mm safety margin is currently recommended for in situ melanoma. For large diameter lentigo maligna or lentigo maligna melanoma, surgical margins greater than 0.5 cm may prove necessary in order to achieve histologically negative margins; otherwise, local recurrences may occur. In invasive melanoma, wide excision with 1 cm safety margins should be performed for tumors up to 2 mm in histological depth and with 2 cm margins for thicker tumors (>2 mm). However, the issue of optimal surgical margins is yet to be clearly resolved and there are still regional guideline variations.

Surgical margins may be modified to accommodate individual anatomic or cosmetic considerations. A 1–2 cm margin might be acceptable in anatomically difficult areas, whereas a full 2 cm margin could be difficult to achieve. Further, micrographic surgery could be considered in special anatomic locations such as the face, the finger, and toes in order to minimize the necessary safety margin and avoid mutilating surgical procedures. However, data on the use of Mohs micrographic surgery in melanoma are limited, limited mostly to cases of lentigo melanoma, and this technique should be reserved for carefully selected cases.

Lymph Node Dissection

Regional lymph node dissection is not recommended if SLNB is negative since there is no therapeutic benefit of prophylactic lymphadenectomy. On the other hand, regional lymphadenectomy can be offered after histological (SLNB) or cytological detection of lymph node micrometastases with fine-needle aspiration cytology (FNAC). The decision for complete lymph node dissection in sentinel lymph nodes with a minimal tumor burden and/or subcapsular location must be made together with the patient and should take in consideration further risk factors such as tumor thickness, ulceration, tumor mitosis rate, number of positive sentinel lymph nodes, and anatomic site of the primary tumor (Fig. 60.3).

Patients presenting with clinically positive nodes (macrometastasis) without radiologic evidence of distant metastases should undergo complete lymph node dissection of the involved nodal basin in order to prevent regional recurrence and pursue a curative approach. If the indication has to be determined by findings other than SLNB, regional ultrasonography by an experienced examiner is superior to plain clinical examination by palpation. In case of a recurrence in a lymph node basin that has been previously operated, lymph node dissection should be considered, if there is no further evidence of metastases.

Surgical Treatment of Locoregional Metastases

Cutaneous metastases up to 2 cm from the excision scar of the primary tumor are described as satellite metastases, while those on the lymphatic course toward the regional lymph nodes are defined as in-transit metastases. In both cases, surgical excision of operable locoregional metastases remains the mainstay of treatment. In case of inoperability due to an increasing number of metastatic lesions, other interventional or medical options should be considered, e.g., intratumoral IL-2 injection, intratumoral electrochemotherapy with bleomycin or cisplatin, local immunotherapy with diphencyprone (DCP), radiation, and isolated limb perfusion with the chemotherapeutic melphalan (Fig. 60.3 and 60.4).

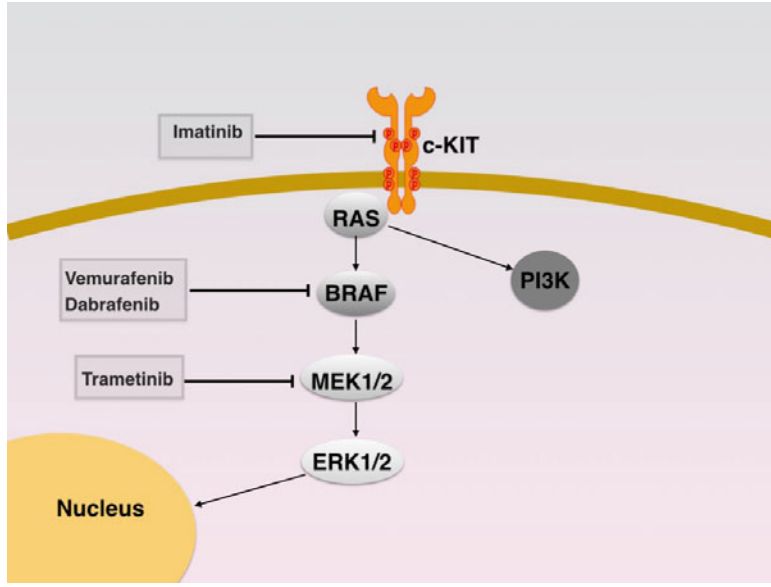

Fig. 60.4 MAPK/ERK kinase signaling pathway and targeted treatments

Treatment of Distant Metastases

Patients in stage IV with limited or localized metastatic disease should be offered a surgical excision of the metastases if a complete curative resection (R0) is technically feasible with no unacceptable functional deficit (Fig. 60.5). A low number of metastases and a long duration of the metastasis-free interval are currently seen as positive prognostic factors and should influence the treatment decision in favor of a curative surgical approach. Palliative surgery when an R0 resection is not possible remains an option in cases where the patient's quality of life could be distinctively enhanced.

Adjuvant Medical Treatment

High-risk melanoma patients should be offered an adjuvant therapy after surgical excision of the primary tumor with the goal of reducing the risk of relapse and achieving a cure. Provided treatment should have a reasonable safety profile though. The only approved agent for the adjuvant treatment of melanoma is interferon alpha. Vaccination therapies, immunostimulation with levamisole, isolated limb perfusion with melphalan ± TNF, and chemotherapy should not be considered in an adjuvant setting.

Interferon

Clinical trials so far have shown a small but significant benefit in overall survival and a significant benefit for recurrence-free survival in patients treated with interferon alpha. Yet no single interferon regimen has been shown to be significantly superior to others. A variety of different interferon agents (IFN a2a vs. IFN a2β, pegylated interferon), dosage schemes (high vs. low dose), patient subsets, treatment duration, and administration routes (subcutaneous vs. intravenous or

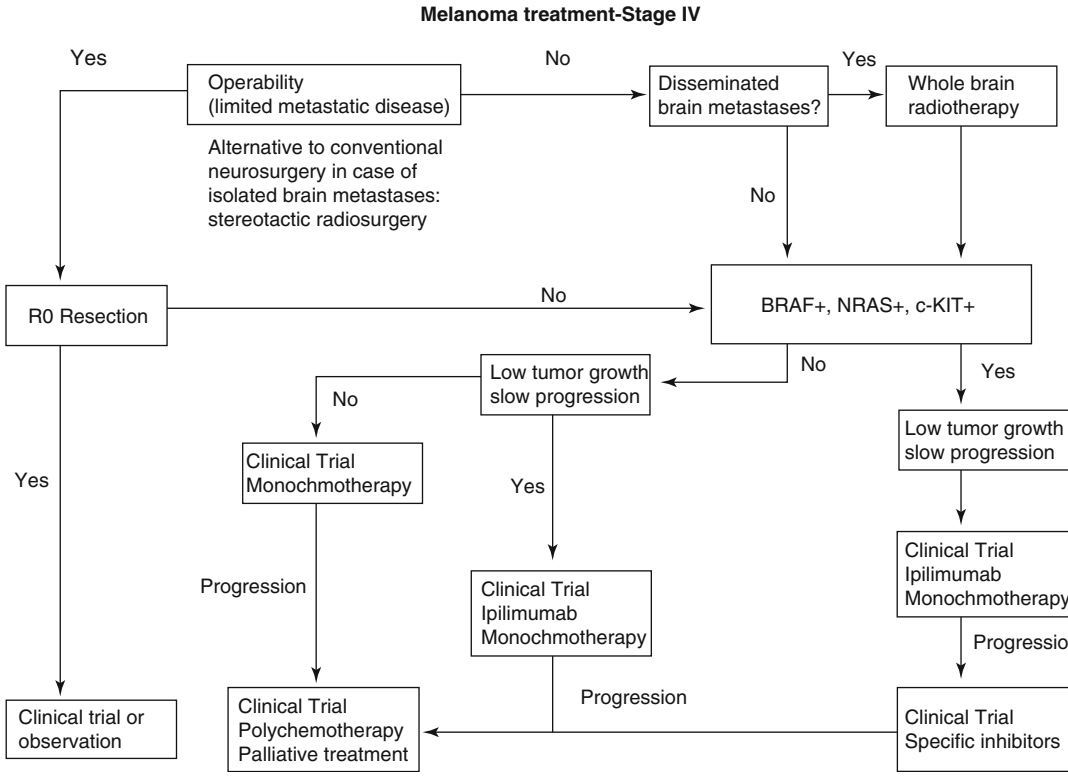

Fig. 60.5 Melanoma treatment: stage IV

pulsed intravenous regimens) have been discussed so far. A subset of patients may benefit from adjuvant treatment with interferon, but this benefit often comes at the cost of reduced tolerability. The most common adverse reactions include flu-like symptoms, depression, hair loss, and leukopenia.

The major regulatory authorities (FDA and EMEA) have approved a high-dose interferon regimen for high-risk patients in stages IIB/IIC and III. After the initial induction over 4 weeks with 20 MIU/m2 IV 5× per week follows the maintenance phase with 10 MIU/m2 SC 3× per week for 48 weeks. EMEA has also approved a low-dose regimen for patients in stage II with 3 MIU IV 3× per week for 18 months. An adjuvant treatment with pegylated interferon a2b once per week for 5 years is approved by the FDA for stage III patients and from Switzerland for stage IIIA patients.

With regard to currently existing guidelines, adjuvant treatment options for low-risk patients in stages IB and IIA include participation in clinical trials with interferon or clinical observation. After a proper consideration of the patients' medical background, and the potential adverse events and their effect on quality of life, stage IIA patients may be offered a low-dose adjuvant interferon treatment or clinical observation. High-risk patients in stages IIB/IIC and III should be offered the participation in clinical trials or the option of adjuvant treatment with interferon or clinical observation.

Nonsurgical Treatment of Locoregional Metastases

Patients with non-operable locoregional metastases should be treated, if possible, in context of clinical trials. If this is not the case, a wide spectrum of nonsurgical strategies can be considered. Intratumoral IL-2 injection, intratumoral electrochemotherapy with bleomycin or cisplatin, and local immunotherapy with diphencyprone (DCP) show the highest response rates. Other options include radiotherapy, CO2 ablation, and isolated limb perfusion with the chemotherapeutic melphalan. The latter should be considered in cases of rapid local disease progression, when the metastases remain uncontrolled under more conventional surgical and nonsurgical treatments.

In case of inoperability, when there is no indication for local treatments or after local treatment failure, systemic treatment options such as those for disseminated disease should be considered.

Medical Treatment of Disseminated Disease

Disseminated disease can be managed by systemic therapy or best supportive care (Fig. 60.5). Until the emergence of novel targeted treatments in recent years, no single agent had demonstrated any substantial impact on survival improvement. Standard chemotherapeutics included intravenous administration of dacarbazine and oral temozolomide. The combination of chemotherapy with interferon or IL-2 led to increased response rates but had no impact on overall survival. This situation has radically changed in recent years with the advent of novel inhibitors of signal transduction (Fig. 60.4) such as the BRAF inhibitors vemurafenib and dabrafenib and of novel immunomodulating agents such as the monoclonal anti-CTLA-4 antibody ipilimumab. Approval of vemurafenib/dabrafenib and ipilimumab has significantly changed the management of patients with metastatic melanoma, but with important limitations. Ipilimumab has a potential for serious autoimmune toxicities and clinical responses may take months to become apparent. Overall response rates are very limited, but there is a subset of patients with a long-lasting response. BRAF inhibitors, on the other hand, demonstrate high response rates, but the median response does not last longer than 5–6 months. Recent data from randomized clinical trials suggest that patients with BRAF-positive metastatic melanoma may benefit from the sequential treatment with ipilimumab and BRAF inhibitors or from the combination of ipilimumab with anti-PD-1 antibodies. This underscores the importance of participating in an ongoing clinical trial, whenever possible.

Inhibitors of Signal Transduction

Vemurafenib is a novel BRAF inhibitor which lately promised to revolutionize the treatment of metastatic melanoma due to unprecedented response rates of about 80 % and a clear impact on progression-free survival >6 months. In clinical trials the median overall survival of 15 months was significantly better than that of dacarbazine (6.5 months). Unfortunately response duration is limited due to resistance development after 5–6 months. Vemurafenib was the first selective BRAF inhibitor to receive FDA approval in 2011 and EMEA approval in 2012. The recommended dose for vemurafenib is 960 mg twice daily. About 50 % of all melanomas are BRAF positive, with 75 % harboring the BRAF V600E mutation and 19 % the BRAF V600K mutation. Both respond to BRAF inhibition with vemurafenib, in contrast to wild-type BRAF melanomas which should not be treated with vemurafenib because of the risk of marked disease acceleration. There is now clear evidence that the use of a BRAF inhibitor alone leads to reactivation of the MAPK/ERK pathway via receptor tyrosine kinase (RTK)-mediated activation of alternative survival pathways or activated RAS-mediated reactivation of the MAPK pathway, suggesting additional therapeutic strategies such as the combination of BRAF with inhibitors of MEK, a downstream effector. The reactivation of the MAPK/ERK pathway explains not only the limited response duration but a very important side effect of the treatment as well, the relative high incidence (18–24 %) of squamous cell carcinoma and keratoacanthomas in treated patients. Other common side effects include rash, arthralgia, and photosensitivity.

Dabrafenib is the second FDA-approved (2013) selective BRAF inhibitor. Dabrafenib is associated with significant episodic and recurrent fevers that should be managed by drug discontinuation and administration of antipyretics and/or NSAIDs. Furthermore, dabrafenib is associated with keratoacanthoma/low-grade squamous carcinomas but in contrast to vemurafenib manifests limited if any photosensitivity.

The combination of a BRAF inhibitor with a downstream inhibitor (MEK inhibitor) may prolong the response duration of BRAF inhibitors and even prevent or limit the development of cutaneous SCCs. Several MEK inhibitors are under development. Trametinib, the first FDA-approved (2013) MEK inhibitor, is not indicated for treatment of patients who have experienced progression of disease on prior BRAF inhibitor therapy. Instead, its principal indication is intolerance to BRAF inhibitors.

Imatinib is a tyrosine kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive chronic myelogenous leukemia (CML). Recent observations suggest that melanoma patients with specific c-KIT aberrations may respond to c-KIT kinase inhibitor therapy, i.e., imatinib (400 mg/d). c-KIT mutations are generally rare in melanoma, and they most likely occur in acral lentiginous and mucosal melanomas. Adverse events are mild to moderate and include gastrointestinal symptoms, elevated liver enzymes, fatigue, and edema.

Immunomodulating Monoclonal Antibodies

Immune checkpoint blockade of lymphocytes has developed to a new powerful tool in cancer therapy and promises to revolutionize the role of immunotherapy in the treatment of metastatic melanoma, even in a first-line setting, regardless of the mutational status of the tumor.

Ipilimumab was the first FDA-approved (2011) human monoclonal antibody that activates the cytotoxic T cells by targeting CTLA-4, a protein receptor on the surface of T cells that downregulates the immune system. In Europe, it has been approved as a second-line treatment of metastatic malignant melanoma. Clinical trials have noted complete remission rates up to 14 % and a significant improvement in overall survival (median overall survival 10 months). Response to ipilimumab may be delayed and not evident until 12 weeks or even a few months after treatment initiation. The recommended dose is 3 mg/kg

administered intravenously over 90 min every 3 weeks for a total of four doses. Patients treated with ipilimumab who experience stable disease of 3 months duration after week 12 of induction or partial or complete response, who subsequently experience progression of melanoma, may be offered re-induction with up to four doses of ipilimumab at 3 mg/kg every 3 weeks. By activating the immune system, there is a potential for significant triggering of autoimmunity in different organs, namely, the gastrointestinal tract, lungs, skin, hypophysis, and urinary tract.

Nivolumab is a fully human IgG4 monoclonal antibody, currently under investigation, with an immunomodulating action that blocks the ligand activation of the programmed cell death 1 receptor (anti-PD-1). By targeting an immune checkpoint different than ipilimumab, nivolumab activates the immune system leading to an earlier antitumoral response with more limited side effects. There is recent evidence that a combination therapy with ipilimumab may prove of benefit for metastatic patients compared to monotherapy with an anti-PD-1 antibody. Programmed cell death 1 ligand 1 (PD-L1) antibodies targeting a different immune checkpoint than ipilimumab and nivolumab are currently under investigation.

Chemotherapy

Chemotherapy, either as mono- or polychemotherapy, has been the mainstay of treatment in the stage of distant metastases until the recent development of novel targeted treatments and immunotherapies. Conventional chemotherapeutic agents include the alkylating cytostatic agents dacarbazine (DTIC) and temozolomide, several platin-based chemotherapeutic agents such as cisplatin and carboplatin, the vinca alkaloid vincristine, the nitrosourea alkylating agent fotemustine, and the mitotic inhibitor paclitaxel.

DTIC has been most frequently used and serves as reference drug for metastatic melanoma; temozolomide, an imidazotetrazine derivative of DTIC, can be administered orally. Nonetheless, none of these chemotherapeutic agents has been proven of being superior to others, and they all demonstrate very modest response rates (under 20 %) in first- and second-line settings, without any effect on overall survival. Patients with tumor progression during previous systemic therapy or initial rapid tumor progression may be offered polychemotherapy. Common adverse events include leukopenia, thrombopenia, anemia, anorexia, nausea, and vomiting.

Biochemotherapy, the combination of conventional chemotherapeutic agents and biologic agents such as interferon and IL-2, may improve progression-free survival, but at the cost of increased toxicity and without improved overall survival rates.

Supportive Care

Patients with osseous metastases should receive aminobisphosphonates, e.g., ibandronate, pamidronate, and zoledronic acid, or a RANK ligand inhibitor such as denosumab. Treatment should be initiated upon detection of bone metastases and continued on a long-term basis to prevent a series of problems associated with bone metastases such as persistent or intermittent pain, fractures, spinal compression, and hypercalcemia.

Pain may have a profound impact on patients' quality of life and effective pain management is an essential part of supportive care. The pain ladder introduced by the WHO (1988) comes evidently into use for systemic pharmaceutical pain management and includes non-opioid analgesics (nonsteroidal anti-inflammatory drugs/NSAIDs), centrally acting analgesics (weak opioids), opioids and opiates, and adjuvant agents (psychotropic and antiseizure drugs, corticosteroids).

Antiemetic drugs should be administered during chemotherapy and radiation since vomiting and nausea are very common adverse events. 5-HT3 receptor antagonists, neurokinin-1 receptor antagonists, and steroids should

be employed in accordance with guidelines to give relief to the patient and improve treatment compliance.

Radiation

Radiation can be discussed in case of inoperable or not fully resectable (R1, R2) primary tumors with the goal of local tumor control, especially of LMM which is not suitable for conventional surgical treatment. Another indication of adjuvant radiation therapy includes desmoplastic melanomas, especially those with neurotropism, or when the excision with adequate safety margins is not technically feasible. Adjuvant radiation therapy after complete regional LND can be considered for high-risk lymph node disease if one of the following criteria is met: high-risk locoregional disease with ≥3 affected lymph nodes, lymph node diameter ≥3 cm, and capsule penetration. After recurrence in a dissected lymph node basin, radiotherapy should be performed after resection of the metastases. Postoperative radiation of a lymph node basin aims to a better local disease control, even though a positive effect on overall survival has yet to be established. A total dose of 50–60 Gy fractioned in 5× 1.8–2.5 Gy per week is recommended for lymph node disease. Fractioned regimens show equal efficacy with respect to local tumor control in comparison to higher individual doses.

Stereotactic radiosurgery and/or whole-brain radiotherapy may be administered either as primary or as adjuvant treatment following surgical resection of brain metastases. Furthermore, in patients with acute signs and symptoms due to epidural compression of the spinal cord, radiotherapy may be performed for local symptom control in a palliative setting. Contrary to common perception that melanoma is radioresistant, radiation often achieves good palliation of symptomatic metastatic disease. In the setting of distant inoperable metastases in the skin, subcutaneous tissues, bones, or lymph nodes, radiotherapy could be discussed with the aim of improving quality of life, preventing pain, and improving local tumor control.

Follow-Up

Follow-up of melanoma patients for a time period of up to 10 years is currently recommended in all major guidelines aiming to an early detection and treatment of recurrences and an improved overall survival. The duration, frequency, and diagnostic workup schedule remain controversial and vary regionally depending on socioeconomic parameters. Only 5 % of all recurrences will occur after 10 years; hence, the recommended 10-year follow-up appears reasonable. However, lifelong surveillance of all melanoma patients by means of a yearly dermatological examination and patient's self-examination is justified not only due to the 5 % risk of recurrence after 10 years for stage I–III patients but also due to the increased lifetime risk (4–8 %) for a second primary melanoma.

Self-examination has gained importance lately and should be recommended during and after the end of physician-orientated follow-up period. Melanoma patients should be instructed to look for suspicious new lesions or changes by regular whole-body inspection as well as palpation of postsurgical scars, locoregional lymph drainage areas, and regional lymph node basins for possible recurrences. Furthermore, skin cancer preventive education including sun protection measures should be promoted in both patients and their families.

Patients with a surgically treated in situ melanoma do not require follow-up, as there is no risk of metastasis. Stage IA patients should be examined clinically every 6 months in the first 3 years and consecutively once yearly up to the tenth year; stage IB–IIB patients should be seen initially every 3 months and every 6 months after the third year. High-risk stage IIC–IV patients should be examined every 3 months in the first 5 years and twice yearly from year 6 to 10.

Elevated serum S100 level may point to distant metastases. As it is dependent of tumor load, it should be measured in the first 3 years every 3 months in patients with stage ≥ IB and every 6 months in patients with stage ≥ IIC in the fourth and fifth year of the follow-up.

Locoregional lymph node ultrasonography is a sensitive way to detect local, in-transit, and locoregional lymph node metastases. Since the majority (>60–70 %) of initial metastases will occur, locoregional lymph node ultrasonography should be recommended as a sensitive, specific, and cost-effective diagnostic tool for early metastasis detection. Stage IB–IIB patients should be examined twice yearly in the first 3 years, while high-risk patients (stage ≥ IIC) should be assessed every 3 months in the first 3 years and twice yearly up to the fifth year.

Imaging procedures should be generally reserved for high-risk patients (stage ≥ IIC), twice yearly in the first 3–5 years of the follow-up. Chest X-ray and abdominal ultrasonography are not recommended any longer; cross-sectional imaging should be offered instead. Brain metastases are better detected with MRI, while, for the diagnosis of osseous metastases, PET/CT and MRI display similar accuracy. PET/CT has indeed a higher sensitivity in detecting distant metastasis compared to regular CT. Due to the substantial financial burden, PET/CT should be reserved for special diagnostic interventions. Hence, whole-body CT remains a sensitive, recommended, procedure for early distant metastasis detection and should be performed routinely in stage ≥ IIC. Nonetheless, extended imaging with MRI and PET/CT can be considered to screen for metastatic or recurrent disease in case of clinical suspicion at the discretion of the physician.

Further Reading

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Melasma

61

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Key Points

- The exposure to ultraviolet radiation and genetic and hormonal factors are the most important causative factors of melasma.
- Melasma can be classified into four histological types, the epidermal type, the dermal type, the mixed type and the indeterminate type. The response to treatment depends on the melasma subtype.
- At present there is no standard therapy for melasma. Topical hydroquinone, alone or in a triple-combination formula, is the first line of treatment. It is the most widely studied agent with reported efficacy for patients with melasma.
- The mainstay of treatment is the use of sunscreen along with topical bleaching agents that inhibit melanogenesis. The use of sun protection in the patient with melasma is a lifetime commitment.
- Fractional laser is the only laser treatment approved by the FDA for melasma and it has shown promising results.
- Melasma treatment should be tailored to the clinical subtype and disease severity to optimize therapy.

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Definition and Epidemiology

Melasma (from the Greek word *melas* meaning black) is a common acquired circumscribed, brown or sometimes greyish-brown hypermelanosis of the face, occasionally the neck and forearms. It is a chronic, often relapsing condition with a negative impact on the quality of life. Although all races are affected, melasma is more common in darker-skinned individuals of Hispanic, Asian or of African or Middle Eastern descent. The reported prevalence of melasma ranges from 8 % among Latinas in the United States to 30 % in Southeastern Asian populations. Women are affected in 90 % of cases.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_61, © Springer-Verlag Berlin Heidelberg 2015

Basic Concepts of Pathogenesis

The major aetiological factors of melasma include genetic influences, exposure to ultraviolet (UV) radiation and female sex hormones. Other possible factors include thyroid dysfunction, cosmetics, phototoxic and antiseizure drugs, ovarian dysfunction, hepatic dysfunction and nutritional deficiency.

Sun exposure is a major triggering and aggravating factor in the development of melasma, likely because of direct melanogenic effects of UV on melanocytes.

Natural and synthetic oestrogen and progesterone have been incriminated for the pathogenesis of melasma because of its frequent association with pregnancy, use of oral contraceptive pills and oestrogen replacement therapy.

Since melanocytes contain oestrogen receptors, the melanocytes in patients with melasma may be inherently more sensitive to the stimulatory effects of oestrogens and possibly to other sex steroid hormones.

Histological examination has shown that melasma lesions, in addition to increased pigmentation, have more elastosis and vascularization than perilesional skin. No increase in the number of melanocytes was noted in those areas, but the melanocytes were larger and intensely stained with very prominent dendrites and showed increased melanogenesis.

Recent studies have proposed a role of the stem cell factor and vascular and neural components in the pathogenesis of melasma.

Clinical Presentation

Melasma is characterized by light to dark brown or brown-gray hyperpigmented patches with irregular borders. The number of hyperpigmented patches may range from one single lesion to multiple patches located usually symmetrically on the forehead, cheeks, dorsum of the nose, upper lip, chin, occasionally on the V area of the neck and forearms. Extra-facial melasma is more frequent in postmenopausal women. According to the distribution of lesions, melasma occurs in one of three patterns: centrofacial, malar and mandibular pattern:

1. The centrofacial pattern. This is the most common pattern. It involves the forehead, cheeks, upper lip, nose and chin.
2. The malar pattern. This involves the cheeks and nose.
3. The mandibular pattern. This involves the ramus of the mandible.

Based on Wood's light examination of the skin, melasma can be classified into four types, with good correlation with the depth of the melanin pigment:

1. Epidermal: light brown, with enhancement of pigmentation under Wood's light. Histologically, it is characterized by a melanin increase in the basal, suprabasal and stratum corneum layers.
2. Dermal: ashen or bluish-grey, with no enhancement of pigmentation under Wood's light. Histologically, there is a preponderance of melanophages in the superficial and deep dermis.
3. Mixed: dark-brown. Enhancement of pigmentation is present under Wood's light in some areas, while not in others. Melanin is increased in the epidermis, and there are many dermal melanophages.
4. Indeterminate: in individuals with dark-brown skin or skin type VI, examination with a Wood's light is of no benefit.

Dermal melanin deposition is common and is unrecognized under a Wood's lamp examination, which may explain the difficulty in treating patients with apparent epidermal melasma.

The Melasma Area and Severity Index (MASI) is a common outcome measure, used to assess melasma patients in clinical trials.

Diagnosis

The diagnosis is clinical and the patient's medical history will provide further necessary information, including pregnancy, use of oral contraceptives, a family history of melasma and history of sun exposure.

Differential Diagnosis

Post-inflammatory hyperpigmentation: distribution of the lesions; history of local inflammation.

Pigmented cosmetic dermatitis (Riehl's melanosis): reddish-brown pigmentation, reticulate pattern; positive patch testing

Hyperthyroidism: thyroid function tests

Actinic lichen planus: papular lesions, histology

HIV infection-related pigmentation: HIV-positive serology

Drug-induced facial hyperpigmentation: history of drug intake (antimalarials, amiodarone, minocycline, phenothiazines, tricyclic antidepressants, anticonvulsants, cytotoxic drugs), blue-grey hue of facial lesions

Poikiloderma of Civatte: reddish-brown, reticulate pattern with atrophy and telangiectasia, usually on the lateral cheeks and the sides of the neck

General Principles of Treatment

Melasma is a cosmetic problem that sometimes causes great emotional suffering. The majority of the existing treatments may temporarily depigment the melasma, but the condition usually relapses. There are, however, various therapeutic modalities that can offer a significant benefit. The principles for melasma therapy include the inhibition of the activity of melanocytes (protection from sunlight and avoidance of precipitating factors), the inhibition of the synthesis of melanin (bleaching agents), the removal of melanin (chemical peeling) and the disruption of melanin granules (lasers). Melasma treatment should be tailored to the clinical subtype and disease severity to optimize therapy.

General Measures

Sun exposure is the most important avoidable risk factor. Melanocytes in melasma are easily stimulated by both UVA and UVB as well as visible radiation. Avoidance of solar exposure is recommended. Broad-spectrum sunscreens should be applied daily during treatment and afterwards.

Discontinuation of oral contraceptives or other oestrogen progesterone agents is advised, if possible. Women, in whom melasma develops during pregnancy, should avoid exposure to sunlight and should use a broad-spectrum sunscreen every day throughout the pregnancy. These patients should have patience because melasma may fade or clear spontaneously within months after pregnancy. They should avoid scented cosmetic products for facial cleansing or make-up.

Topical Treatments

Bleaching Agents

There are three categories of bleaching agents: phenolic compounds, nonphenolic compounds and combination formulas (Fig. 61.1). The selection of the appropriate treatment should be based on pretreatment evaluation.

Hydroquinone (HQ)

Hydroquinone is the most commonly used bleaching agent and the gold standard for melasma treatment. HQ is a hydroxyphenolic compound that inhibits the conversion of dopa to melanin by the inhibition of tyrosinase; it also inhibits RNA and DNA synthesis of melanocytes and degrades melanosomes.

The effectiveness of HQ is related directly to the concentration of the preparation, to the vehicle used and to the chemical stability of the final product. Concentrations of HQ vary from 2 % (over the counter) to as high as 10 %. HQ preparations higher than 5 % have proven to be very irritating without improving the efficacy and are not recommended, except for refractory cases. With controlled use and monitoring, the side effects of these preparations are minimal.

The most suitable vehicle for the formulation is a hydroalcoholic solution (equal parts of propylene glycol and absolute ethanol) or a hydrophilic ointment or a gel containing 10 % alpha-hydroxy acids (AHA). HQ is easily oxidized and loses its potency; therefore, antioxi-

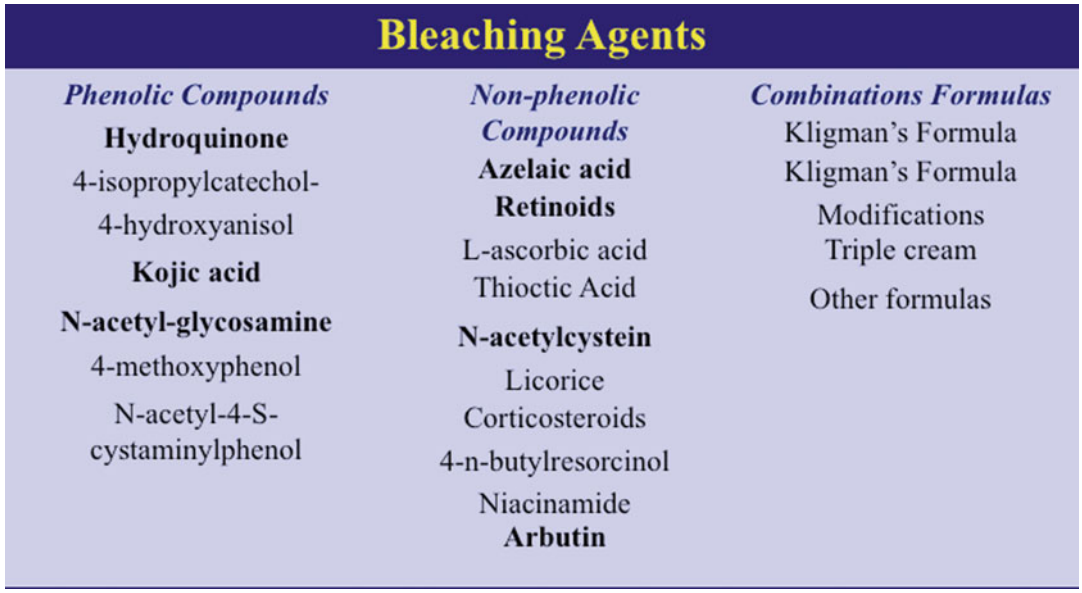

Fig. 61.1 Categories of bleaching agents for melasma

dants such as 0.1 % sodium bisulphate and 0.1 % ascorbic acid should be used to preserve the stability of the formulation. The bleaching effect of HQ may be expected from a few weeks to a few months after application.

Taking into consideration the desired HQ concentration, the vehicle and the chemical stability, the following formula can be prescribed:

- HQ 3 %–5 %
- In ethanol and propylene glycol 1:1 (or in a cream base or an AHA 10 % gel)
- Ascorbic acid 0.1 % (as preservative)

The side effects of HQ mostly include irritation and rarely allergic contact dermatitis, post-inflammatory hyperpigmentation and nail discoloration; these side effects are temporary and are resolved upon the discontinuation of HQ. A very rare complication of HQ use is exogenous ochronosis, especially in darker phototypes. Persistent hypopigmentation after the application of high-concentrated HQ formulas has been termed 'leukoderma en confetti'.

There have been some concerns with the safety of HQ over the last decade. In many countries around the world, the dispensing of over-the-counter hydroquinone formulations containing 2 % HQ has been banned. Indeed, HQ has been banned as a cosmetic skin-bleaching agent in Europe since January 2001 and it is available only in prescription form.

Combination Formulas

It has been demonstrated that the skin-lightening effect of HQ can be enhanced by adding various topical agents such as tretinoin and corticosteroids. Tretinoin accelerates epidermal transfer and cell turnover and facilitates the epidermal penetration of HQ; moreover, it suppresses the steroid atrophy and prevents HQ oxidation. The corticosteroids suppress melanin production and eliminate the irritation caused by HQ and/or tretinoin.

In general, combination therapies have a more effective bleaching effect than monotherapies, and treatment usually begins with one of these formulas applied once daily (at night) and continues with 2 % HQ treatment for maintenance.

Combination formulas are Kligman and Willis formula, Pathak's formula, Westerhof's formula and modifications of Kligman's formula.

The original Kligman and Willis formula utilized 5 % HQ, 0.1 % tretinoin and 0.1 % dexamethasone in ethanol and propylene glycol 1:1 or

in hydrophilic ointment. Depigmentation begins within 3 weeks after twice-daily application and it is used for a maximum of 5–7 weeks. This formulation is not preserved by antioxidants and therefore should never be more than 30 days old.

Pathak's formula contains 2 % HQ and 0.05 %–0.1 % tretinoin, omitting steroids and suggesting that they should be added only if irritation from HQ or tretinoin is observed.

Westerhof's formula consists of 4.7 % N-acetylcysteine, 2 % HQ and 0.1 % triamcinolone acetonide. The mode of action of N-acetylcysteine may be attributed to the intercellular increase of glutathione concentration that stimulates pheomelanin instead of eumelanin synthesis. The formula leads to significant bleaching within 4–8 weeks.

A modified formula proposed by Katsambas and Antoniou contains HQ 4 %, tretinoin 0.05 %, hydrocortisone acetate 1 % in ethanol and propylene glycol 1:1 or in hydrophilic ointment. In this formula the concentration of tretinoin is 0.05 % and hydrocortisone acetate 1 % is used instead of dexamethasone. By lowering the concentration of tretinoin and with the use of a nonfluorinated steroid, the aim is to minimize the irritation caused by tretinoin and eliminate local steroid side effects. The above formulation is applied twice a day until improvement with a maximum duration of 8–10 weeks. This formulation should be dispensed in a 25-mL volume, in a dark-coloured bottle with an airtight screw cap and it should be kept in a refrigerator at 2–4 °C.

Another treatment suggestion is the use of 0.05 % tretinoin, 2 % HQ and 1 % hydrocortisone acetate cream successively through the day.

Another modification of the Kligman and Willis formula is the following triple combination cream:

Hydroquinone	(HQ)	4%
Tretinoin	(TR)	0.05%
Fluocinolone Acetonide	(FA)	0.01%

in a hydrophilic cream base. In a total of 641 patients with facial melasma, Taylor et al. reported that this triple cream was better than the dual combination of HQ with either tretinoin or fluocinolone acetonide. At week 8, complete clearing of melasma was reported in 26.1 % of patients, and 70 % of patients had a 75 % reduction in pigmentation. The most common adverse events included erythema, skin peeling, burning and stinging.

4-Hydroxyanisole (Mequinol)

The combination of 2 % mequinol and 0.01 % tretinoin was shown to be effective in the treatment of melasma in men.

N-Acetyl-4-S-cysteaminylphenol (NAC)

NAC is a phenolic thioether that acts as a substrate for tyrosinase and selectively targets cells with active melanin synthesis; it is much more stable and less irritant than hydroquinone.

Nonphenolic Compounds

Azelaic Acid (AzA)

AzA is a naturally occurring dicarboxylic acid, isolated from *Pityrosporum* cultures and associated with the hypomelanosis seen in tinea versicolor. In vitro, azelaic acid reversibly inhibits tyrosinase activity and may also interfere with DNA synthesis and mitochondrial oxidoreductase. Azelaic acid does not appear to affect normal melanocytes but has an antiproliferative and cytotoxic effect on abnormal melanocytes; it has anti-inflammatory, antibacterial and antioxidant activities. At 10–20 % concentration, twice-daily application may treat melasma with minimal side effects; most patients report a mild but transient irritation and dryness of the skin at the beginning of the treatment. A recent study suggests that 20 % azelaic acid cream applied twice daily may be more effective than hydroquinone 4 % in improving mild melasma, while the combination with topical tretinoin 0.05 % and glycolic acid 15–20 % seems to augment its efficacy.

Kojic Acid

Kojic acid (5-hydroxy-4 pyran 4–1-2 methyl) is a fungal metabolite (*Aspergillus oryzae*) that inhibits the catecholase activity of tyrosinase and is a potent antioxidant. Kojic acid is used in concentration 2 %–4 %, alone or in combination with tretinoin, hydroquinone and/or a corticoste-

roid. Although kojic acid alone is less effective than HQ 2 %, the combination with glycolic acid 10 % and HQ 2 % seems to have a synergistic action.

L-Ascorbic Acid (Vitamin C, AsA)

As an inhibitor of the melanin formation, ascorbic acid is often used to treat melasma in 5–10 % concentrations and can be formulated with other depigmenting agents, such as HQ. Other advantages of vitamin C include antioxidant effects and anti-inflammatory and photoprotective properties. A weakness of AsA is its chemical instability in aqueous solutions; the hydrophilic nature of AsA also limits its skin penetration. Magnesium ascorbyl phosphate, ascorbyl palmitate and sodium ascorbyl phosphate are stable derivatives of ascorbic acid which differ in hydrolipophilic properties. Iontophoresis has been used to increase the penetration of vitamin C into the skin.

Topical Retinoids

Tretinoin accelerates the cell turnover promoting the rapid loss of pigment via epidermopoieses. Used at a concentration of 0.05 %–0.1 %, tretinoin is usually applied once nightly. Although tretinoin can be effective as monotherapy, it requires 20- to 40-week treatment periods. The most common adverse effects include burning, erythema and scaling. Retinoid dermatitis may itself lead to post-inflammatory hyperpigmentation, especially in dark-skinned individuals. Adapalene 0.1 % was also proposed as a safe and efficacious monotherapy in the treatment of epidermal melasma with a lower potential for skin irritation compared to tretinoin.

Miscellaneous Treatments

Multiple novel and experimental agents are being investigated for the treatment of melasma, including plant extracts, such as arbutin, licorice extract, aloesin, flavonoids, saponin, oregonin, soy, green tea, orchid extracts, coumaric acid, ellagic acid and liquirtin. At present there are no adequate controlled studies investigating the efficacy and safety of these compounds.

Chemical Peels

Superficial chemical peels can be used for the treatment of melasma in fair-skinned individuals. Alpha-hydroxy acids (AHAs) glycolic acid 50%–70 & peels (every 2–3 weeks) for 4–6 sessions, light Jessner's peels (every 2–3 weeks) for 4–6 sessions and trichloroacetic acid (TCA) 25 %–35 % once, have been used alone or in combination with other depigmenting agents. Glycolic acid peels may be a useful adjunct to topical treatment, especially after a patient's pretreatment with hydroquinone for 2 weeks to minimize the risk for post-procedure hyperpigmentation. However, it has to be emphasized that the response of melasma to chemical peels is rather unpredictable; there is a tendency for pigmentation changes after chemical peel, especially in darker-skinned individuals. After the peel, a maintenance therapy with HQ 2% is recommended.

Device-Based Therapies

Based on actual evidence, the use of this technology should be restricted to patients with recalcitrant disease. Post-inflammatory hyperpigmentation (PIH) remains the most important side effect, particularly in darker-skinned patients. Pretreatment and post-treatment maintenance with the use of bleaching creams is necessary.

Lasers

Various laser and light systems have been tried in the treatment of melasma, with variable results. Multiple treatments are required and recurrences are common. Melanin is the main chromophore, and melanosomes are the primary target of the laser-induced damage.

Sheth et al. reported that Q-switched ruby lasers and erbium-YAG lasers have been shown to worsen melasma. Also, the combination of CO_2 laser with Q-switched alexandrite laser is not beneficial for melasma and may induce PIH in darker-skinned persons. Fractional laser is the only laser treatment approved by the FDA for melasma with promising results. It has been proposed to use lower fluences and variable pulses and pretreatments with HQ for up to 6 weeks before laser therapy, in order to avoid the risk for hyperpigmentation especially in patients with a history of PIH.

The use of pulsed dye laser and the newer anti-angiogenic lasers (copper bromide laser) for the treatment of melasma is based on evidence showing an increased vascularization in melasma lesions as compared with the surrounding unaffected skin. A study by Passeron et al. comparing the use of Kligman's formula alone or combined with PDL (flat handpiece of 7 mm; pulse duration, 20 ms; fluency, 10 J/cm^2, dynamic cooling device, 30/40) showed significantly better results and fewer relapses with the combination approach.

Intense Pulsed Light

Intense pulsed light (IPL) is a nonlaser light source that emits light with wavelengths between 515 and 1,200 nm. From various experiences, it seems that epidermal melasma treated with intense pulsed light can reach a clearance of 70–100 % from baseline; but the risk of PIH still remains high. However, individuals with dermal and mixed melasma showed only a fair or poor clearance. It is a good approach to use low fluences and a long delay between pulses.

Conclusions

A recently published systematic review of interventions used for the management of melasma, by Jutley et al., identified only 20 eligible randomized controlled trials. All interventions, except tretinoin, were evaluated only in one study each. It was reported that there is no standard therapy for melasma. Topical HQ (3 %–4 %) was the most common topical monotherapy used. The triple-combination cream was more effective than any of the ingredients used in a dual-combination cream in one study. No studies provided long-term data or quality of life results. The authors mentioned that the evidence is insufficient to provide guidance for the clinical practice of treating melasma, due to the poor methodology of the trials, the lack of standardized outcome measures and the short duration of studies.

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Mite Bites and Tick Dermatoses

62

Giorgio Leigheb

Mite Bites

Key Points

- Mites are arthropods belonging to the class Arachnida and to the subclass Acari. They have very small size (less than 1 mm. or little more than 1 mm.), four pairs of legs and are represented by numerous genera and species and have parasitic behaviour.
- Some mites such as *Sarcoptes* and *Cheyletiella* or *Neotrombicula* and *Dermanyssus* parasite specific animals (mammals, birds, insects) biting them with their mouth apparatus for feeding. Man is an occasional host; his only real ectoparasite is *Sarcoptes scabiei hominis*.
- Mite bites on human skin cause peculiar and frequently misdiagnosed entomodermatoses.
- Prevention consists in avoiding the contact with infested animals and in their treatment with acaricides, in the case of a contagion caused by domestic animals. Environmental mites (mainly parasites of insects) such as *Pyemotes* and *Ornithonyssus* are sensible to repellents such as DEET and pyrethroids used for prevention of their bites.
- Human infestation is treated with soapy baths or showers and topical application of permethrin, especially in case of trombidiasis. Itchy lesions are treated with corticosteroid creams.

Definition and Epidemiology

Besides the mite of human scabies (*Sarcoptes scabiei hominis*) (0.3–0.5 mm), many other acari which are parasitic on animals or which infest various vegetables, foods, organic waste or soil may occasionally attack man (facultative parasitism versus obligatory parasitism in the case of scabies). The bites of the mites considered in this chapter are the accidental cause of entomodermatitis. These represent very frequent events, especially in certain geographical areas or in peculiar habitat, but they often are not diagnosed. In some instances they can be considered professional diseases.

Basic Concepts of Pathogenesis

The most common acariasis is the various types of animal scabies or pseudoscabies. Frequent human infestations are caused by dog scabies

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_62, © Springer-Verlag Berlin Heidelberg 2015

(due to *Sarcoptes scabiei canis*), cat scabies (due to *Notoedres cati*), rabbit scabies and other domestic or pet animal scabies.

Cheyletiella (0.3–0.5 mm), a parasite of dogs (*C. yasguri*), cats (*C. blakei*) and rabbits (*C. parasitivorax*), can also infest man, causing multiple small papular lesions with serious itch. Often the dermatitis occurs after the introduction of a new animal from a kennel or a breeding house.

Avian gamasid mites that infest domestic poultry or birds wild or nesting in or near human habitation may parasite man, as *Dermanyssus gallinae* and *Ornithonyssus sylviarum*.

Acari present in the environment include so-called harvest mites such as "chiggers" (trombiculid mites). *Neotrombicula autumnalis* (1–2 mm), one of the most common in Europe, lives on vegetables feeding on small arthropods. The larvae (0.2–0.3 mm) (called red bugs or chiggers) can attack, also in great strength, vertebrate animals or man. The very itchy multiple lesions are papular with a central small hole where the parasite sucking lymph from the epidermis is present. The affection, more frequent in autumn, is known as trombidiasis or mange of the woods. Frequently affected are countrymen, gardeners, forest guards, hunters, excursionists and even children playing on fields or in gardens.

Mites of the genera *Tyroglyphus* and *Glycyphagus* (0.4–0.5 mm) cause lesions in warehouse personnel, stockmen and grocers. *Pyemotes ventricosus* (0.16–0.22 mm), an ectoparasite of the larvae of the coleopteran of the wood (infesting old furniture or timbers), is also a frequent occasional parasite of man. *Pyemotes tritici* (straw itch mite) is an ectoparasite of larval stage of lepidoptera and of coleopteran feeding on the alimentary agricultural products such as cereals; it lives in haycocks, straw and dead leaves. Environmental mites often infest man in great numbers not only on uncovered skin but also migrating under the clothes. Skin lesions are very erythematous, oedematous and itchy and last a long time. Infestation is frequent in the countryside after sitting on the ground or walking among the bushes. Itch may arise some hours after contagion.

Clinical Presentation

Animal pseudoscabies (animal scabies) in man is characterised by multiple, small, erythematous-pomphoid or erythematous-papular lesions, sometimes with a central small vesicle or pustule. The lesions cause severe itching. They are present on exposed parts of the skin or on the edge of tight-fitting garments. Contagion may be direct or indirect: clothing and seats, for example. The symptoms appear rapidly after contact with the mites. The infection heals promptly once contact with the affected animals is interrupted or when these are suitably treated but reappear every time the patient again comes into contact with the affected animals. The bites of gamasid mites of the genera *Ornithonyssus* (*O. sylviarum* is 0.45–0.50 mm) and *Dermanyssus gallinae*, parasites of poultry, birds and mice, cause intense itching and numerous, often haemorrhagic, papules in man.

Diagnosis

The history is important: contact with domestic or wild animals, profession, contact with vegetables and other affected persons in the same family. The absence of cuniculi in pseudoscabies is an essential feature in differential diagnosis with scabies. The lesions are rather characteristic and very itchy. It is usually hard to demonstrate the responsible mites in the cutaneous lesions except in trombidiasis as the small larva (0.2 mm) of *Trombicula* attached in the middle of the lesions is visible with a lens. The parasite remains on the host, feeding for 2–3 days. Itching starts some hours after the bite but papules appear 12–24 h later.

Infestation by *Tyroglyphus* and *Pyemotes* and by other environmental mites is associated with multiple or very numerous lesions, preceded by intense itching.

Differential Diagnosis

- Human scabies
- Urticaria
- Papular urticaria
- Prurigo
- Other arthropod bites (mosquitoes, Hymenoptera, bed bugs)
- Entomodermatosis caused by poisonous hairs of the caterpillars of some species of Lepidoptera
- Irritating exogenous factors (phytodermatitis, chemical compounds, irritating constituents of clothing, glass– wool)
- Drug-induced eruptions

General Principles of Treatment

It is not strictly necessary to treat animal scabies in man, in case of correct diagnosis, because the dermatitis heals spontaneously when contact with the affected animal ceases. In fact animal *Sarcoptes* do not like human skin after a bite and they do not reproduce on man. It is necessary to treat infested animals with insecticides.

Human lesions improve quickly with corticosteroid creams in a few days. ORAL antistamines can be used to relieve itching.

In case of environmental mite bites, hot soapy baths or showers will help remove attached and nonattached mites. For extensive or persistent infestation, the same antiparasitic remedies used for scabies can be applied (benzyl benzoate, pyrethroids).

For prevention, repellents such as dimethyl phthalate, diethyltoluamide (DEET) and permethrin are very active and are used also to impregnate clothing.

Recommended Therapies

In more severe cases of multiple mite bites, however, the use of acaricides is helpful. Many of them are the same products employed for scabies.

Polysulphide creams and pastes containing 2.5–10 % of sulphur and benzyl benzoate 10 % in galenical preparations, applied in adults and boys for 12–24 h, are now replaced by modern remedies but still used in poor sanitary conditions.

Pyrethroids are the more active pesticides and in particular permethrin, against mites and ticks.

Permethrin, a synthetic pyrethroid, is a pesticide and a repellent with a very low mammalian toxicity. It is non-staining, nearly odourless and resistant to degradation even after water immersion and maintains its activity for more than 2 weeks when applied on garments. Permethrin is available in emulsion, creams and sprays and is particularly active in 5–10 % concentrations for the skin which has to be washed 8–10 h later. For adults, do not apply more than 30 g of permethrin cream and for children (2 months–1 year old), no more than 3.75 g with medical control. Do not use in children under 2 months.

An active molecule, cyfluthrin (gel 0.1 %) is a good repellent.

The best repellents for prevention are DEET (N1N-diethyl-3m-toluamide), 10–30 % in lotions, sprays and creams used also for protection against mosquito bites, and permethrin. Both substances can be applied to the skin and clothing. Avoid application on eyelids, mouth and sensible skin.

Soapy baths are useful also in infestation by gamasid acari. Oral antihistamines will mitigate itching. Antibiotics are given in the case of superimposed bacterial infections. Topical or systemic corticoids are useful in the case of intense itching or infiltrated and refractory lesions.

Tick Dermatoses

Definition and Epidemiology

Ticks are very widespread cosmopolitan arachnid arthropods, haematophagous parasites to wild and domestic mammals, birds and reptiles. There are about 650 species of hard ticks (family Ixodidae) and about 150 species of soft ticks (family Argasidae). Besides their usual hosts, which represent the real reservoir of these parasites, they can adapt themselves to alternative hosts, including man. Ticks cause erythematous

and nodular cutaneous lesions (granulomas and necrosis) at the site of the bite and often provoke local or generalised allergic reactions especially in previously sensitised persons. They are also carriers of many bacterial and viral infections (borreliosis, rickettsiosis, tularaemia, viral neurologic infections), some of which have not yet been studied fully (e.g., arboviruses). The most common dermatoses due to tick bites are described briefly below. The most common species of hard ticks in Europe are *Ixodes ricinus* (sheep tick) and *Rhipicephalus sanguineus* (dog tick).

Clinical Presentation

Tick granuloma result from an erythematous-oedematous nodular lesion which appears after some days at the site of the bite. At first the lesion causes very little itching, so that the patient often remains unaware of the presence of the parasite, which can remain attached to the skin for several days sucking blood and enlarging its abdomen. Subsequently, the tick may drop off spontaneously having gorged on blood, or the hypostome (mouth apparatus) may remain fixed into the skin after vain attempts to detach the parasite. In the latter case, a foreign body granuloma develops. Thereafter, a delayed sensitisation reaction may develop. Itching is considerable and the lesion may persist for many months. In the case of further bites, common in farmers, gardeners, shepherds, sportsmen and hikes, for example, the local and systemic symptoms (eczematous patches or diffuse papulonodular lesions simulating the initial granuloma) become more serious and chronicise. Diagnosis often is misdiagnosed.

Diagnosis and Differential Diagnosis

The diagnosis is easily made when the tick is seen and bedded in the skin. After the parasite has dropped off, the presence of a small hole in the centre of the granuloma is pathognomonic. The delayed onset of itching and the history (presence of animals, presence in gardens or in the countryside) can also suggest the diagnosis. The differential diagnosis involves granulomas due to insect or mite stings and foreign body granulomas.

General Principles of Treatment

Besides adopting suitable preventive measures such as the use of boots and repellents (DEET, dimethyl phthalate, pyrethrum, permethrin), the disinfestation of affected animals and of the infested areas and to correctly remove the parasites embedded in the skin are important.

Recommended Therapies

The most effective method is to apply a cotton wool pad soaked with ether or petrol over the tick for 15 min. This causes paralysis of the parasite's muscles and hits subsequent spontaneous detachment. To avoid possible regurgitation of infective bacteria, many authors suggest an immediate removal of the tick with forceps. Alternatively, oil or liquid paraffin can be applied so as to suffocate the tick. The granulomas are treated with antibiotic and corticoid creams or with galenic preparations containing 5–10 % coal tar. Systemic corticosteroids are useful in the presence of disseminated secondary nodular or eczematous lesions due to sensitisation to the tick. ORAL antistamine are used as symptomatic measures to alleviate the pruritus.

In the case of lesions due to *Argas reflexus* (pigeon tick), which are becoming increasingly common on account of the presence of these birds in urban areas, suitable preventive measures consisting in the elimination of the pigeons and in the disinfestations of the windows, balconies, mouldings and roof gutters with chlorhexidine and pyrethrum preparations are essential. The cutaneous lesions are treated with antibiotic-corticoid creams. There remains the problem of the possible systemic complications that may arise in sensitised patients who, after being bitten, may develop serious, even fatal, anaphylactic reactions. Such cases require emergency medical treatments consisting of the administration of epinephrine, intravenous corticoids and antihistamines.

Many insecticidal formulations can be applied to domestic pets to rid them of their ticks: 0.5–5 % malathion, 1 % carbaryl, 0.1 % dioxathion, 1 % coumaphos, trichlorphon dusts applied to the coats of pets. The tick repellent collar for dogs is very active. Floors of doghouses, porches and balconies where infected animals sleep should be sprayed with oil solutions or emulsions of 1 % propoxur, 0.5 % diazinon and 2 % malathion.

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Molluscum Contagiosum

63

Mirjana V. Milinkovic and Ljiljana M. Medenica

Key Points

- Molluscum contagiosum (MC) is a benign, self-limited viral disease of the skin and rarely mucous membranes caused by molluscum contagiosum virus (MCV), a double-stranded DNA poxvirus. The disease mainly affects children, sexually active adults, and immunocompromised individuals.
- The typical lesion is a shiny, pearly white, hemispherical papule with central umbilication and an average diameter of 3–5 mm. Giant lesions may be as large as 3 cm in diameter.
- In immunocompetent patients MC is a benign disorder that resolves spontaneously within 6–18 months, although it may persist for as long as 5 years. Disseminated lesions, as seen in immunocompromised patients, are persistent and recurrent, and they may be a marker of advanced disease.
- Diagnosis of MC is usually made relatively easy on the basis of clinical presentation. Rapid freezing with ethyl chloride or liquid nitrogen may accentuate their distinctive umbilication.
- Therapy of MC should be undertaken in an individualized manner; a specific treatment does not exist.
- Treatment method should be chosen after consideration of the age and immunocompetence of the patient, the extent of the disease, and the areas involved.
- Treatment has focused on removing the cutaneous lesions either by surgery or by producing epidermal injury and subsequent desquamation of the molluscum and surrounding uninvolved skin.
- Curettage is a relatively painless and easy-to-perform procedure. It is suggested to be performed if the lesions are young and small in number. A sharp curette is used to scrape the lesion. In children, pretreatment with topical anesthetic is applied.
- Cryosurgery can be completed with specially designed liquid nitrogen spray units or with cotton-tipped swabs (dipstick technique). It is less painful and it is not necessary to use local anesthetics.
- Application of cantharidin is very effective in children. It has the advantage of being a painless office procedure.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_63, © Springer-Verlag Berlin Heidelberg 2015

- Podophyllotoxin cream as a 0.5 % preparation is a safe, home-based first-line therapy for curing MC.
- Imiquimod cream 5 %, a topical immune response modifier, is suitable and safe for both children and adults.

Definition and Epidemiology

Molluscum contagiosum (MC) is generally a benign, self-limited viral infection of the skin and rarely mucous membranes caused by molluscum contagiosum virus. The disease mainly affects children, sexually active adults, and immunocompromised individuals.

MC is primarily a disorder of children, with peak incidence at 3–10 years of age and 10–12 years for school children. In the sexually active population, peak correlates with sexual contact; the greatest number of cases occurred among patients 20–29 years old. Published data estimate the incidence of MC to be between 1.2 and 22 % of the population worldwide. The prevalence of MC among HIV-infected individuals ranges from 5 to 18 %.

MCV is spread mainly by direct skin-to-skin contact; however, several routes of transmission are recognized for MCV. Viral transmission in children occurs by close contact with an infected individual or with fomites or by autoinoculation. The possibility of sexual abuse should be considered when MC is seen on the genital, perianal, and surrounding skin of children, even though the vast majority acquires infection by casual contacts. Infectivity is enhanced in warm, humid crowded environments. Use of swimming pools also correlates with childhood infection. In adults, MCV is most often sexually transmitted. It has also been reported in isolated cases among wrestlers, masseurs, and surgeons.

The incubation period is in the range of 7 days to 6 months.

Molluscum contagiosum is associated with several diseases with impaired cell-mediated immunity including atopic dermatitis, epidermodysplasia verruciformis, and HIV infection. Unusually disseminated molluscum contagiosum has been reported in patients with sarcoidosis and chronic lymphocytic leukemia and patients on immunosuppressive therapy and with HIV disease, suggesting that cell-mediated immunity is significant in the control and elimination of the infection.

Basic Concept of Pathogenesis

Molluscum contagiosum virus (MCV) is a member of the family *Poxviridae* (genus *Molluscipoxvirus*). MCV is a double-stranded DNA poxvirus which cannot be grown in tissue culture cells or in an animal model. It is the largest true human virus infecting only human beings. It replicates in the cytoplasm of infected cells and induces hyperplasia.

Three different MCV types have been identified in humans: MCV-I to MCV-III. MCV-I is more prevalent than others, accounting for up to 90 % of lesions. In patients infected by human immunodeficiency virus, majority of infections are caused by MCV-II. Lesions produced by either of the subtypes are indistinguishable.

The pathogenesis of the lesions is uncertain, but an epidermal growth-like polypeptide has been postulated to have a role in pathogenesis. In the basal layer of lesional skin, the rate of cell division is twice that of normal skin. The number of receptors for epidermal growth factor (EGF) increases in infected cells, which is indirect evidence that MCV synthesizes an EGF-like growth factor. The infected keratinocytes move more quickly than uninfected ones through the epidermis. Free virus cores have been found in all layers of the epidermis.

Although the role of humoral immunity in this disorder is not clear, dependent on the presence of viral antigen in infected cells, virus-specific antibodies can be detected in 80 % of patients with MCV. Most patients infected with MCV produce antibodies predominantly of the IgG class. Anticellular IgM antibodies and fibrillar anticellular IgM antibodies can be found in over 60 % of infected patients. Cell-mediated immunity is probably more important in the pathogenesis of the disease. Reinfections are common.

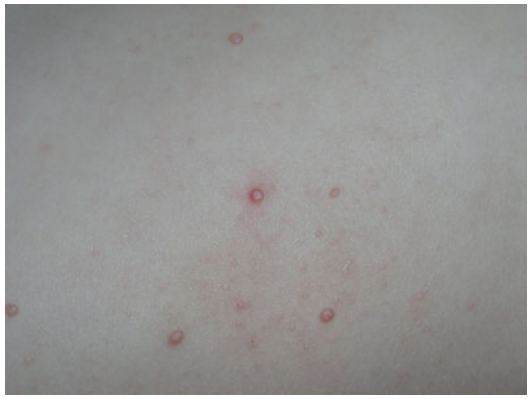

Fig. 63.1 Molluscum contagiosum – with white, hemispherical papule with central umbilication

Clinical Presentation

The typical lesion is a shiny, pearly white, hemispherical papule with central umbilication and an average diameter of 3–5 mm (Fig. 63.1). Rarely giant molluscus may be as large as 1.5–3 cm in diameter. The lesions may be flesh-colored, white, translucent, or light yellow in color. The number of lesions is usually less than 20, although a single lesion or several hundreds can be seen. There may be a surrounding eczematous reaction (so-called molluscum dermatitis). Patients with MC are usually asymptomatic, but few may complain of pruritus or tenderness.

Lesions may be located anywhere; in children, lesions are distributed on the face, trunk, and extremities, although the anogenital region may be also involved. In healthy sexually active adults, lesions are usually located on the groin, genital region, and on the lower abdomen and inner thighs. The disease rarely can affect the oral mucosa, conjunctiva, and cornea.

Molluscum contagiosum is a common viral disorder associated with HIV infection; its clinical features are often atypical, and its course is usually progressive and recalcitrant to treatment. The lesions most often involve the face, neck, and trunk.

In immunocompetent patients MC is a benign disorder that resolves spontaneously within 6–18 months, although it may persist for as long as 5 years. Temporary remission of up to 2 months has occurred. Disseminated lesions, as seen in immunocompromised patients, are persistent and recurrent, and they may be a marker of advanced disease.

Diagnosis

Diagnosis of MC is usually made relatively easily on the basis of clinical presentation. Rapid freezing with ethyl chloride or liquid nitrogen may accentuate their distinctive umbilication. Direct light microscopical examination of an unstained expressed core, skin biopsy, or ultrastructural studies of the lesional skin establish the diagnosis. Histopathological examination reveals a hyperplastic, cup-shaped invagination of the epidermis composed of multiple lobules. Characteristic intracytoplasmic inclusion bodies, molluscum bodies, are formed.

Differential Diagnosis

The differential diagnosis includes: basal cell carcinoma, histiocytoma, trichoepithelioma, keratoacanthoma, intradermal nevus, syringoma, hidrocystoma, sebaceous adenoma, warts, varicella, pyoderma, papillomas, lichen planus, Darier's disease, and dermatitis herpetiformis.

In HIV-infected patients, molluscum contagiosum must be differentiated from basal cell carcinoma, keratoacanthoma, and cutaneous horn. Conversely, in AIDS patients, cryptococcosis and histoplasmosis may mimic molluscum contagiosum; for these reasons, biopsy of atypical-appearing cutaneous lesions is often warranted.

General Principles of Treatment

There is no specific treatment for MC.

- The main question, as with warts, is whether to treat or not. In many cases lesions resolve spontaneously within 6–18 months without scarring. The decision is crucial and must take

into account that MC is a benign, self-limited condition and that treatment is far from being perfect. On the other hand, the lesions are a source of great embarrassment for both carers and children, often affecting attendance at school and limiting social activity.

- Therapy of MC should be undertaken in an individualized manner; a specific treatment does not exist. A vaccine is not available.
- Care should be taken not to traumatize patients unnecessarily with painful treatments, particularly children, who are the largest patient group. Benign neglect may be the most appropriate approach in immunocompetent children with the infection.
- Although MC may be self-limited and asymptomatic in healthy individuals, therapy is warranted to prevent autoinoculation or transmission of the virus to close contact, to relieve symptoms (if any), and, most often, for cosmetic and social reasons.
- Treatment method should be chosen after consideration of the age and immunocompetence of the patient, the extent of the disease, and the areas involved. The individual patient preference, fear, and financial status, as well as the distance from the office, should be also taken into consideration.
- Patients should be advised to avoid swimming pools, communal baths, contact sports, and shared towels, for example, until clear.
- Therapies for MC may be destructive, immune enhancing, or antiviral in nature. In general, treatment has focused on removing the cutaneous lesions either by surgery or by producing epidermal injury and subsequent desquamation of the molluscum and surrounding uninvolved skin.
- Sexual partners should be examined and treated, to prevent reinoculation.

Recommended Therapies (Fig. 63.2)

(a) Mechanical methods—curettage
(b) Cryotherapy—cryosurgery with liquid nitrogen
(c) Electrodesiccation
(d) Chemical agents

Mechanical Methods: Curettage

Curettage is a relatively painless and easy-to-perform procedure. It is one of the most commonly used office-based therapies for MC and is suggested to be performed if the lesions are young and small in number. A sharp curette is used to scrape the lesion. In children, pretreatment with topical anesthetic, such as the eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA® cream), may be necessary. One hour before the treatment, a maximum of 10 g of EMLA® cream should be applied to the mollusca. One gram of the cream is sufficient to cover a skin area of approximately 2.5 × 2.5 cm. The cream is covered with an occlusive dressing (Tegaderm®) and after 60 min it is wiped off. The curettage usually commences within 5 min after the cream has been wiped off. Local reactions to the cream could be redness, pallor, and edema. Curettage is found to be more efficient and had a lower rate of side effects then other therapeutic options. However, it may be associated with scaring and is not well tolerated by children if performed repeatedly, owing to pain and fear. It is also a time-consuming procedure.

Other simple mechanical methods like expression of the contents of the papule by squeezing it with forceps held parallel to the skin surface, superficial curettage, or shaving off the lesions with a sharpened wooden spatula may each suffice, although it is usual to add an application of a caustic agents, such as silver nitrate stick, phenol, podophyllin, or strong iodine solution.

Cryotherapy

Cryosurgery can be completed with specially designed liquid nitrogen spray units or with cotton-tipped swabs (dipstick technique). It is less painful and it is not necessary to use local anesthetics. The lesion and a narrow border of normal surrounding skin should turn white before application is stopped. This usually takes 6–10 s. Destruction of the molluscum body (white, smooth, walled core) will result in resolution of an individual lesion. The treatment should be repeated at weekly intervals if lesions persist. Cryotherapy, though effective at controlling the

Immunocompetent patients

Children
-curettage*
-cryotherapy*
-cantharidin
-sliver nitrate 40 %
-imiquimod 5 %
-propridine iodine 10 %
-pulsed dye laser
-KOH 5 %

Adults
-curettage
-cryotherapy
-electrodessication
-cantharidin
-TCA 25–50 %
-tretinoin 0.05–0.1 %
-podophyllotoxin 0.5 %
-sliver nitrate 40 %
-imiquimod 5 %
-pulsed dye laser

AIDS patients
-cidofovir 3 %
-imiquimod 5 %
-pulsed dye laser
-electron-beam
-picibanil
-interferon-α

*pre-treatment with topical anesthetic

Localized lesions
-curettage
-cryotherapy
-electrodessication
-cantharidin
-TCA 25–50 %
-tretinoin 0.05–0.1 %
-propridine iodine 10 %
-podophyllotoxin 0.5 %
-imiquimod 5 %
-KOH 5 %
-electron-beam

Widespread lesions
-cimetidine
-cidofovir 3 %
-pulsed dye laser
-silver nitrate 40 %

Office-based therapy
-curettage
-cryotherapy
-electrodessication
-cantharidin
-TCA 25–50 %
-sliver nitrate 40 %
-propidine iodine 10 %
-pulsed dye laser
-electron-beam
-interferon-α

Home-based therapy
-podophyllotoxin 0.5 %
-imiquimod 5 %
-tretinoin 0.05–0.1 %
-KOH 5 %
-cidofovir 3 %
-cimetidine

Fig. 63.2 Molluscum contagiosum – therapeutic algorithm

problem, practical, cost-effective, and has good cosmetic results, is also uncomfortable and often requires many weekly treatment sessions.

Electrodesiccation

Electrosurgical destruction of MC by electrodesiccation, as a physician-administrated treatment, can be done with little, if any, scarring. Small lesions may be treated without anesthetic. Subepidermal local anesthesia is required for big ones. The lesions should be prepared with a non-alcohol-containing skin cleanser. The electrode is brought into contact with the mollusca. Only a low spark should be generated in order to minimize excessive tissue destruction and to avoid scarring. The lesion usually changes in color and consistency as it is destroyed. It can be easily removed with a curette or simply by rubbing the site with gauze. Punctate bleeding can be controlled with pressure, spot electrocoagulation, or topical hemostatic agents such as aluminum chloride. Unfortunately, even with application of a local anesthetic, these ablative procedures may be associated with pain, irritation, soreness, and mild scarring.

Chemical Agents

(i) Cantharidin solution
(ii) Trichloroacetic acid
(iii) Topical vitamin A acid
(iv) Silver nitrate paste
(v) Propridine iodine solution and salicylic acid plaster
(vi) Podophyllotoxin cream
(vii) Imiquimod cream

Cantharidin

Cantharidin is derived from a beetle (*Cantharis vesicatoria*) that causes blistering of the skin if handled. Applied as a 0.7 % cantharone in a flexible collodion-type vehicle, cantharidin is a phosphodiesterase inhibitor that causes vesiculation of the skin. Skillfully employed by a physician, as a gentle local destruction of MC, it is safe and effective and may be a treatment of choice in young children. It should be used by precise application of a small amount to each lesion using a pointed stick (a toothpick) with treatment of a maximum of 20 lesions per visit. The patient should be immobilized for 3–5 min until the medication has completely dried to restrict the blistering agent to the lesions. Occlusion should only be used on lesions not responding to uncovered applications. When occlusive tape is used, it is mandatory to insure complete drying before applying the tape. Patients are instructed to rinse the treated areas with water after 2–6 h, with little discomfort afterwards. Usually between two and four such treatments, with a 7-day interval, are required to eradicate molluscum lesions.

Application of cantharidin is very effective in children. It has the advantage of being a painless office procedure. However, it may cause significant local irritation with blister formation several hours later, depending on the quantity applied, the duration of application, and the individual patient's sensitivity. Testing it on a few lesions at the initial office visit before treating all lesions is recommended. Residual erythema and depigmentation can occur temporarily, but scarring is absent. Cantharidin is not recommended for treatment of facial lesions or those in the diaper area.

Trichloroacetic Acid (TCA)

Trichloroacetic acid is a safe and effective agent that erodes the skin and generally is not absorbed systemically. Application of 25–50 % TCA with cotton-tipped swab often causes sufficient destruction to cure these lesions. The solution should be applied to individual papular lesions for a few seconds until they turn white. This causes a burning sensation that lasts a few minutes. The white treated papules will slowly form crusts and heal within 10 days. In order to reduce the significant irritation or pigment alterations, the pointed edge of broken cotton-tipped applicator can be used to repeatedly apply the TCA until a white frost appears. Care is taken to apply the solution only to the center of individual lesions while avoiding the surrounding healthy skin.

A TCA peel 25–50 % is a useful adjuvant therapy in the treatment of extensive MC in immunocompromised patients. MC lesions are typically recalcitrant to therapy in HIV-infected persons. First of all, a test site measuring

2.5 × 2.5 cm and including the greatest density of lesions on the face should be chosen to determine the most effective concentration of TCA. Serial peeling of the same test site is performed at 2–3-week intervals to determine the lowest effective concentration of TCA (25, 30, 35, 40, or 50 %). After that, full or partial peels should be performed every 2–3 weeks. The concentration of TCA is usually 25–35 %. There is no superinfection, delayed healing, or scarring.

Retinoic Acid (Tretinoin)

Successful therapy with self-administrated topical vitamin A acid has been described in patients with genital lesions. Twice daily application of 0.1 % or 0.05 % tretinoin cream or nightly in the highest tolerated concentration is proposed. The mechanism of action of vitamin A may relate to its ability to produce marked inflammatory reaction of the skin. Local irritation is common. It is not recommended to be used in children.

Silver Nitrate Paste

Widespread, small MC lesions, as often seen in atopic children, can be successfully treated with 40 % silver nitrate paste. It is as effective as the aqueous solution but does not run onto normal skin causing irritation. With the blunt toothpick, a small amount of the paste is dabbed on the center of each lesion and gradually spreads to the entire lesion. Within 1 day, black crusts form. After 2 weeks MCs drop off the skin. Lesions heal without leaving scars. It has a high cure rate, it is painless in most cases, and it is cost effective.

Propridine Iodine Solution and Salicylic Acid Plaster

Ten percent propridine iodine solution and 50 % salicylic acid plaster are recommended (a) for children and patients with multiple lesions as it is not painful, (b) for diabetic patients as the infection is less frequent, and (c) for use in the dermatology office without equipment for liquid nitrogen therapy, so it is less expensive for the patient.

The combined treatment is much more successful and shorter in duration than 10 % iodine solution or 50 % salicylic acid plaster alone. The procedure is performed once daily. The 10 % iodine solution is applied and left to dry. The 50 % salicylic acid plaster is cut into small pieces and patched onto the lesions, covering the area with micropore sticking tape. When the lesion becomes reddened, usually in 3–7 days, it is sufficient to apply only iodine solution until the lesion becomes flat. If necessary, the whole procedure can be repeated. The inflammatory sign (erythema) appears after 3–7 days. However, the more marked the erythema after the application, the more quickly the lesions disappear.

Podophyllotoxin Cream

Podophyllotoxin cream as a 0.5 % preparation is a safe, home-based first-line therapy for curing MC. It is easily self-administrated twice daily for 3 consecutive days. If total elimination is not achieved with one trail (six topical applications), the same treatment can be extended to 3 more weeks (24 topical applications), when 95 % of lesions are cured. Tolerable moderate to mild frequent side effects are erythema, burning, and pruritus.

Imiquimod Cream

Imiquimod, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, is a topical immune response modifier that produces a localized immune response at the site of application and stimulates the monocyte/macrophage and dendritic cells to produce interferon alfa (IFN-α), tumor necrosis factor (TNF), and several interleukins. Patients are instructed to apply imiquimod 5 % cream on each lesion with a cotton-tipped applicator before bedtime, 3–5 days per week, for up to 16 weeks, and to wash the areas in the morning. Adverse reactions, erythema, erosions, and post-inflammatory hyperpigmentation, are limited to application sites and are tolerable. Imiquimod cream is suitable and safe for both children and adults. It appeared to be the most efficacious in patients with HIV-1 disease and in the genital area in immunocompetent adults. Lesions on the face could be treated with imiquimod.

Combination topical treatment of MC with cantharidin, followed by imiquimod 5 % to new or

persistent lesions in children, has been suggested. Using a destructive therapy such as cantharidin to begin with will clear most of the lesions, making the immunomodulatory effect of the imiquimod achievable without significant cost.

Alternative and Experimental Treatments

Topical Agents

Potassium Hydroxide Solution (KOH)

Five percent KOH aqueous solution may be an effective and inexpensive alternative for the management of MC in children. It is based on its property of dissolving epithelial compounds. Parents are instructed to apply a small amount of the solution twice daily, with cotton swab to all lesions for 6 weeks. The stinging sensation is absent or minimal. Even perivaginal and perianal lesions can be treated the same way. A 5 % KOH solution proved to be as effective and less irritating when compared to the 10 % KOH solution.

Cidofovir

Cidofovir is a potent nucleoside analog of deoxycytidine monophosphate that has antiviral activity against a broad range of DNA viruses, when applied topically or administrated by intralesional injection. No significant systemic side effects have been noted, although application site reactions are common and can occasionally be severe. Successful use of topical 1–3 % cidofovir in a combination vehicle, once a day, 5 days a week, for 2–8 weeks, is an effective and well-tolerated therapeutic alternative option for treatment of recalcitrant MC in children and adults with AIDS and other immunocompromised patients.

Nitric Oxide (NO)

Nitric oxide has been shown to have antiviral affects in DNA, RNA, enveloped, and encapsidated viruses. Topical acidified nitrite cream is an NO liberating cream. It is shown to be an effective treatment for MC. Five percent sodium nitrite co-applied with 5 % salicylic acid, once a day for 3 months, is recommended. The treatment is time-consuming and can provoke local irritation.

Systemic Agents

Griseofulvin

This can be used orally for 4–6 weeks, at dosages of 500 mg daily to patients over 14 years of age and 250 mg to younger ones. No recurrence was seen in the 6–8-month follow-up period.

Cimetidine

Cimetidine, a histamine (H2) receptor antagonist with potent immunomodulatory effects, appears to offer a safe alternative form of therapy for multiple, widespread lesions of MC, particularly in atopic patients. It is started at a dosage of 40 mg/kg/day orally in three to four divided doses. A 2- to 3-month course may be safe and cost-effective.

Intralesional Agents

Topical Injection of Picibanil (OK-432)

OK-432 (penicillin-treated and heat-treated lyophilized powder by a substrain of *Streptococcus pyogenes* A3) was expected to be effective for immunosuppression. The skin lesions disappeared almost completely within 3 months.

Intralesional Interferon-α

That has been used to treat recalcitrant MC. Each lesion was injected with one megaunit of IFN-α weekly for 4 weeks. Molluscum less than 0.5 cm in diameter and those in patients without AIDS are more likely to respond.

Other Agents

Pulsed Dye Laser

Pulsed dye laser treatment may offer another therapeutic modality that is effective, quick, and safe in the treatment of widespread and recurrent MC. The lesions are treated by double-pulsing them with a 585-nm pulsed dye laser with a pulse duration of 450 μsec at 1 Hz (one pulse per

second). Spot sizes that are usually used (to match the diameter of the lesions) are 3 mm at fluences of 7.0–8.0 J/cm^2, 5 mm at fluences of 6.8–7.2 J/cm^2, and 7 mm for energy density 6–7 J/cm^2. The lesions could be quickly treated at the rate of one every 2 s. The laser is generally non-scarring and produces a brief snapping sensation on the skin. Because of a possibility of viral particles in the laser plume, a smoke filtration system is utilized.

Electron-Beam Therapy

The use of electron-beam radiation is a promising alternative treatment for patients with localized MC lesions. It is administered by using megaelectron voltage (9 MeV or 12 MeV) electron-beam energy, five times per week for up to 18 treatments per site. The daily proposed radiation dose is 180 cGy (face and neck) or 200 cGy (body). Response to irradiation is rapid and complete. Mild skin erythema is the only reported side effect.

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Morphea (Localized Scleroderma)

64

Aurora Parodi

Key Points

- Morphea or localized scleroderma (LS) is a fibrosing disorder of the skin without systemic involvement.
- No causal treatment for LS exists but topical and systemic drugs are used to treat morphea as well as phototherapy.
- Topical treatments are adequate for limited morphea, while systemic therapy is needed for the generalized forms.
- Treatment should be used in the active phase of the disease.
- Topical corticosteroids are the mainstay of topical treatment.
- Calcipotriol and tacrolimus are also used and they seem improve some forms of morphea.
- UVA1 improves the skin scores.
- Among systemic treatments, methotrexate is considered the first-line option.
- Mycophenolate mofetil should be taken into consideration for the more aggressive and nonresponder forms.

Definition and Epidemiology

Morphea, also known as localized scleroderma, is a fibrosing disorder of the skin usually differentiated from systemic sclerosis based on the absence of sclerodactyly, Raynaud's phenomenon and systemic involvement.

Morphea is more common in whites and females but the prevalence is equal in adults and children. The incidence is between 0.4 and 2.7 per 100,000 people. About 90 % of children present the disease between 2 and 14 years of age; adults are often affected in the middle age.

Basic Concepts of Pathogenesis

The pathogenesis is not completely understood. The development of morphea requires an underlying predisposition and environmental factors. An imbalance of collagen production and destruction, inflammation and vascular changes are important features. Trauma and radiation have been reported before the onset of morphea. Drugs such as bisoprolol, bleomycin, D-penicillamine, bromocriptine, carbidopa, pentazocine and balicatib have also been associated with the development of morphea. Borrelia has been implicated as a possible infectious cause but other studies have refuted the association. Two to 5 % of children with morphea have another autoimmune disease such as vitiligo, insulin-dependent diabetes mellitus, Hashimoto

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_64, © Springer-Verlag Berlin Heidelberg 2015

thyroiditis, Graves disease and ulcerative colitis. The role of microchimerism as in systemic sclerosis has been investigated but other data are needed to evaluate its importance in the pathogenesis of the disease. In conclusion the exact pathway by which the increased deposition of collagen happens remains a mystery. According to the endothelial theory of the pathogenesis of morphea, the endothelial injury releases cytokines that increase the expression of vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM-1) and E-selectin. These adhesion molecules recruit T cells which produce profibrotic molecules such as IL-4, IL-6 and transforming growth factor-β (TGF-β). The upregulation of TGF-β increases the production of collagen, fibronectin and proteoglycan, decreases the production of proteases and increases the production of proteases inhibitors. Matrix metalloproteinases (MMP) are decreased, and antibodies capable of inhibiting MMP collagenase activity have been detected. In addition, patients with morphea have increased expression of insulin-like growth factor (IGF) which enhances collagen production, recruits fibroblasts and increases extracellular matrix deposition. Recent data on gene array analysis revealed evidence for four separate gene signatures subcategorized as inflammatory, proliferative diffuse, limited and normal-like. The inflammatory one was present in patients with morphea and limited and diffuse systemic sclerosis, the proliferative one only in patients with diffuse systemic sclerosis and the limited one only in patients with limited systemic sclerosis. This is important to distinguish the different forms of scleroderma as distinct disease subtypes.

Clinical Presentation

Morphea is classified based on its clinical presentation. In 1995, Peterson et al. recommended five subtypes of morphea:

1. Plaque type: including morphea en plaque, guttate, atrophoderma of Pasini and Pierini, keloidal and lichen sclerosus et atrophicus.
2. Generalized type when lesions involved two or more body areas.
3. Bullous type when bullae develop on the plaques.
4. Linear type when a linear morphology develops. This variant includes linear morphea of the extremities, morphea "en coup de sabre" and progressive facial hemiatrophy.
5. Deep type, including morphea profunda or subcutaneous morphea, eosinophilic fasciitis and pansclerotic morphea.

This classification is controversial; in fact it includes atrophoderma, lichen sclerosus et atrophicus and eosinophilic fasciitis which some clinicians consider separate entities. In addition, this classification does not include the mixed types of morphea.

In 2006 Laxer and Zulian suggested the following classification in five different types:

1. Circumscribed
2. Linear
3. Generalized
4. Pansclerotic
5. Mixed variants of morphea

The first stage of the disease is characterized by an erythematous-violaceous plaque; the central region becomes white and sclerotic while the active borders remain red (lilac ring). Over time the active stage subsides, leaving sclerotic plaques that can be white or pigmented. Adnexal structures are destroyed (Fig. 64.1).

Circumscribed morphea is the most common form of the disease, it may be both superficial and deep, and it is usually localized on the trunk. In adults, circumscribed morphea can develop in areas of trauma, and breasts are commonly involved with sparing of the nipples.

Generalized morphea is rarer than the circumscribed form. Sometimes it is difficult to differentiate this form from systemic sclerosis; however patients with generalized morphea do not present Raynaud's phenomenon and sclerodactyly (Fig. 64.2).

Linear morphea is the most common subtype in children. It is strongly correlated with the lines of Blaschko. About 25 % of the patients present a bilateral form. The "en coup de sabre" subtype usually occurs on the paramedian forehead and can be associated with underlying ocular and central nervous system involvement; it is usually associated with alopecia and typically follows Blaschko lines. The

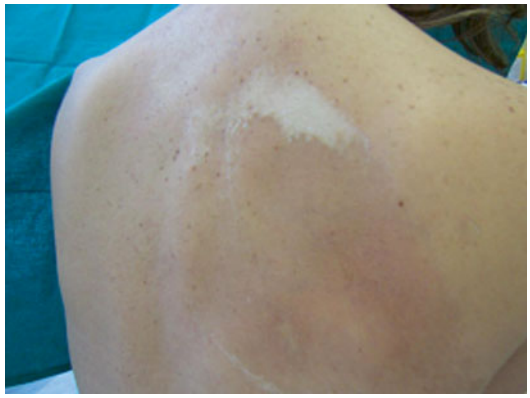


Fig. 64.1 Plaque-like morphea in an adult

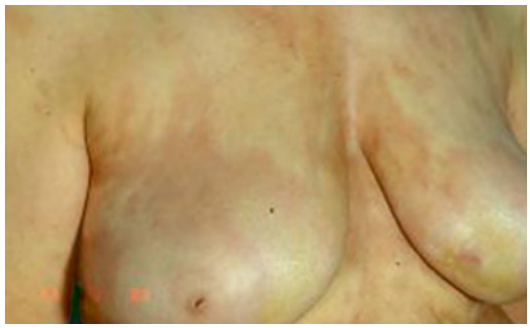


Fig. 64.2 Generalized morphea

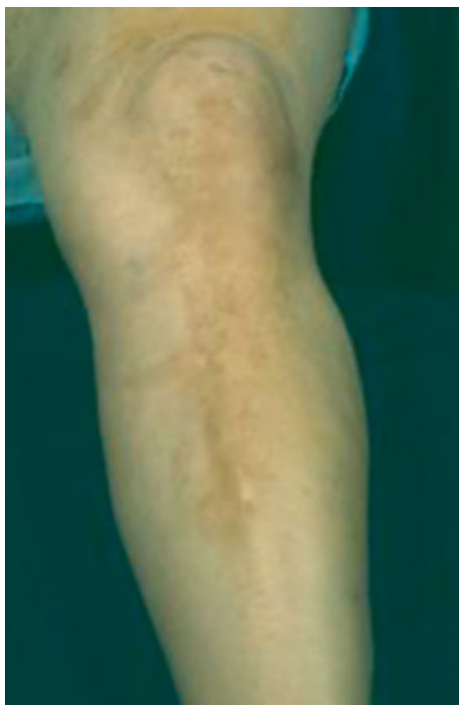


Fig. 64.3 Linear morphea of a limb

"progressive hemifacial atrophy", also known as Parry-Romberg syndrome, is characterized by significant atrophy of the subcutaneous tissue with minimal overlying cutaneous changes. Linear limb morphea is associated with muscle atrophy and joint contractures (Fig. 64.3).

Bullous morphea presents tense bullae on sclerodermoid affected plaques.

Deep morphea affects the deep dermis, panniculus, fascia or superficial muscle. It can lead to functional disability. Deep morphea includes eosinophilic fasciitis, subcutaneous morphea and morphea profunda. In eosinophilic fasciitis, the skin is normal because the inflammation is in the fascia. The inflammation usually spares the perivascular areas. Eosinophilia, hypergammaglobulinemia and increased sedimentation rate can occur. Hematologic malignancies have been reported in association with eosinophilic fasciitis.

Panscleroticmorphea is the most debilitating form of the disease. It affects subcutaneous tissues including bones at times. It is characterized by muscle atrophy, joint contractures and non-healing ulcers which have an increasing risk for squamous cell carcinomas.

Mixed variant morphea is a combination of two or more of the subtypes of the disease.

Diagnosis: Histology

In the early stage, a perivascular infiltrate of lymphocytes with plasma cells and eosinophils is found in the reticular dermis. In the late stage, the collagen bundles of the reticular dermis are thickened and crowding in on each other. The adnexal are atrophic and the subcutaneous fat appears "trapped" in the dermis. The histologic features of morphea cannot be differentiated from those of systemic sclerosis.

Complications

Myalgias, arthralgias and fatigue can be present. Neurologic manifestations, including seizures, head ache, peripheral neuropathy, vasculitis and ocular complications, are more common in "en coup de

sabre" or progressive hemifacial atrophy. Depression is common in patients with morphea. Positive autoantibodies (anti-histone, anti-DNA antibodies) are found in patients with linear scleroderma.

A novel antibody, antitopoisomerase II alpha, has recently been described. It is present in 85 % of patients with generalized morphea.

General Principles of Treatment

No causal treatment for localized scleroderma (LS) exists; however a variety of therapeutic options are available. In LS, treatment should be used in the active phase of the disease.

Topical and systemic drugs as well as phototherapy are used. Usually topical therapy is adequate for limited morphea, whereas systemic treatments are used for the generalized forms.

Topical Treatments

Corticosteroids are the mainstay of topical treatments. Moderate to high potent steroids should be used in the active phases of the disease; their application should be restricted to 3 months. Intralesional steroids could be used in linear forms. The injections should be performed into the active margins.

Topical calcipotriol 0.005 % twice daily was also used for the treatment of morphea. Two uncontrolled studies exist on the use of calcipotriol. In one study it was used along with low-dose ultraviolet A1 (UVA1) phototherapy, while in another study it was applied under occlusion. The studies suggest that calcipotriol should be used when sclerosis is superficial.

Topical tacrolimus 0.1 % was evaluated in open studies and in one double-blind placebo study. In this study it was seen to improve morphea significantly, in particular when early inflammatory lesions were evaluated.

In some patients imiquimod has been used. It seems to improve pigmentation, sclerosis and erythema. Its mechanism might be explained by induction of interferon (IFN)-γ which inhibits transforming growth factor (TGF)-β. However it is not suggested to treat morphea with imiquimod because more data are needed.

Phototherapy

In the 1990s, phototherapy was widely used to treat LS. The rationale is the fact that UV can induce interstitial metalloproteinases. Later, most authors have focused on the treatment of morphea with UVA because UVA penetrate deeper into the dermis; however, only one randomized controlled study was performed to compare UVA (low-dose UVA1 and medium-dose UVA1) and narrow-band UVB therapy. All three regimens improved the skin scores but medium-dose UVA1 was better than narrow-band UVB. Before initiating UV phototherapy, it should be considered that UV only penetrate into the dermis but not into deeper structures (fat tissue, fascia, muscle or bone), so the subtypes of deep morphea must not be treated with phototherapy. The disease is expected to begin improving after 10–20 treatments and most trials are stopped after 20–30 treatments. Some authors reported that patients continue to improve after treatment cessation. UVA1 are usually used at the dosage of 20–70 J/cm^2 for 20–30 treatments. Psoralen plus UVA (PUVA) was reported in uncontrolled studies and bath PUVA showed to provide benefit to some patients with morphea.

Systemic Treatments

Among systemic treatments, the best evidence exists for the use of methotrexate (MTX). The rationale is MTX inhibits cytokines that play a central role in sclerotic skin changes (IL-2, IL-4, IL-6). MTX is currently considered the first-line option for the severe forms of morphea (linear, generalized and deep subtypes). MTX doses are 15–25 mg/week in adults and 0.3–0.4 mg/kg/week in children. In a work of Zulian et al., MTX plus prednisone was compared with oral prednisone alone. Sixty-seven percent of the MTX-treated patients, compared with 29 % in the

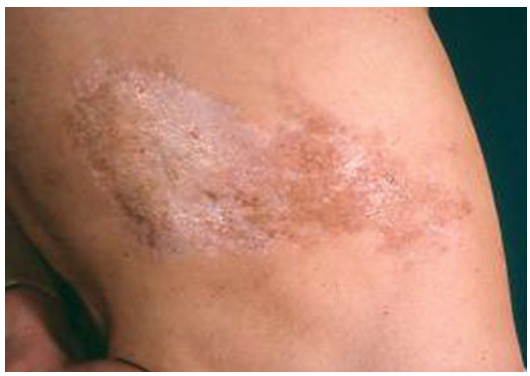
control group, had a clinical response. Recently, the same group of authors reported the therapeutic role of MTX in children after a prolonged period of follow-up. The authors studied a cohort of young patients previously enrolled in a double-blind, randomized controlled trial. A group of patients was treated with MTX 15 mg/m^2/week plus prednisone for 3 months, and a second group was treated with prednisone alone 1 mg/kg/day (maximum 50 mg). After 3 months prednisone was gradually tapered over 1 month, while MTX after remission was achieved, was maintained for at least 12 months. About 74 % of the patients treated with MTX were responders, and, among them, 73 % maintained clinical remission for a mean of 25 months. The medication was generally well tolerated with rare occurrence of adverse effects. The authors concluded that long-term maintenance MTX treatment is beneficial for LS in young patients.

Mycophenolate mofetil (MMF) was assessed as a treatment adjunct in patients who were already taking MTX and systemic steroids. Most patients improved with the addition of MMF.

Other systemic therapies such as IFN-γ, oral steroids, penicillamine, antimicrobials and antimalarials are not supported by current evidence.

Physical therapy is often recommended particularly in linear morphea of the limbs and generalized and pansclerotic LS. This therapy does not appear to exacerbate the disease and may be of value in minimizing joint contractures.

Proposed algorithms to the morphea treatment.



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Nevi (Benign Melanocytic)

65

Alexander C. Katoulis, Dimitrios Sgouros,
and Nikolaos G. Stavrianeas

Key Points

- Melanocytic nevi (MN) are benign hamartomas of the skin that are almost always present in light-skinned individuals.
- MN can arise in any anatomic location and can show up from birth to the sixth decade of life.
- They are classified into congenital and acquired. The latter are further categorized into common, dysplastic (atypical), blue, Spitz, and halo nevus.
- Dermoscopy is the gold standard method for the diagnosis and follow-up of MN.
- Their direct association with malignant melanoma is debated.
- Regarding their benign nature, as a general rule they do not require any treatment.
- However MN with a clinical-dermoscopic presentation simulating a melanoma or nevi showing changes that do not comply with their expected natural history have to be excised surgically.

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Melanocytic Nevi (MN)

Definition, Epidemiology

Melanocytic nevi (MN) are benign neoplasms or hamartomas, clinically appearing as well-circumscribed pigmented lesions and histologically consisting of nevus cells.

Nevus cells derive from the neural crest and migrate during embryogenesis to selected ectodermal sites, primarily skin, central nervous system, but also eyes and ears. Through a process of maturation and downward migration, type A nevus cells (epithelioid) evolve into type B (lymphocytoid) and then into type C (neuroid) dermal nevus cells. The following morphological features differentiate nevus cells from melanocytes, the epidermal pigment-producing cells:

- Absence of dendrites
- Arrangement in nests
- Larger size
- More abundant cytoplasm, containing coarse granules
- Location in the epidermis and/or in the dermis and rarely in the subcutis

It has been suggested that nevus cells represent the final stage of evolution of a neural crest precursor cell, the nevoblast. On the other hand, some authorities believe that differences between nevocytes and melanocytes are secondary adjustments and that both types of cells originate from the melanoblast.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_65,

MN are classified into:

Congenital

Acquired

Acquired MN are further classified into:

- Common acquired MN
- Dysplastic or atypical MN
- Blue nevus
- Spitz nevus
- Halo nevus

Basic Concepts of Pathogenesis

Melanocytic nevi are so common that some authorities believe they cannot be considered as defect or abnormality. Worldwide, the prevalence in ethnic groups with dark skin is lower than that observed in persons with fair skin. This could be attributed to the inherent protection of melanin against solar radiation. In addition, in light-skinned individuals, MN show a predilection for the trunk, while in dark-skinned individuals, for the extremities. Northern Europeans not uncommonly have large atypical nevi or a large number (>50, up to several hundred) of hypopigmented MN.

Although melanocytes have been postulated to exhibit some degree of sex hormone responsiveness (MN commonly darken and/or enlarge during pregnancy) due to cytosolic receptors for estrogens and androgens they possess, only subtle differences may exist in the prevalence of MN between women and men.

Congenital MN are present at birth, although some small congenital nevi are clearly tardive in their clinical presentation. The incidence of acquired MN increases throughout the first three decades of life, reaching its peak in the fourth to fifth decade of life. Then, the incidence decreases, and they slowly involute, becoming inconspicuous in the elderly. It must be noted that nevus subtype incidence may also vary with ages. Consequently, the appearance of a new "dysplastic," "blue", or "halo" nevus in persons older than 50 years should be considered suspicious.

MN are biologically stable and completely benign lesions. However, they can be found in association with melanoma. The exact risk of an individual nevus transforming into a melanoma is thought to be 1 in 200,000. The true frequency of malignant transformation is not known. The estimated prevalence of melanomas histologically associated with a precursor MN varies widely in the literature, from 10 % up to 40 %, or 50 % in patients younger than 30 years.

Both acquired and congenital MN are considered risk factors for the development of melanoma. Congenital MN, especially giant, hold the greater risk. This is believed to be a consequence of the fact that the number of lesional melanocytes within large lesions is greater, and thus the chances of a transformative event are proportionately greater.

The exact etiology behind the development of MN is complex and multifactorial and remains incompletely understood. The development of MN is believed to be influenced by genetic and environmental factors. The dysplastic nevus syndrome and the familial atypical mole and melanoma syndrome express an autosomal mode of inheritance. Their onset is believed to be, at least in part, a response to sun exposure. The so-called eruptive MN have been observed to develop after major blistering events, such as second-degree thermal burns or sunburns, toxic epidermal necrolysis, or hereditary epidermolysis bullosa. It appears to be induced by trauma through scattering of nevus cells and release of growth factors by proliferating keratinocytes.

Congenital MN result from an error in the development and migration of neuroectodermal elements originating from the neural crest. Therefore, they may be interpreted as congenital malformations or hamartomas. Errant embryological migration is also believed to be the source of melanocytic nevus cell "rests," observed in the capsules of lymph nodes and, occasionally, in the subcapsular space or within lymph node trabecula. Their importance is that they can sometimes be mistaken for metastatic deposits because of their extracutaneous location. These rests of cells are sometimes referred to as benign metastases because they may result from an intralymphatic migration of benign melanocytes. In contrast, acquired MN are considered benign neoplasms. They are believed to develop either from epidermal melanocytes that have completed their migration from the neural crest to the dermoepidermal junction in fetal life or to arise from dermal melanocytes that have become arrested in the dermis and have never reached their normal site.

Common Acquired MN

Definition and Epidemiology

Common acquired MN (CAMN) are small (<1 cm), well-circumscribed, evenly pigmented lesions that are composed of nevus cells. Depending on the location of the groups of nevocytes, CAMN are subdivided into junctional (cells at the dermoepidermal junction above the basement membrane), dermal (cells exclusively in the dermis), and compound nevi (cells in both the epidermis and the dermis).

CAMN are seen in almost all individuals with their number varying from few to hundreds. Caucasians, especially those with lighter skin color, have a greater prevalence of CAMN than black people or Asians, who have more nevi on the palms/soles and nail beds. Both sexes are equally affected. The number of CAMN increases with age, reaching a peak during adolescence and early adulthood. Thereafter, they may undergo involution. Increased number of CAMN has been observed among members of the same family. A strong positive correlation between sun exposure and number of nevi has been documented.

CAMN have a very low malignant potential. However, the association of CAMN with cutaneous malignant melanoma (CMM) is well established. Histological studies have shown that one-third of CMMs are associated with nevus remnants. In addition, increased numbers of CAMN is a risk factor for CMM.

Basic Concepts of Pathogenesis

Nevus cells are thought to derive either from nevoblasts or from melanoblasts, which migrate from the neural crest to the epidermis. Junctional nevi result from the proliferation of nevus cells within the epidermis. Migration and proliferation of nevus cells into the dermis give rise to compound nevi or to dermal nevi when no residual cells are found in the epidermis. Some authorities believe that the three types of CAMN represent sequential developmental stages in their life history, i.e., evolution from junctional nevus to compound, then to dermal, and finally involution with fibrosis.

Genetic and environmental factors (mostly solar radiation) seem to play a pathogenetic role.

Clinical Presentation

CAMN are asymptomatic, well-defined, round to oval lesions, smaller than 1 cm in diameter, with regular or slightly irregular borders and uniformly distributed color, usually shades of brown and black. They may occur anywhere on the body. Junctional nevi appear as macular hairless lesions, medium to dark brown in color, most commonly located on the trunk, the upper extremities, or the face (sun-exposed areas). Compound nevi are variably elevated papular lesions with smooth or slightly warty surface and dark brown to black coloration. Bristle-like terminal hair may be present. The face is the most frequent location. Dermal nevi are papular or nodular, dome-shaped, or, occasionally, papillomatous or pedunculated lesions. They are tan to light brown in color. Telangiectasias are often present. They are usually located on the face, neck, or trunk. CAMN of the nail bed present as brown longitudinal bands (melanonychia striata) with regular distinct margins and uniform pigmentation (Fig. 65.1).

CAMN tend to remain unchanged in color and in shape. Increase in size and/or in pigmentation may occur in adolescence and early adulthood or during pregnancy. In an Australian study, 16 % of benign melanocytic lesions changed over a digital follow-up period of 2.5–4.5 months, and the proportion was higher among persons aged 0–35 years.

Diagnosis

Diagnosis is mostly clinical.

Evaluation of the patient should include:

- Personal and family history for CMM or dysplastic nevi and other risk factors for CMM.
- Total body examination (presence and number of nevi).

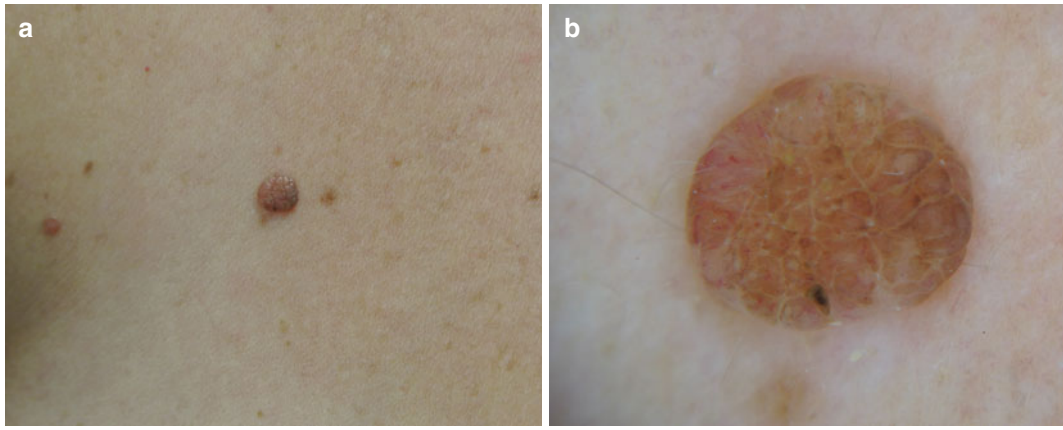


Fig. 65.1 Dermal nevus. (**a**) Papillomatous, skin-colored dermal nevus (Unna type). (**b**) Dermoscopic picture of dermal nevus exhibiting cobblestone pattern with remnants of pigmentation and comma-shaped vessels

- Dermoscopic examination: flat CAMN show symmetry and uniform pigmentation, a regular global pattern (reticular, globular, homogenous) with no specific or other local features. Dermal CAMN of the face (Miescher) are characterized by pseudonetwork or homogenous or unspecific global pattern, comma vessels, and, occasionally, milia-like cysts, comedo-like openings, and one to two prominent hairs. Dermal CAMN nevi of the trunk (Unna) exhibit a globular, cobblestone, homogenous or unspecific global pattern, comma vessels, and exophytic papillary structures as local features and, occasionally, milia-like cysts, comedo-like openings, and prominent hairs.

In unequivocal cases, excisional biopsy and histological examination can document diagnosis (nevus cells arranged in clusters in the epidermis and/or in the dermis).

Differential Diagnosis

Macular pigmented lesion:
- Freckle, solar lentigine
- Lentigo simplex
- Lentigo maligna
- Pigmented actinic keratosis.

Papular pigmented lesion:
- Seborrhoeic keratosis
- Dermatofibroma
- Neurofibroma
- Epidermal nevus
- Spitz nevus
- Blue nevus
- Dysplastic nevus (larger size; asymmetry; not well-defined, irregular border; multiple colors)
- Trichoepithelioma
- Pigmented basal cell carcinoma
- Nodular melanoma

General Principles of Treatment

For CAMN, no treatment is necessary. There is no reason to remove CAMN on a routine basis, although it is not contraindicated, whenever removal is thought necessary. Although not completely clarified as yet, it is highly improbable that manipulations, such as plucking hair from a mole, or repeated trauma may result in malignant degeneration.

Recommended Therapies

Any suspicious pigmented lesion must be removed completely by excisional biopsy down to the subcutaneous tissue and should be histologically evaluated, often with sectional examination. Reference to specialists is also a good practice.

Indications for excision of a CAMN are the following:

- Atypical clinical appearance, suspicious for CMM
- Changing lesion, e.g., size has increased or the color has become variegated or the border has become irregular
- Symptomatic lesion, i.e., if pain, pruritus, or bleeding is present
- Evidence of malignancy detected by dermoscopy
- New lesion rapidly growing in a high-risk individual or in an adult
- Lesion differing from all other moles of the same patient ("ugly-duckling sign")
- Sites of repeated irritation, or sites associated with increased risk for CMM, or sites that do not permit self-examination, such as palms, soles, penis, scalp, mucous membranes, anogenital region
- Cosmetically disfiguring lesion

Removal of CAMN should be performed by simple complete excision and closure by sutures. A histological examination should always follow, even when there are no clinical indications for atypicality. Destruction of the lesion by electrocautery, cryotherapy, or laser surgery is wisely avoided because these modalities do not allow histological evaluation and do not ensure complete excision. Nevertheless, if a destructive method is chosen, in case of recurrence, surgical excision and histologic examination are mandatory. On the other hand, after an incomplete surgical excision, the residual pigmentation at the scar site can be removed using electrodesiccation or cryotherapy, if atypicality or malignancy has been excluded.

Congenital MN

Definition and Epidemiology

Congenital melanocytic nevi (CMN) are benign pigmented neoplasms composed of nevomelanocytes that are usually present at birth. According to their projected adult size (Table 65.1), they can be distinguished as small (<1.5 cm in diameter), intermediate (from 1.5 to 9.9 cm), large (from 10 to 19.9 cm), and giant (>20 cm). The estimation of the projected adult size of a CMN in a given age takes into consideration the different growth dynamics of nevi in various anatomic locations and results from specific charts that derive by averaging parameters of nevus size, height, and weight for males and females from birth to adulthood. Population-based prevalence of CMN is estimated to be 0.6–6 % depending on the study. Large and giant CMN occur in 1 in 20,000 and 1 in 50,0000 newborns, respectively. There is no race or sex predilection. Familial tendencies have been described.

Table 65.1 Estimated size of nevus at birth necessary to reach 20 cm in full-grown adult

Location of CMN	Diameter at birth (cm)
Head	12
Hands, feet, torso, forearms, arms, buttocks	7
Thighs	5.8
Legs	6

Adapted from Marghoob et al. (1996)

Basic Concepts of Pathogenesis

Nevomelanocytes are derived from the neural crest as a result of a developmental defect of melanoblasts. CMN probably develop between the tenth and the 24th week of gestation. Many CMN have been found to harbor N-RAS mutations in contrast to acquired nevi or melanomas arising on intermittently sun-exposed skin, which typically have B-RAF mutations.

Clinical Presentation

CMN are almost invariably present at birth (birthmarks). Occasionally, they may arise during the first 2 years of life (congenital nevus tardive).

Small, intermediate, and large CMN appear as slightly elevated, round or oval, well-demarcated, hairy or hairless plaques with uniform light to dark brown coloration and regular or irregular contours. The surface is sometimes pebbly, rugose, or coarse. CMN may appear at any site. They are usually solitary. Fewer than 5 % are multiple.

Giant CMN present as deeply pigmented, irregularly shaped plaques with coarse terminal dark hairs and focal nodules or papules, termed "proliferative nodules," which can be clinically and pathologically confused with CMM. They cover large areas of the head, trunk, or the extremities, often having the distribution of a garment, such as a bathing trunk, a cap, a sleeve, or a stocking. Multiple smaller satellite lesions may also be present. These are actually small CMN and can be present at birth or arise months to years later.

With advancing age, CMN increase proportionally to the anatomical area they occupy. Occasionally, they become darker, or assume a verrucous appearance, or develop a halo.

The potential for malignant transformation is well documented for all CMN, regardless of size. Lifetime risk for CMM development is <1 % for small and medium CMN according to several studies. However, for giant CMN, the risk is estimated to be between 2.5 % and 13.9 %, since the risk of melanoma development is closely associated with the size of the nevus. Histological features of CMN have been found in 8.1 % of primary melanoma specimens studied. CMN-associated melanoma usually occurs early in childhood and has a poor prognosis. Rarely, malignant soft tissue tumors may arise on CMN. Additionally, giant CMN or multiple satellite nevi can be associated with involvement of the leptomeninges and/or brain parenchyme (neurocutaneous melanosis), resulting in neurologic manifestations (Figs. 65.2 and 65.3).

Diagnosis

Clinical diagnosis is based on history, physical examination, and dermoscopic assessment.

Dermoscopic characteristics of CMN are protean. The predominant patterns are the globular, reticular, homogeneous, and, often, multicomponent. The globular pattern usually corresponds to CMN of the head, neck, and trunk, whereas CMN exhibiting the reticular pattern are mostly located on the extremities. Dermoscopically, CMN show various shades of brown and black. Additional dermoscopic features include perifollicular hyper- or hypopigmentation, prominent hairs, milia-like cysts, and comedo-like openings. Several vascular structures, especially comma vessels and target network with vessels, can be observed.

Histological examination documents diagnosis: nevomelanocytes arranged in theques in the epidermis and the dermis, which often invade the lower reticular dermis or the subcutaneous fat, the walls of blood and lymphatic vessels, the skin appendages, the nerve fascicles, and the arrectores pilorum muscles. Nevertheless, the histologic findings are not always specific.

Differential Diagnosis

- Common acquired melanocytic nevus
- Nevus spilus
- Dysplastic nevus
- Spitz nevus

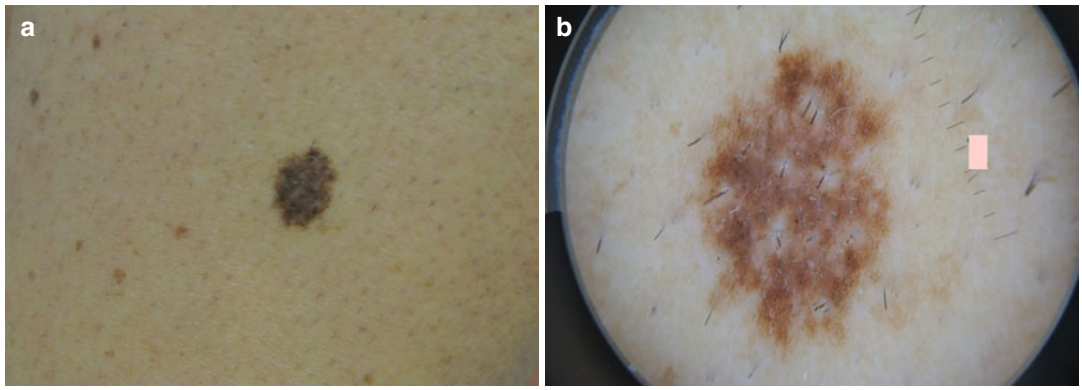


Fig. 65.2 Small congenital nevus (small CMN). (**a**) A small congenital melanocytic nevus on the shin. (**b**) Reticular pattern with perifollicular hypopigmentation and multiple dots

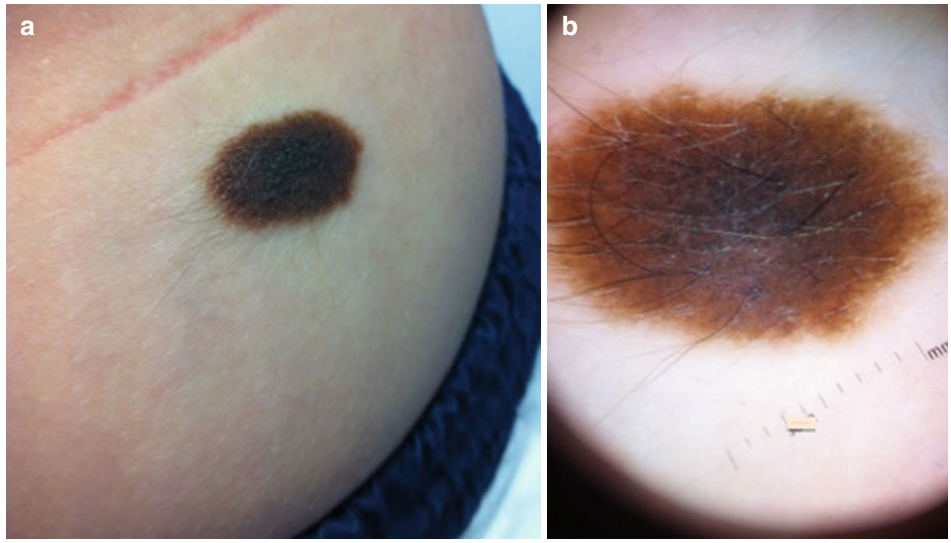


Fig. 65.3 Medium congenital nevus (medium CMN). (**a**) Medium-sized congenital nevus appearing as a well-demarcated *dark brown* plaque with multiple coarse terminal hairs. (**b**) A combination of cobblestone and homogeneous pattern with multiple hairs

- Congenital blue nevus
- Becker's nevus
- Malignant melanoma
- Pigmented epidermal nevus
- Pigmented basal cell carcinoma
- Seborrhoeic keratosis
- Paget's disease with pigmentation
- Nevi of Ota and Ito

General Principles of Treatment

Treatment is individualized depending on age, location, size, appearance, and risk for CMM. Since the lifetime risk of malignant transformation for small and medium CMN has not been proven to be significantly increased (<1 %), the prophylactic excision is no longer proposed, except for cosmetic reasons. CMN manifesting benign clinical and dermoscopic features should be managed with digital dermoscopy monitoring and regular follow-up. However, large and giant CMN show a well-established high risk of malignant transformation. Thus these lesions should be removed as soon as possible. Excision should be performed after the perinatal period when the risks from general anesthesia are diminished. Small and medium CMN or giant CMN that have not been excised should be monitored clinically with conventional and digital dermoscopy on a regular basis for life, and patients must seek medical advice when a change in the lesion has occurred.

Recommended Therapies

Excision of suspicious small and medium CMN can be delayed until late childhood, because the risk for CMM increases in puberty. On the contrary, giant CMN should be removed as soon as possible due to the high risk for early aggressive CMM. However, as mentioned above, excision should be performed after the perinatal period when the risks from general anesthesia are diminished.

Surgical excision is the only acceptable method. Full-thickness skin graft, swing flaps, tissue expanders, or patient's skin grown in tissue culture may be required. Small- and medium-sized nevi (up to 5 cm in diameter) can be removed by an one-stage procedure with suturing of the wound, local plasty, or free-tissue skin graft. Blepharal and central facial lesions are best reconstructed with full-tissue skin grafting. Nevi

with a diameter >5 cm mandate a staged excision or removal at one stage with prior use of a tissue expander or pre-suturing. Giant nevi require staged treatment with the use of an intermediate-thickness skin graft.

Alternative and Experimental Therapies

Partial removal of superficial nevus cells by dermabrasion, laser therapy (Q-switched ruby, Q-switched alexandrite), curettage, or shave excision is less traumatic than excision surgery and produces an acceptable cosmetic result. Chemical peels, e.g., phenol, are an acceptable alternative method of therapy for those lesions that are too large for excision and primary closure or for lesions in which excision would result in unacceptable scars in areas such as the face. However, none of these techniques completely removes the risk for malignant transformation.

Halo Nevus

Definition and Epidemiology

Halo nevus (HN) is a melanocytic nevus surrounded by a depigmented zone or halo. The melanocytic nevus, which often undergoes spontaneous involution, may be a common acquired (dermal or compound), congenital, atypical, Spitz, or a blue nevus. According to a recent concept, HN should not be regarded as a distinct entity but as a halo phenomenon occurring in a wide variety of nevus types. HN have been erroneously confused with melanoma and have been the source of much anxiety among both clinicians and patients.

HN is seen in all races. No sexual predilection is reported. It most commonly affects adolescents and young adults (average age of onset is 15 years) with an estimated incidence of 1 % in individuals under 20 years of age. Family history is not unusual. Of the patients, 18–26 % have vitiligo. Furthermore, it may be a heralding manifestation of vitiligo.

HN are entirely benign lesions and of only cosmetic significance.

Basic Concepts of Pathogenesis

HN results from an immune response (both cellular and humoral) directed against either antigenically altered nevus cells undergoing dysplastic changes or nonspecifically altered nevus cells in response to various influences. The inflammatory infiltrate consists predominantly of T-lymphocytes with a cytotoxic (CD8) to helper (CD4) lymphocytes ratio of approximately 4:1 and scattered macrophages. The precipitating cause as well as the exact role of the lymphocytes remain unknown. Cytokines may act as mediators for the development of the white halo. Epidermal melanocytes in the halo component are completely absent, suggesting a similar pathogenetic mechanism with vitiligo. Immune mechanisms have been implicated also for the involution of the central nevus. A theory of direct cytotoxic effect of lymphocytes on melanocytes seems plausible. In advanced lesions, dermal macrophages containing portions of nevus cells were observed. Circulating antibodies to the cytoplasm of melanoma cells have been detected in patients with HN that disappeared after removal of the nevus. These antibodies are believed to result from the release of cytoplasmic proteins from damaged melanocytes.

Clinical Presetnation

HN is composed of a central macule or papule with uniform dark brown to pink color and regular well-defined border, encircled by a symmetrical, round or oval, sharply demarcated, white or hypopigmented rim. It is usually asymptomatic or slightly pruritic. HN are most often located on the trunk, especially on the back, but they can develop anywhere on the body. In 25–50 % of patients, multiple lesions are present.

The halo usually develops around preexisting melanocytic nevus within months. The course is variable. Only rarely HN remains unchanged. More often, the central nevus spontaneously regresses completely, followed by repigmentation of the white halo. This process lasts from months to years. In some cases, a depigmented

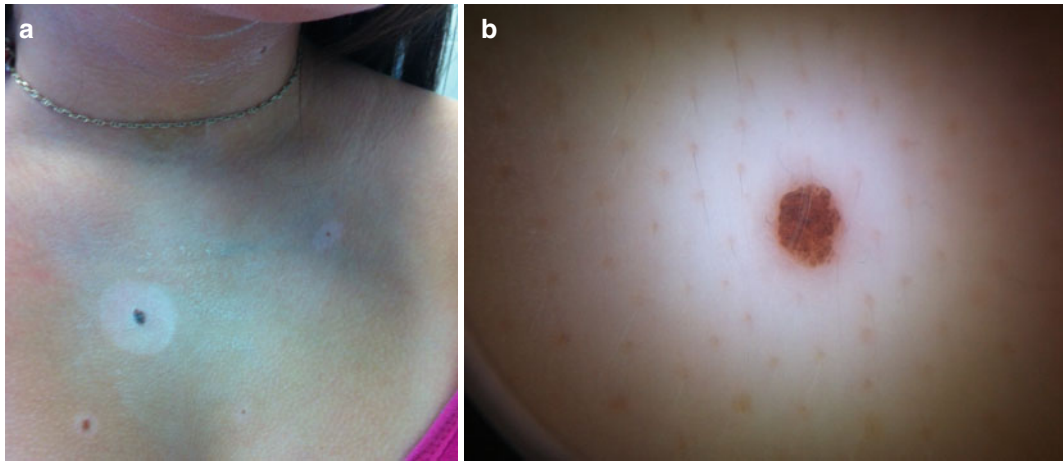


Fig. 65.4 Halo nevus. (**a**) Multiple common nevi on the trunk with a peripheral halo of depigmentation. (**b**) A small congenital nevus exhibiting a globular pattern surrounded by a *white* halo

macule remains, or in others, the halo repigments while the central nevus remains unchanged.

A depigmented halo may develop around a primary CMM. In older adults, the sudden appearance of multiple HN has been associated with the development of a primary CMM at another site (Fig. 65.4).

Diagnosis

Diagnosis of HN is easy on the basis of the distinctive clinical presentation. However, lesions that are not uniform in shape and color or are inconsistent with the patient's epidemiological profile or have a papular component are very important to be evaluated clinically and dermoscopically for malignancy, because a halo phenomenon can develop around a primary CMM. Family history and total skin examination for other HN, dysplastic nevi, vitiligo, or CMM are crucial. To exclude malignancy definitely, histological assessment may be necessary.

Dermoscopically, HN show a globular, homogenous, or, later, an unspecific global pattern. There are no specific local features. The characteristic confounding feature is the depigmentation of the peripheral skin.

The histology of HN varies depending on the age of the lesion. In most cases, a dense, somewhat band-like lymphocytic infiltrate is present in the papillary and often reticular dermis with nests of nevocytes located centrally. Macrophages may be seen within the infiltrate, although, surprisingly, there are less than would be expected in an inflamed melanocytic lesion. In more mature lesions, nevocytes may appear to be absent or decreased in number. The presence of halo clinically does not correlate with the degree of inflammation histologically. The most important lesion to differentiate from HN is melanoma.

Differential Diagnosis

Common acquired MN with halo must be differentiated from other pigmented nevi with halo:

- Spitz nevus.
- Blue nevus.
- Congenital melanocytic nevus.
- Dysplastic nevus.
- Malignant melanoma with surrounding leukoderma: primary CMM is usually solitary and most commonly affects adults; usually present for an extended period of time; the white zones represent areas of regression; the "halo" of a regressing melanoma is irregular in shape and variable in radial width; the central "nevus" is usually large with striking irregularity of color and structure.

Hypopigmented non-melanocytic lesions to be considered include:

- Dermatofibroma
- Seborrhoeic keratosis
- Basal cell carcinoma
- Flat warts
- Molluscum contagiosum
- Lichen planus
- Lichen sclerosus et atrophicus
- Psoriasis
- Sarcoidosis
- Vitiligo

General Principles of Treatment

HN with clinically and dermoscopically benign appearance does not require excision. The patient should be reassured and followed up periodically. The presence of a new "halo nevus" in an older adult (>40 years) or with a family history of CMM or dysplastic nevi (dysplastic nevus syndromes or multiple dysplastic nevi) should be regarded with a high index of suspicion for melanoma and may warrant performing a biopsy.

Nevus Spilus

Definition and Epidemiology

Nevus spilus (NS) is a slightly hyperpigmented macular lesion dotted with darker flat or raised spots.

It is usually acquired in childhood. An incidence of 2–3 % among Caucasians has been reported.

Basic Concepts of Pathogenesis

These are similar to that of CAMN. Ultraviolet radiation has no pathogenetic role. Segmental or zosteriform distribution suggests localized malformation.

Clinical Presentation

Oval or irregularly shaped, light brown, hairless macule (1–20 cm in diameter) containing scattered dark brown to black macules or papules (2–3 mm in diameter). Larger lesions may exhibit a lateral, segmental, or zosteriform distribution. NS persists indefinitely. CMM very rarely may arise in NS.

Diagnosis

The diagnosis is clinical. The macular pigmented lesion shows dermoscopical and histological features of lentigo simplex, while the spots are usually junctional or compound nevi or, rarely, dysplastic or Spitz nevi.

Differential Diagnosis

- Congenital melanocytic nevus
- Becker's nevus

Treatment

Risk of CMM development warrants periodic follow-up (with baseline photography), especially for congenital or large lesions. Changing clinical picture or atypical features must be assessed histologically. Complete surgical excision and closure with sutures is required.

Spitz Nevus

Definition and Epidemiology

Spitz nevus (SN) is a benign nodular melanocytic nevus with distinctive histopathological features that may be confused with CMM. Several attempts were made to establish objective criteria that would clearly delineate SN and melanomas. Even today, no set of criteria can be used to predict the clinical outcome of atypical Spitz tumors with absolute assurance. Perhaps SN and CMM exist along one continuum of disease.

SN are seen more frequently in fair-skinned individuals, but are not restricted to white patients. Estimated incidence rate of SN in

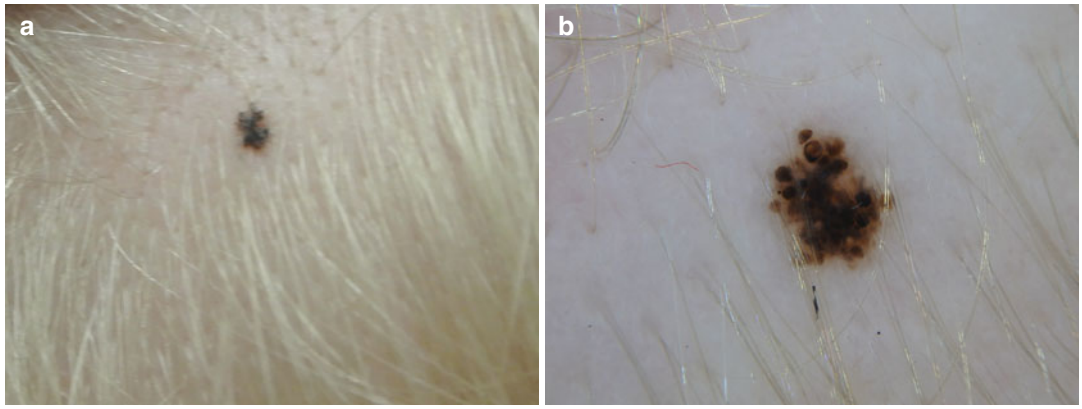


Fig. 65.5 Spitz nevus. (**a**) Small *brown* to *black* lesion on the scalp of a 3-year-old boy. (**b**) A pigmented Spitz nevus showing homogeneous *brown-black* pigmentation in the center of the lesion and multiple globules in the periphery

Australia is 1.4 cases per 100,000. It represents 1 % of all surgically excised melanocytic nevi in childhood. It is usually acquired. One-third of the patients are under 10 years of age, 36 % are between 10 and 20 years, and only 31 % are over 20 years. No familial distribution has been recognized. Both sexes are equally affected, or there is a slight female predominance.

These lesions are clinically benign. Atypical SN pose a minimal threat of mortality but have an increased risk of melanoma and a moderate risk of metastasis to regional nodes.

Basic Concepts of Pathogenesis

SN derives from cells originating from the neural crest. No pathogenetic associations have been documented. A SN can arise de novo or in association with an existing melanocytic nevus.

Clinical Presentation

SN presents as an asymptomatic, well-circumscribed, hairless, dome-shaped or flat, papule or nodule, 2 mm to 2 cm in diameter, varying in color from pink or orange red to tan or dark brown. The color is uniformly distributed. The surface is smooth or verrucous. It is most commonly located on the head and neck or the legs. There are rare cases with multiple or clustered SN.

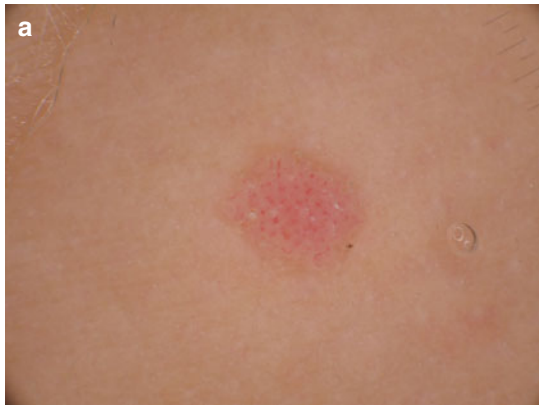
Usually there is a history of sudden onset and rapid growth. After that it becomes static. The biological behavior of SN remains obscure. SN may evolve into conventional compound melanocytic nevus. Some undergo fibrosis, eventually resembling dermatofibromas. Very rarely SN may involute spontaneously. CMM may arise within SN, but this event is uncommon.

Malignant SN is an aggressive variant of SN that results in regional lymph node metastases (Figs. 65.5 and 65.6a).

Diagnosis

Clinical picture, young age, recent onset, and rapid growth suggest diagnosis.

Dermoscopy has significantly increased the diagnostic accuracy for SN, especially regarding the pigmented variant (Reed nevus). Nonpigmented SN displays an unspecific or homogenous global pattern, sometimes with some dotted vessels. Reed nevus typically (50 %) shows a starburst pattern (pigmented streaks symmetrically distributed at the periphery of the lesion) with central reticular blue-white structures (reticular depigmentation) or, less frequently, a regular and prominent pigment network. In 25 % of the cases, a regular globular pattern with brown to gray-blue pigmentation in the center, and often a characteristic peripheral rim of large brown globules is present. Brown to



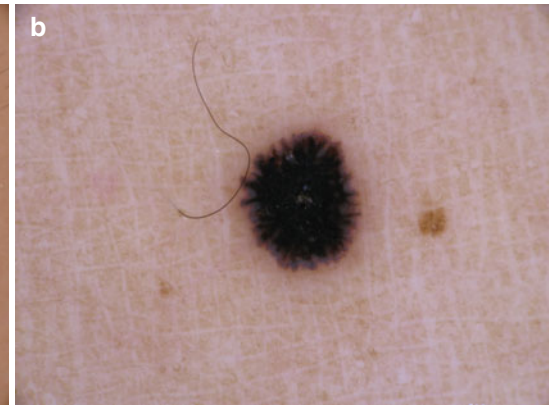


Fig. 65.6 (**a**) Spitz nevus (Courtesy of Professor Iris Zalaudek and Professor Giuseppe Argenziano). A *pink* nodule with regularly distributed dotted vessels and a reticular depigmentation. (**b**) Reed nevus (Courtesy of Professor Iris Zalaudek and Professor Giuseppe Argenziano). Jet-black structureless pigmentation in the center and radial streaks in the periphery ("starburst pattern")

gray-blue globules and dots may be detected. Another 25 % of cases may exhibit an atypical dermoscopic appearance characterized by an uneven distribution of colors and structures (irregular, diffuse, gray-blue pigmentation, pigment network, brown globules, black dots, hypopigmentation, irregular peripheral streaks). Remarkably, melanomas may rarely display either the starburst or the globular pattern seen in Reed nevi (Fig. 65.6b).

Histological confirmation is always necessary. The sine qua non histological feature is the presence of nests of admixed large spindle-shaped melanocytes and epithelioid cells extending from a hyperplastic and acanthotic epidermis into the reticular dermis in an inverted-wedge configuration. Striking symmetry, sharp lateral demarcation, absent (or rare) mitoses, absence of atypical mitoses, presence of eosinophilic and periodic acid-Schiff (PAS)-positive globules (Kamino bodies), and non-disruptive (single-file-like) infiltration of collagen are important features indicating the diagnosis of SN. Single-file melanocytes may also be observed in the reticular dermis located at the base of the lesion (dispersion). Atypical SN is characterized by prominent cellularity and increased mitotic activity. The greater the atypia, the more difficult the differentiation from CMM. Histopathologic differentiation from melanomas is equivocal in up to 8 % of case.

Immunohistochemistry and comparative genomic hybridization have proved helpful. SN stain diffusely with S100A6, demonstrate no deep Ki-67 positive cells, and show a gradient with HMB-45 staining. Melanomas show the opposite patterns.

Differential Diagnosis

Nonpigmented SN must be differentiated from:

- Pyogenic granuloma
- Hemangioma
- Verruca
- Molluscum contagiosum
- Dermatofibroma
- Mastocytoma
- Juvenile xanthogranuloma
- Dermal melanocytic nevus

Pigmented SN may be confused with:

- Dysplastic nevus
- Cutaneous malignant melanoma

In order to differentiate SN from CMM, excisional biopsy is warranted. Criteria that in concert strengthen the probability of SN diagnosis include a young patient, a well-demarcated and symmetrical lesion, maturation and dispersion of melanocytes at its base, and the presence of epithelial hyperplasia, but no criterion is absolutely reliable. Misdiagnosis of SN as melanomas and

vice versa is a possibility. In one study, 6.5 % of cases diagnosed clinically as melanomas were SN.

Treatment

Typical SN in children can be followed up. Atypical SN or lesions revealing the characteristic clinical and dermoscopic features of SN, when arising in adult patients and showing a history of recent change, should be excised.

Complete surgical excision (with margins of 0.5–1 cm for atypical variants) of the lesion and histopathologic evaluation is recommended, followed by re-excision of positive margins, if present. Incomplete excision often results in recurrence that should be also treated with re-excision. Periodic follow-up at 6–12-month intervals is advisable.

In a series of 12 cases with atypical SN, one-third of the patients showed nodal micrometastases suggesting a yet not understood metastatic potential. However, sentinel lymph node biopsy is not justified for surgical staging.

Blue Nevus

Definition and Epidemiology

Blue nevus (BN) is a benign, gray to dark blue, papular or nodular skin lesion, representing a localized proliferation of melanin-producing dermal melanocytes and characterized by spindled cytomorphology.

Although considered congenital, BN are uncommon at birth or in the first few years of life, usually appearing in childhood and adolescence. They are twice as common in women than in men. BN are most frequently seen in Asians populations with an estimated prevalence 3–5 % in adults. They are found in 1–2 % of white adults, and they are very rare in blacks. Most cases remain entirely benign. Rare cases of CMM have been reported arising in association with cellular blue nevi.

Basic Concepts of Pathogenesis

BN results from ectopic accumulation (in the dermis) of melanin-producing melanocytes, which have migrated from the neural crest during fetal life, but have failed to reach the epidermis. The optical phenomenon that accounts for clinical blueness is known as the Tyndall effect, i.e., the preferential absorption of longer wavelengths by the deep-seated brown pigment and the scattering by collagen bundles of shorter wavelengths (blue light), giving a bluish hue to such lesions.

On the basis of the variation of BN in different populations, a genetic predisposition has been suggested. However, familial cases are exceedingly rare. BN are not associated with chromosomal aberrations, and they show fewer *B-RAF* mutations compared with congenital and acquired nevi.

Clinical Presentation

The color varies from gray-blue to brown to bluish black depending on the degree of pigmentation. An amelanotic variant also exists. BN are usually relatively small and reasonably symmetric. Some may be large and nodular with high cellularity under the microscope. BN typically occur on the distal extremities or scalp, but they can occur at any body site. BN are often firm because of associated stromal sclerosis.

Three types of BN have been identified:

Common BN: small (0.5–1.0 cm), sharply circumscribed macule or dome-shaped papule or nodule, most commonly located on the dorsa of the hands or feet. Although usually solitary, it may be multiple or clustered. Malignant transformation does not occur in common BN.

Cellular BN: blue gray to black nodule, 1–3 cm or larger, with smooth or irregular surface. Sites of predilection include the buttocks, sacrococcygeal region, scalp, face, and feet. Malignant transformation can occur rarely.

Combined BN: nodular blue-brown to blue-black lesions with smooth surfaces. The face is the most common site. It represents an association of BN with overlying melanocytic nevus.

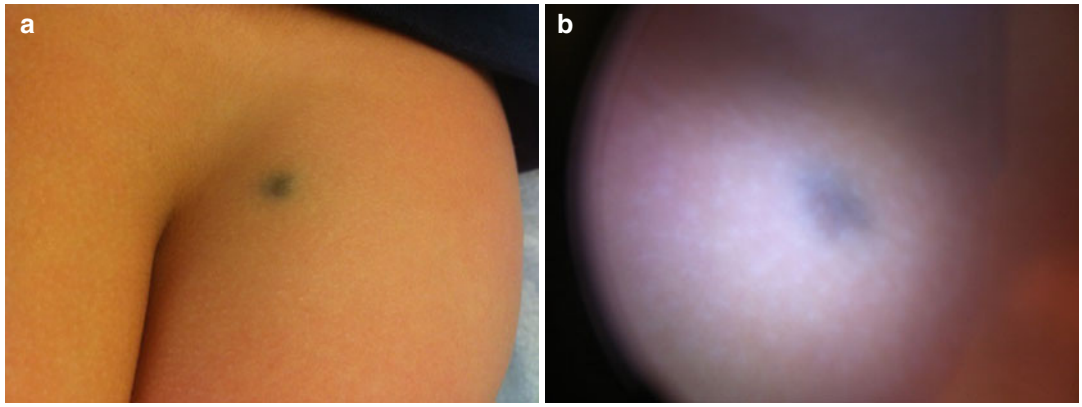


Fig. 65.7 Blue nevus. (**a**) A *bluish* nodule on the sacrococcygeal area of a 5-year-old boy. (**b**) Homogeneous and structureless deep *blue* pigmentation

There are occasional reports of BN in the vagina, cervix, prostate, spermatic cord, oral cavity, bronchus, and lymph nodes.

BN usually remains unchanged. Less often, it regresses, by flattening and fading in color, but still remaining symmetric. Malignant change in cellular blue nevi may be heralded by a sudden increase in size and, occasionally, ulceration (Fig. 65.7).

Diagnosis

Clinical findings along with dermoscopy suggest the diagnosis. Dermoscopically, BN is characterized by homogenous global pattern with complete absence of local features, sharp demarcation, and bluish color. Not uncommonly, diffuse hypopigmentation (increased collagen in the reticular dermis) can be observed in the fibrosing type of BN.

Histopathological examination confirms diagnosis. In common BN, a vaguely nodular collection of poorly melanized spindled melanocytes and deeply pigmented dendritic melanocytes within thickened collagen bundles is observed, as well as scattered melanophages. In cellular BN, medium-sized, spindled to oval melanocytes, tightly arranged in fascicles and nests, form a well-demarcated nodule with scattered melanophages in the reticular dermis, occasionally extending into the subcutaneous fat. Rare mitoses may be present, but significant cytologic atypia and areas of necrosis are absent.

Differential Diagnosis

The following skin conditions should be considered:

- Dermatofibroma
- Vascular lesions (sclerosing hemangioma, angiokeratoma, venous lake)
- Glomus tumor
- Apocrine hydrocystoma
- Pigmented basal cell carcinoma
- Pigmented spindle cell nevus
- Dysplastic nevus
- Primary or metastatic malignant melanoma
- Nevus of Ito, nevus of Ota
- Tattoo reactions

Treatment

Any BN smaller than 1 cm without atypical clinical features does not require excision. On the other hand, a new "blue nevus" in an adult, or a changing blue lesion, or a multinodular or plaque-like lesion warrants excisional biopsy and histological evaluation. For a solitary lesion, simple excision is usually curative. Complete prophylactic excision of cellular BN should be considered due to its malignant potential.

Common BN have been successfully treated with the Q-switched ruby laser. Dermal injection of riboflavin followed by exposure to near-ultraviolet/visible radiation (ribophototherapy) has been tried in BN recalcitrant to laser therapy.

Incomplete excision of a BN may be followed by recurrence. The latter is manifested by satellite lesions around the original excision site that are difficult to distinguish from malignant BN (malignant melanoma mimicking a benign melanocytic lesion).

Dysplastic Melanocytic Nevus

Definition and Epidemiology

Dysplastic melanocytic nevus (DMN) is an acquired melanocytic lesion with atypical clinical and histological features, compared to common acquired melanocytic nevi (CAMN). Clinical and histologic definitions for DMN are controversial and still evolving. The terms atypical moles and dysplastic nevi continue to be used interchangeably, regardless of clinical or histologic appearance. DMN occupies an intermediate position in the disease spectrum ranging from CAMN to malignant melanoma. The atypical mole and melanoma syndrome is defined as the presence of a large number (>50) of melanocytic nevi, some of which have atypical features. It is classified into familial atypical mole and melanoma (FAMM) syndrome and sporadic, depending on the presence or not of family history (one or more first degree relatives) of CMM.

The prevalence of DMN has been reported to be 5 % in the general white population in the USA and 5–10 % in Australia and New Zealand. DMN are found in 1.8–18.0 % of various populations. DMN are present in almost all patients with familial CMM and in 30–50 % of patients with sporadic CMM. The white race is predominantly affected, especially persons of northern European background (Celtic) with light-colored hair and freckles. DMN are rare in black, Asian, or Middle Eastern populations. There are no sex differences. Most DMN, especially those familial, appear during childhood and adolescence, sometimes by crises. Sporadic lesions may appear at any time in life (as late as the sixth decade). Atypical moles may also change or regress throughout adulthood. New or changing pigmented nevi are not uncommon in adults, but new or changing nevi in patients older than 50 years are more likely to be melanoma.

DMN is considered a potential precursor of CMM and a marker of persons at high risk for CMM. While most melanomas arise de novo, superficial spreading melanoma may arise from atypical moles. Patients with familial or sporadic atypical mole syndrome are at increased risk for CMM. Anatomical association with DMN has been observed in 8–36 % of patients with sporadic CMM, in about 70 % of patients with familial CMM and in >90 % of persons with familial atypical mole and melanoma syndrome. Among whites in the USA, the lifetime risk of developing CMM is approximately 0.6 %, or 1 in 150 individuals. In patients with DMN, the risk for CMM is significantly increased reaching 6 % or 10–15 %, when family history of CMM is present or not, respectively. For patients with FAMM, the overall lifetime risk of melanoma has been estimated to be 100 %. CMM risk increases with: increasing number of DMN, increasing atypia, and family history of DMN or CMM. CMM in DMN patients may arise either de novo (on normal skin) or within preexisting DMN, more often during the fourth decade of life.

Basic Concepts of Pathogenesis

Atypical moles can be inherited or sporadic. For familial DMN, an autosomal dominant mode of inheritance with fairly high penetrance has been recognized. A polygenic aetiology has been suggested. Germline mutations in three genes, *CDK2NA* and *CDK4*, mapped to 9p21 and 12q14, and *CMM1*, mapped to 1p, have been linked to a subset of hereditary melanomas and FAMM syndrome. In addition, somatic mutations in *PTEN*, *BRAF*, and *MCR1* (melanocortin-1 receptor) have been associated with melanoma. Other genomic events such as loss of heterozygosity

(LOH) for tumor suppressor genes are also responsible for the progression from atypical nevi to melanoma. Sun exposure, especially a pattern of acute and intermittent exposures, is considered as a precipitating factor for DMN development. However, DMN may occur in completely covered areas of the body. Ultraviolet light (UV-A and UV-B) has been proposed as both an initiator and a promoter in the transformation of melanocytes into atypical melanocytes or melanoma. A meta-analysis concluded that use of UV tanning beds before age 30 years increases the risk of melanoma by 75 %. Immunosuppression provides a favorable setting for DMN progression to malignancy. Endocrine, dietary, and environmental factors may also play a part.

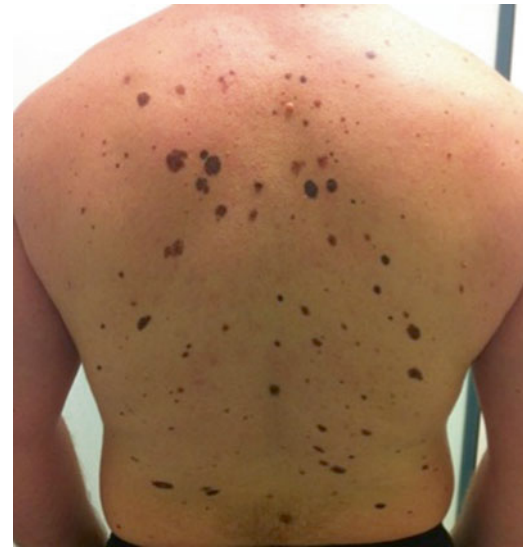


Fig. 65.8 Atypical mole syndrome (AMS). A patient with sporadic atypical mole syndrome manifested by >20 dysplastic nevi and numerous common nevi

Clinical Presentation

Clinically, DMN are characterized by:

- Macular lesion with papular components.
- Asymmetry.
- Greatest diameter larger than CAMN, usually ranging between 5 and 15 mm.
- Irregular and ill-defined border.
- Flat, pebbled, or cobblestone surface with accentuation of skin markings by side-lighting.
- Irregular pigmentation pattern, including shades of brown, tan, flesh, pink, and brown black.
- Erythema may be present within or around the lesion (halo).
- Round, oval, or ellipsoid shape.
- Solitary or, more often, multiple, randomly dispersed lesions, usually one to ten in sporadic cases and up to hundreds, especially in familial cases (FAMM).
- Distribution: anywhere on the body, both exposed and covered areas. Most often occur on trunk (back, chest, breasts), arms, legs, dorsa of the hands and feet, buttocks, and scalp. Mucosae may be involved.
- No symptoms are present.

Unusual clinical subtypes include: fried egg compound DMN, bull's eye or targetoid variant, lentigo-like or seborrhoeic keratosis-like, erythematous, and simulant of melanoma variant.

Atypical moles may arise anytime during a patient's lifetime. Although most lesions remain stable or evolve into benign dermal MN, some may change over time, or new lesions may develop. DMN is one of the most important precursor lesions of CMM (Fig. 65.8).

Diagnosis

Clinical diagnosis may be assisted by dermoscopy. Imaging studies are not necessary. Differentiating atypical nevus from melanoma in situ and early invasive melanoma needs skills and experience. It is one of the most important and difficult tasks of dermoscopy.

According to their global dermoscopic pattern, DMN are classified into three types: reticular, globular, and homogeneous. Frequently a combination of two of these patterns can be observed. If all three patterns are present, a special attention is required because a multicomponent pattern is frequently found in early melanoma. The reticular type is the most common, and it is characterized by typical pigment

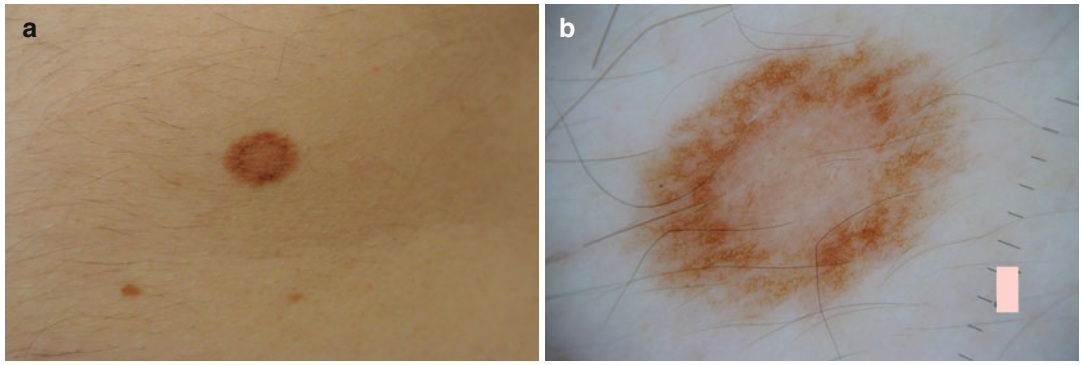


Fig. 65.9 Dysplastic nevus. (**a**, **b**) Dysplastic nevus with central hypopigmentation ("fried egg")

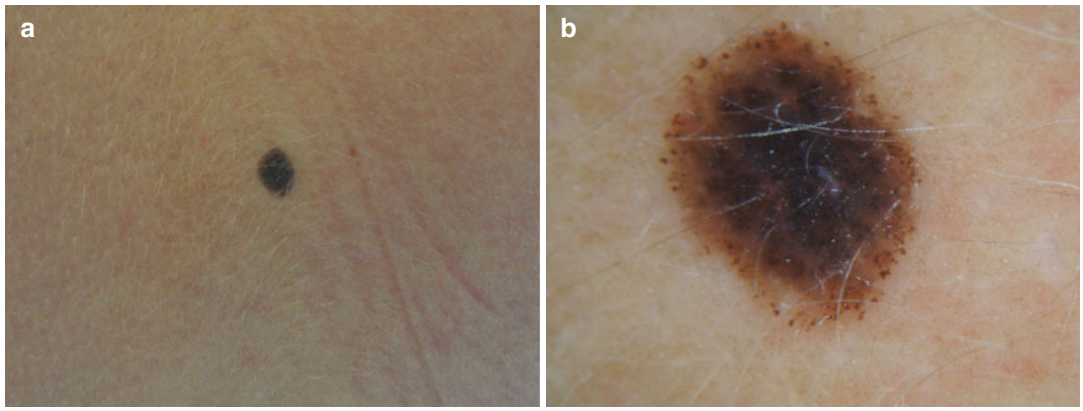


Fig. 65.10 Dysplastic nevus. (**a**, **b**) A growing dysplastic nevus with a homogeneously pigmented *dark brown* center and a peripheral rim of regular *brown* globules

network evenly distributed that fades in the periphery and possibly by atypical network. The globular type consists of numerous globules and dots of variable size and shape. The less frequent, homogeneous type exhibits a diffuse brown pigmentation with isolated reticular or globular areas. There are no specific local dermoscopic features. Additional local criteria include atypical network, streaks, blue-white structures, regression, and blotch. The vascular patterns commonly seen are comma or dotted vessels.

Based on variations in pigmentation, four dermoscopic subtypes can be distinguished: DMN with central hyperpigmentation (black nevus), DMN with central hypopigmentation ("fried egg" nevus), DMN with multifocal hyper-/hypopigmentation, and DMN with eccentric hyperpigmentation (of uppermost importance because this presentation overlaps with early melanoma) (Figs. 65.9, 65.10 and 65.11).

Histological examination is the gold standard to confirm diagnosis. Typical histopathologic features, which are superimposed on those of a typical junctional or compound nevus, include:

- An increased number of single melanocytes along the basal layer, with elongation of rete ridges.
- Extension of the junctional component beyond the last dermal nest to produce "shoulders."
- Cytologic atypia of melanocytes, usually confined to the shoulder region, with enlarged, hyperchromatic nuclei in the junctional component. Diffuse atypia is more worrisome.
- A horizontal arrangement of melanocytes that vary in shape from round to spindled.

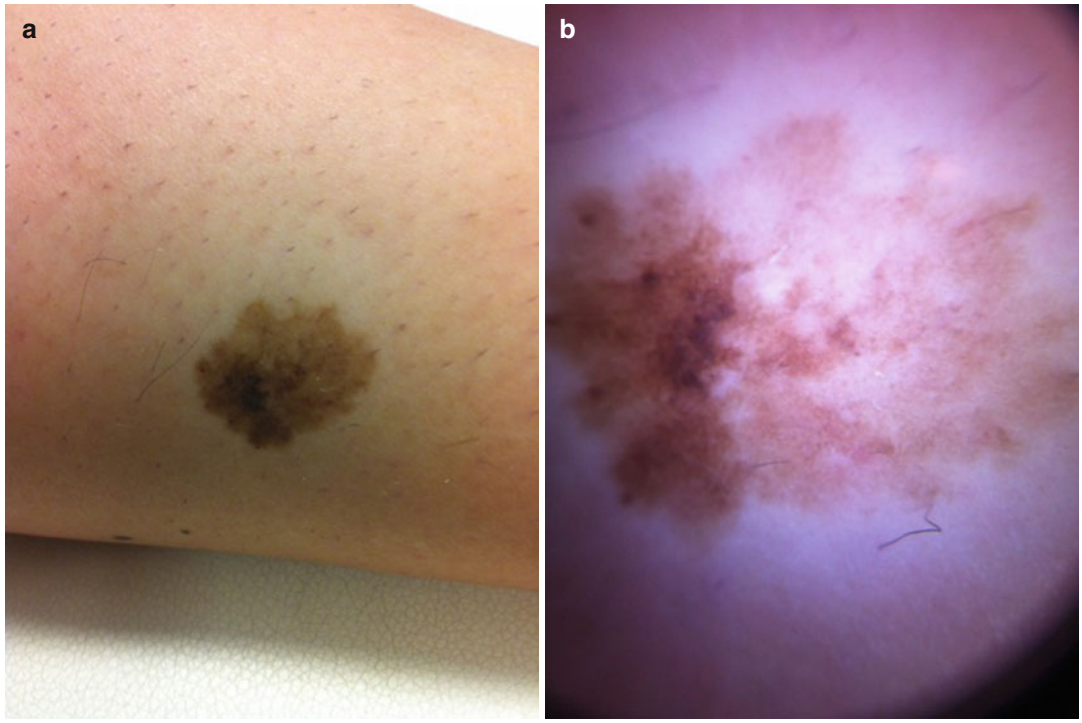


Fig. 65.11 Dysplastic nevus. (**a**, **b**) A dysplastic nevus appearing as an asymmetric multicolored patch with eccentric hypopigmentation and extensive regression. The differentiation from superficial spreading melanoma can be made only by histology

- A tendency for melanocytes to aggregate into variably sized nests, which fuse with adjacent rete ridges to produce bridging.
- Presence of lamellar and concentric dermal fibroplasia.
- Presence of a lymphocytic infiltrate (patchy or diffuse) in the superficial dermis.

It must be noted that some clinical atypical moles are normal histologically.

Differential Diagnosis

DMN must be differentiated from:
Melanocytic lesions:

- Common acquired nevi
- Small congenital MN
- Pigmented spindle cell nevus
- Nevus spilus
- Spitz nevus
- Blue nevus
- Solar lentigo
- Melanoma in situ and CMM (greater asymmetry, irregular margins with prominent notching, striking variations of color, including shades of red, gray, white, and blue black).

Non-melanocytic lesions:

- Pigmented actinic keratosis
- Seborrhoeic keratosis
- Solar lentigines
- Dermatofibroma
- Pigmented basal cell carcinoma

Treatment

Management depends on the number of DMN, history of CMM, and family history of DMN or CMM.

Patients with multiple DMN should be followed up periodically for life. Evaluation should include (a) total skin surface examination, (b) baseline and serial clinical color photography, (c) body charts that are

periodically updated, and (d) digital dermoscopic follow-up (mole mapping). Patients should be warned of the potential hazards of sun exposure and should be educated in methods of protecting themselves and their children. Sun avoidance and use of sunscreens of sun protective factor 30 or greater should be encouraged. Sunbathing and tanning parlors must be avoided. Blood relatives should also be examined for DMN and CMM and should be followed up regularly as well.

Clinically atypical nevi do not require excision as a routine procedure. Patients with few lesions must be followed up yearly or every 6 months if there is a family history of CMM. Patients with numerous lesions should be followed up every 6 months or every 3 months if there is personal or family history of CMM.

Recommended Therapies

As most melanomas develop de novo and because the risk for malignant transformation of any one atypical nevus is low, prophylactic removal of all atypical moles is not recommended. Lesions that require excision include:

- All lesions suspicious for CMM
- Changing lesions, i.e., increasing in size or changing in pigmentation, in shape, and/or in border
- Lesions that cannot be easily followed by self-examination (scalp, genitalia, upper back) or if the patient is unreliable for follow-up
- Lesions at special locations, such as palms, soles, or nail bed
- Based on dermoscopic criteria, lesions with multicomponent pattern or eccentric hyperpigmentation or atypical network

Complete surgical excision with narrow margin is the treatment of choice. Initial margins of 5 mm are sufficient. If the lesion is atypical or present in margins, excision with clear margins is necessary. If severe atypia is present, re-excision with 5–10-mm margins is recommended. Histological examination, preferably by specialists, to document diagnosis and to exclude malignancy, should always follow. If the suspicious mole is too large or is located in a cosmetically significant or functionally sensitive site, one or more incisional biopsies guided by dermoscopy may be considered. A wider excision may be indicated after histological examination.

Lasers, electrosurgery, cryotherapy, or other modalities resulting in physical destruction of the lesion should be avoided, because they do not permit histopathological examination of the lesion.

Management of Melanocytic Nevi at a Glance

Melanocytic nevi are benign lesions that only rarely require prophylactic excision. Unfortunately, as the golden standard for the diagnosis is histopathology, it is impossible to have a definite diagnosis for the enormous number of pigmented lesions under consideration during clinical practice. Therefore, it is of paramount importance to develop methods and practices for the in vivo evaluation of pigmented skin lesions. Clinical and dermoscopic examination and follow-up of melanocytic nevi is synonymous to the secondary prevention (early diagnosis) of malignant melanoma. When evaluating a pigmented lesion, the management decision may be excision, follow-up, or no action. When the clinical suspicion for a benign melanocytic lesion is verified by dermoscopy, no further action should be taken. Only for large or giant congenital melanocytic nevi (whenever possible) and Spitz nevi a prophylactic excision is warranted. When the clinical diagnosis does not coincide with the dermoscopic diagnosis; the lesion shows atypical features; there are some melanoma-specific dermoscopic criteria present (but not enough to establish a dermoscopic diagnosis of melanoma); a deviation in the natural history is noted; we are dealing with a new and/or changing lesion or a lesion that differs from the rest of the pigmented lesions of the same patient (“ugly duckling”), especially in high-risk patients; or the diagnosis is completely in doubt, excisional or incisional biopsy or short-term follow-up (3 months) should be considered. Nodular doubtful lesions should never be followed up. Single doubtful lesion should better be excised. Multiple suspicious lesions should be followed up by digital dermoscopy, either short term or long term.

On short-term digital follow-up (3 months), any dermoscopic change warrants excision. On long-term follow-up (6 months), lesions with substantial dermoscopic changes require excision. All persons should have a total skin examination yearly. Mole mapping with total body photography and digital dermoscopy should be reserved for high-risk individuals for melanoma development, i.e.:

- Personal or family history of melanoma
- Multiple dysplastic nevi or dysplastic nevus syndrome
- Large number of nevi, fair skin, light eye and hair color, and freckles
- History of sunburns in childhood and adolescence
- Excessive sun exposure and sun bed use
- Genetic syndromes (xeroderma pigmentosum, Gorlin syndrome, alphism)

In these persons clinical and dermoscopic examination should be performed every 3–6 months.

Future Perspectives

During the last decade, there have been many efforts to develop accurate and reliable techniques for the in vivo assessment of skin tumors in the context of early diagnosis of malignant melanoma. Most of these techniques are still under development. Most importantly, they are still very expensive and not user friendly. These diagnostic techniques include:

- Reflectance confocal microscopy
- Multispectral image analysis
- Optical coherence tomography
- High-resolution ultrasounds
- Magnetic resonance imaging
- Measurement of tumor oxygen status
- Raman spectroscopy
- Electrical impedance scanning

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Necrobiosis Lipoidica

66

Istvan Juhasz

Abbreviations

DM Diabetes mellitus
NBL Necrobiosis lipoidica

Key Points

- Necrobiosis lipoidica is of unknown etiology.
- It has a higher prevalence in diabetic patients, but the association between NBL and diabetes is debated.
- Microangiopathy and tissue hypoxia may play a leading role in the pathogenesis; ulceration and infection may contribute to persistence.
- Treatment is difficult, often resulting only in partial response and frequent relapses. Topically applied steroids or calcineurin inhibitors in combination with compression serve as baseline therapy, while various forms of phototherapy come as second line.
- New approaches emerge, such as photodynamic therapy and fractional laser therapy, local fumaric acid ester, intravenous immunoglobulin, and systemic targeted therapy with biologicals, but their effectiveness needs to be further evaluated.

Definition and Epidemiology

NBL presents as a mostly solitary, but not uncommonly multiple, chronic granulomatous infiltrative lesion of unknown etiology in the dermis of predominantly female patients. It has a higher prevalence in diabetic patients, but the association between NBL and DM is debated.

Basic Concepts of Pathogenesis

The most accepted theory attributes vascular changes often seen in NBL to microangiopathy due to proteoglycan deposition in vessel walls. This can be present in latent DM as well. Lower partial O_2 tension detected with laser Doppler imaging suggests hypoxia playing a role in the pathogenesis. Detection of spirochaetal microorganisms in lesional skin of NBL patients suggests an infectious etiology analogous to the evolution of morphea plaques (Eisendle et al. 2008). Familial cases both with and without

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_66, © Springer-Verlag Berlin Heidelberg 2015

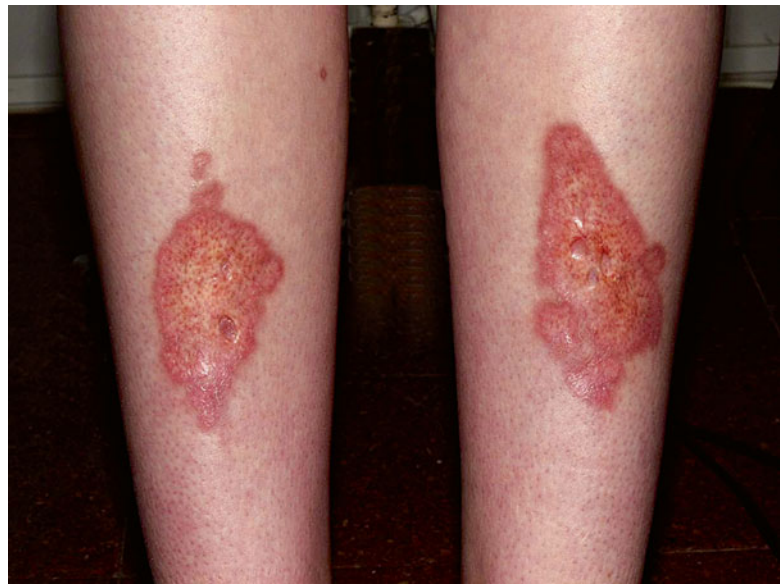

Fig. 66.1 Typical clinical presentation of necrobiosis lipoidica (NBL) with multiple infiltrated telangiectatic, opaque whitish plaques under shiny atrophic epithelium on both lower legs of a 52-year-old female patient

diabetes have been reported extensively drawing an attention to possible genetic predisposition. However, the comparison of HLA antigens between insulin-dependent diabetics with and without necrobiosis lipoidica revealed no significant differences (Soler and McConnachie 1983). Increased expression of the glioma-associated oncogene homologue (gli-1 oncogene) was found in necrobiosis lipoidica diabeticorum and other granulomatous skin disorders, like sarcoidosis (Macaron et al. 2005).

Clinical Presentation

Appearance of mostly single but sometimes multiple lesions with a predilection for the lower extremities of patients is typical for NBL (Fig. 66.1). Initially asymptomatic circumscribed papules are present, which may coalesce into yellowish-red waxy plaques with violaceous border (Fig. 66.2). These lesions are painless due to associated nerve damage. If painful, it is in most cases associated with ulceration which has a poor tendency to heal. The diagnosis of NBL can be set up in most cases based on the clinical picture, and in doubtful instances, biopsy is performed for histopathological examination. There are reports of carcinomatous transformation of NBL; these are most likely consequences of the premalignant status of the chronic ulceration itself.

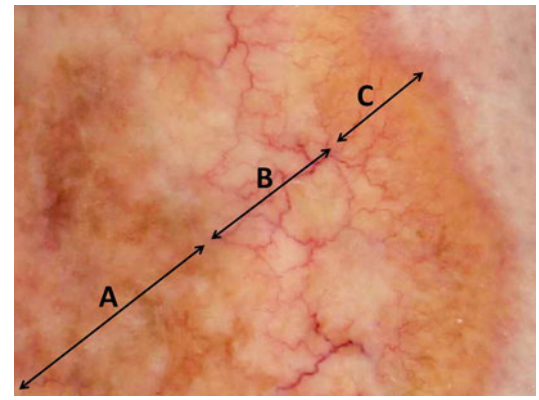

Fig. 66.2 Close-up photography of a NBL lesion showing its typical concentric (iris) structure (from *left* to *right*): *A* oldest sclerotic, slightly hyperpigmented portion, *B* intermediate atrophic part with dilated capillaries, and *C* infiltrated zone with peripheral interstitial inflammation

The association of NBL and diabetes is currently debated. There are reports on incidence of DM among NBL patients as high as 65 % and as low as 16 %. Incidence of NBL among diabetics is reported as 0.3 %, so this rather low association underlines the importance of possible other susceptibility factors in disease development. Proper determination of the association with comorbidities requires further prospective studies on large cohorts.

Differential Diagnosis

The sine qua non lesion for NBL is the waxy infiltrative plaque or plaques consisting of discolored dermis under atrophic epithelium. Granulomatous conditions, such as sarcoidosis, necrobiotic xanthogranuloma, and granuloma annulare (GA), are clinically similar lesions; therefore they need to be differentiated. These all may present with opaque discoloration, central atrophy, and telangiectasias. The dermatoscopy picture of NBL is characteristic with sharply focused, elongated serpentine telangiectasias typically located over a whitish, structureless background. This structure is different from GA and from other forms of granulomatous diseases. Histologically degenerated collagen is present in the dermis with an infiltrate of various inflammatory cells, lymphocytes, plasma cells, and histiocytes, together with multinucleated giant cells (Fig. 66.3). The most severe inflammatory signs are present in the lower part of the dermis and in the subcutis. Palisade-oriented inflammatory cells often form granulomas. Important differentiation item is the sclerotic transformation of the reticular dermis in NBL that is not seen in GA. On the contrary, deposits of acidic mucosubstances that cause bundles of collagen to separate in GA are not present in similar foci of palisaded histiocytes and degenerated collagen in NBL.

General Principles of Treatment

As with ailments that are difficult to treat, numerous therapeutic approaches have been applied, but none of them can be considered as gold standard. Avoidance of trauma to prevent ulceration of the lesion is an important factor, often requiring changes in previous lifestyle of individuals with NBL. Koebner phenomenon is frequently reported; therefore, surgical approaches are of limited importance. Dermal replacement is an interesting new approach whose practical value needs to be determined in the clinical setting.

Topical Treatments

Topically applied steroids as potent anti-inflammatory agents, usually in combination with compression therapy, are used most frequently, followed by topical calcineurin inhibitors. The rationale for the use of the latter might be their potential to inhibit gli-1 signaling besides

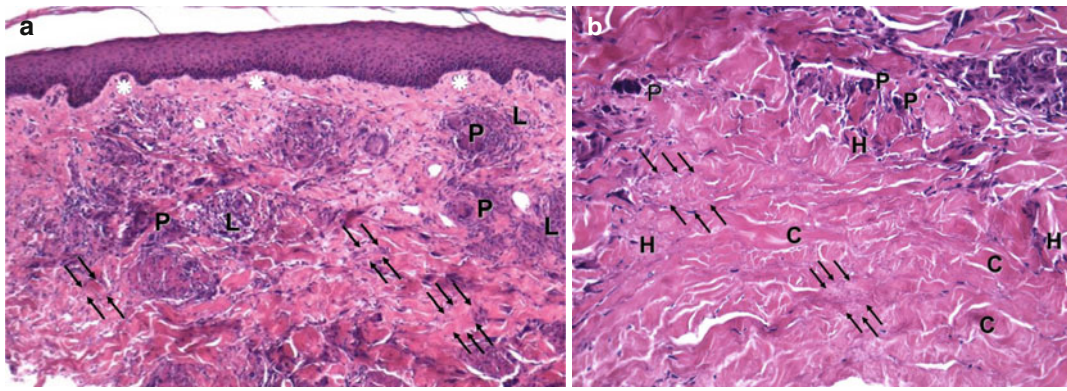

Fig. 66.3 (**a**) Cross-section of lesional skin at 100× magnification, H+E stain. Presence of relatively conserved epithelium with shallow rete ridges (*asterisk*). The dermis contains numerous foci of necrobiotic collagen (*arrows*) surrounded by granulomatous reaction. Marked perivascular focal lymphocytic infiltration is seen (*L*) with multinucleated giant cells (*P*). These initial changes mark the whole width of the dermis. (**b**) Deep layer of lesional skin at 200× magnification, H+E stain. The lower reticular dermal portion is loaded with cell-free degenerated collagen (*C*). The cellular components of the infiltrate are mainly lymphocytes (perivascular orientation), scattered with histiocytes (*H*) and polynucleated giant cells (*P*)

providing some sparing of the side effect profile of steroids. Diverse forms of phototherapy, mostly PUVA or high-dose UVA, emerge as second-line therapy. Popularity of photodynamic therapy and fractional laser therapy are increasing, although standardized guidelines are missing. Experimental use of local therapies such as fumaric acid esters or human recombinant platelet-derived growth factor (PDGF, becaplermin) needs to be further evaluated. Negative pressure wound therapy is an effective treatment option for slow-healing wounds, and it has shown benefit for the closure of ulcerative NBL lesions as well.

Systemic Treatments and Future Perspectives

Many systemic agents that are believed to influence metabolism, microcirculation, or inflammation of diseased tissues have been tried, resulting mostly in partial improvement or even occasional worsening (for review, see Reid et al.). Most therapeutic suggestions are based on reports of cases or small patient series however. Pentoxifylline with its anti-inflammatory, immunomodulatory, and positive rheological effects is a strong candidate for systemic treatment of NBL. There is also rationale for administration of aspirin alone or in combination, although it was tested as being ineffective in an early RCT. Treatment with immunosuppressants, such as cyclosporine or mycophenolate mofetil, results in temporary improvement with early relapse after cessation of therapy, but also long-term effectiveness is reported. Thiazolidinediones, a new class of oral antidiabetic drugs, act as potent agonists for peroxisome proliferator-activated receptor gamma (PPAR gamma), an important mediator of differentiation of adipocytes and lipid storage in adipose tissue. This therapy is reported to improve NBL in diabetics, most probably by its anti-TNF-α (alpha) effect. Marked improvement of lesions was also reported after administration of colchicine and antimalarial agents. Intravenous immunoglobulin (IVIG) therapy, possibly due to its immunoregulatory effect, has also been applied successfully. Resistance of the disease to conventional therapeutic approaches and the initial encouraging therapeutic success with anti-inflammatory biological therapies may justify the off-label use of this kind of therapy for NBL. Successful use of anti-TNF-α (alpha) therapy was reported with adalimumab, etanercept, and infliximab. Most of the publications describe the action as limited or temporary and suggest some form of maintenance therapy. None of the previously listed systemic agents have established protocols for optimal dose and duration of treatment. These therapeutic options should be assessed for efficacy and safety in the future preferably by randomized and controlled trials.

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Nummular Eczema

67

Antonia Todorova, Harald Bruckbauer, and Johannes Ring

Key Points

- Nummular eczema is a noninfectious inflammatory dermatosis, characterized by severe pruritus and well-demarcated coin-shaped lesions.
- Aggravating factors as atopy, contact allergy, skin dryness, staphylococcal superinfection, dental infectious foci, viral infections, venous stasis, impaired liver function, and systemic medication may trigger the onset or a relapse of disease.
- Treatment is based on elimination of trigger factors in combination with topical and systemic anti-inflammatory and antimicrobial therapy.
- Topical treatment is performed according to stage of disease. Therapy of first choice during the acute stage (vesicles, erosion, exudation) is topical – rarely also systemic – corticosteroids in combination with desiccating, antiseptic solutions and wet bandages. In subacute and chronic eczema, topical corticosteroids as pastes and calcineurin inhibitors are recommended.
- Combination with phototherapy can be useful in disseminated or relapsing eczema.
- Systemic antimicrobial and anti-inflammatory therapy (antibiotics, corticosteroids) is indicated in severe cases or recurrent refractory eczema.
- Systemic antimicrobial treatment should be performed upon microbiological cultures with broad-spectrum antibiotics, effective against specific bacteria (*Staph. aureus*).
- Systemic corticosteroids are applied over 5–7 days in tapering dose.
- In single cases immunosuppressive therapy with other agents (ciclosporin, methotrexate) may be necessary to achieve remission.

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Definition and Epidemiology

Nummular eczema is characterized through a chronic noninfectious inflammation of the epidermis and dermis and single or multiple

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_67, © Springer-Verlag Berlin Heidelberg 2015

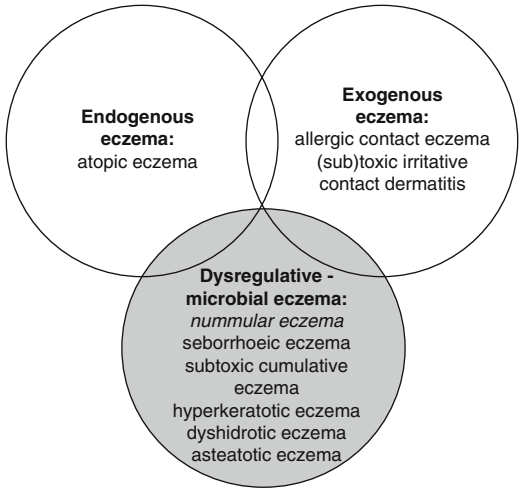

Fig. 67.1 Classification of eczema into three main groups (according to Hornstein)

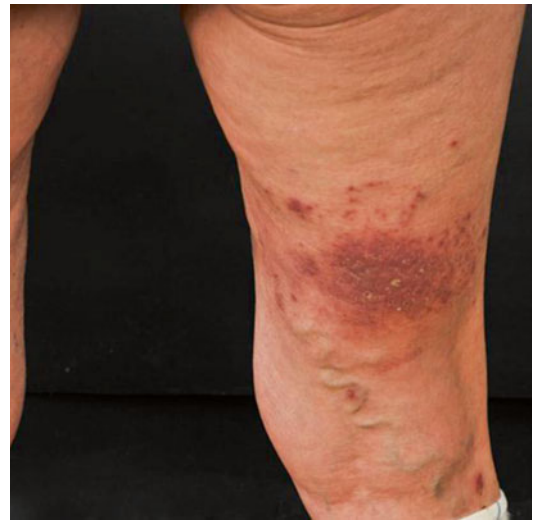

Fig. 67.2 Nummular eczema and varicosis

coin-shaped, well-demarcated lesions. It undergoes the common eczema stages: initial stage with erythematous plaques and papules, alteration of the papules into itching and oozing vesicles, crust formation, and eventually healing.

Histological characteristics of nummular eczema are spongiosis, acanthosis, and parakeratosis with lymphocytic infiltration.

Hornstein's classification (Fig. 67.1) reveals three basic eczema groups: endogenous, exogenous, and dysregulative-microbial eczema with its subtype nummular eczema.

Epidemiological data indicate higher incidence of nummular eczema in male patients between 50 and 70 years; however single studies refer to female gender predominance (Jiamton et al. 2012).

Basic Concepts of Pathogenesis

The pathophysiology of nummular eczema has not been fully cleared yet. Multifactorial trigger in combination with epidermal barrier dysregulation is assumed to play a major role in the onset and maintenance of the disease. Among the common aggravation factors are atopy and dry skin. Recent studies report up to 50 % atopy in patients with nummular eczema. Contact sensitization to common allergens like metals, fragrance, rubber, and preservatives, but also sensitizations to bacterial antigens (*Staphylococcus spp*.) with subsequent T cell activation have been described as probable trigger. Bacterial (dental infections, sinusitis, tonsillitis, bronchitis, prostatitis) or viral infections (hepatitis) can represent an internal chronic activator of inflammation. Several case reports point out coincidence of nummular eczema and venous stasis (Fig. 67.2). Onset or exacerbation of eczema has been reported under medical treatment with gold preparations, isotretinoin, or antiviral combinations (ribavirin, interferon, telaprevir). Emotional stress, liver dysfunction, or extensive alcohol consumption had also been discussed to have negative impact on the course of disease. Recent study reports elevated tryptase in children with nummular eczema in absence of mastocytosis or atopic eczema.

As nummular eczema is a chronic disease, many authors relate to the significant impairment of quality of life in affected individuals.

Clinical Presentation

Common affected areas are the distal limbs (lower extremities > upper extremities; Figs. 67.2, 67.4 and 67.5).

In severe cases dissemination onto trunk, face, and neck can be found. Some authors suggest an

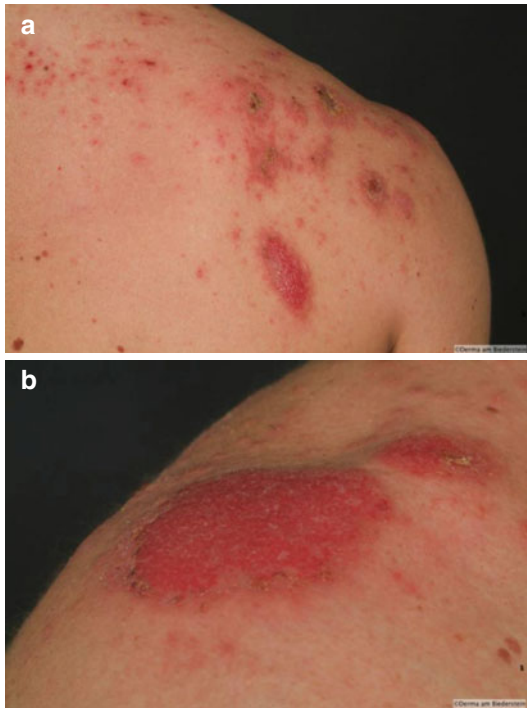

Fig. 67.3 Nummular lesion in acute stage. (**a**) Widespread eczema; (**b**) detailed image

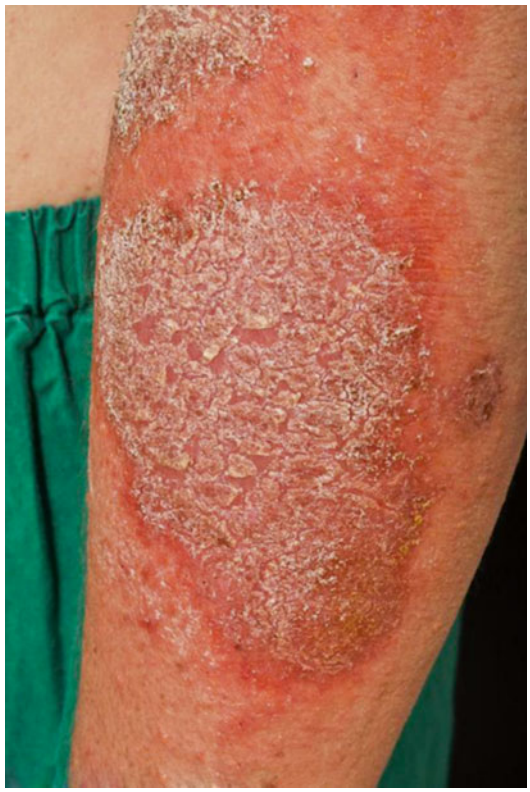

Fig. 67.4 Nummular eczema in chronic stage

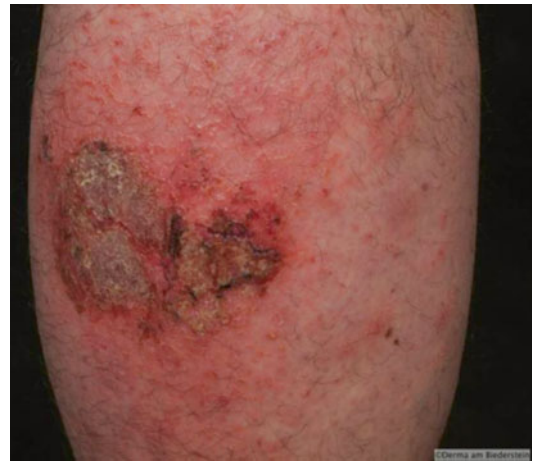

Fig. 67.5 Nummular eczema: well-demarcated lesion and skin exsiccation

association between the eczema location and an underlying xerosis cutis.

Based on the clinical appearance and duration of disease, nummular eczema can be classified as acute or subacute/chronic. During the acute phase occur erythematous plaques with diameter of 1–5 cm and distinct edges. Shortly upon onset papules, papulovesicles and vesicles develop on the surface of the plaques. Severe pruritus is characteristic for this stage. After the vesicles once erode (Fig. 67.3a and b), oozing, crusting, and scaling follow (Fig. 67.5).

Diagnosis

The diagnosis of nummular eczema is based on the typical clinical features of coin-shaped eczema with sharp demarcated edges and severe pruritus. To rule out differential diagnoses, a detailed history has to be taken. There are no specific laboratory markers available for nummular eczema. In some cases, trigger factors such as infection, atopy, and allergic contact sensitization can be determined.

Blood Tests

Blood tests are performed to detect underlying infectious diseases, atopy or allergies (Table 67.1).

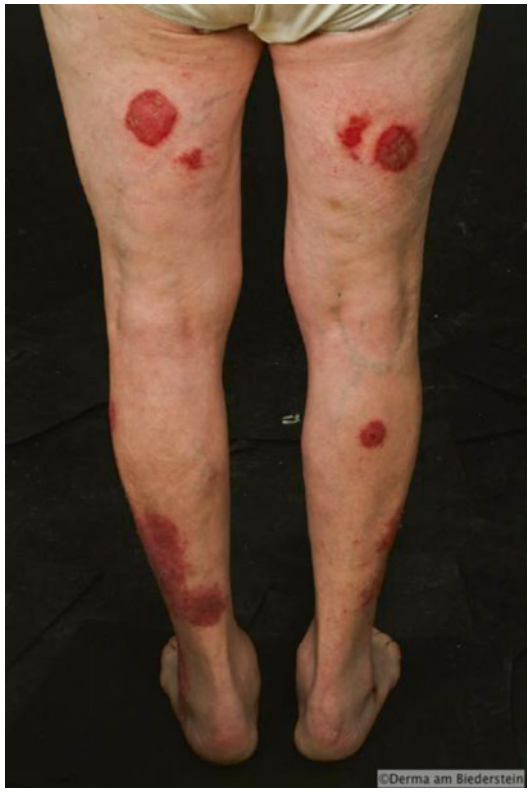

Fig. 67.6 Nummular eczema under topical treatment

Table 67.1 Laboratory markers of underlying diseases

Blood test	Indication
Markers for bacterial infections	
• Leukocytosis	Bacterial infections
• Elevated erythrocyte sedimentation rate (ESR)	Bacterial infections
• Elevated anti-staphylolysin antibodies (ASTA)	Staphylococcal infections
• Elevated anti-streptolysin antibodies (ASO)	Streptococcal infections
• ReactiveTreponema-pallidum-Particle-Agglutination (TPPA) test	Syphilis
Markers for viral infections	
• Lymphopenia	Viral infection
• Monocytosis	Viral infection
• Hepatitis, HIV serology	Hepatitis A/B/C, HIV
Allergy diagnostics	
• Total-IgE, RAST, Prick test	Atopy/atopic eczema
• Patch test	Contact allergy

Histopathology

Skin biopsy from affected area shows acanthosis, hyperkeratosis (orthokeratosis and parakeratosis), and spongiosis with diffuse lymphocytic infiltration, eosinophils, and neutrophils. Spongiosis with vesiculation may be found in the early stages. Periodic acid–Schiff (PAS) stain is performed to rule out tinea infection.

Bacteriological Swabs

In cases of a superinfection, bacteriological swabs from the lesions can be useful to determine affecting bacteria and resistance spectrum.

Mycological Culture

Scales from affected area should be cultured to exclude tinea corporis.

Differential Diagnosis

Common relevant differential diagnoses are listed in Table 67.2.

Table 67.2 Differential diagnoses of nummular eczema

Name of disease	Clinical features
Psoriasis with nummular pattern	Family history of disease, no vesicles, no/discrete pruritus
Parapsoriasis	No vesicles, typical distribution pattern in Langer's lines
Atopic eczema with nummular pattern	Susceptibility for atopic diseases, manifestation in childhood, chronic eczema (lichenification)
Prurigo with nummular lesions	Prurigo nodules
Sulzberger–Garbe exudative discoid and lichenoid chronic dermatosis	Polymorph clinical appearance, diffuse, nummular and lichenoid pattern of lesions, genital affection (penis, scrotum)
Allergic contact eczema	Distinct trigger +/– positive patch test
Tinea corporis	Positive direct detection or culture, pets
Impetigo contagiosa	Positive bacterial analysis for streptococci or staphylococci, contagious
Leprosy	No pruritus, dysesthesia
Mycosis fungoides	Persisting lesions in same location, no vesicles, different histology

Table 67.3 Stage adequate treatment of nummular eczema

Clinical stage	Clinical characteristics	Treatment	General measures
Acute nummular eczema	Vesicles, exudation, erosion, crusts	In severe and extended cases: systemic therapy with steroids (0.5–1.0 mg/kg prednisone) for about one week in tapering dose	Treatment of underlying disease Antipruritic therapy with antihistamines Psychosomatic counselling Avoid worsening factors
		In super infected eczema: systemic antibiotic therapy (e.g., cephalosporins)	
		Topical exsiccating, antiseptic and anti-inflammatory treatment: dyes (Sol. pyocatnini, Sol. castellani), glucocorticoid cream (O/W) in combination with wet dressings (clioquinol or KMnO solutions)	
Subacute nummular eczema	Erythema, edema, papules, Seropapules, scales	Mild exsiccation: dyes, glucocorticoid cream (O/W) with wet dressing, zinc oil, soft paste, lotion (powder in water) on nonexudative lesions	
Chronic nummular eczema	Dry scaling, psoriasiform scaling, lichenification papules	Glucocorticoid cream or ointment, Occlusive soft paste lipophilic ointment, Tars (Ichthyol- tumenol-LCD – Pix lithanthracis) 3–5 % in soft paste or ointment	Ultraviolet B phototherapy Oil bath
	Hyperkeratotic lesions	Keratolytic ointments (urea 10 % or salicylic acid 5 %)	

General Principles of Treatment

Causative and symptomatic treatment should be performed according to clinical manifestations (stage of disease) (Table 67.3).

Triggering factors as infections, dry skin, and contact with sensitizing substances need to be eliminated and avoided. Venous stasis should be treated. Medications, considered as trigger, should be withdrawn or substituted.

In patients with xerosis cutis, sufficient basis therapy is essential. In case of systemic infections, causative systemic antibiotic or antiviral therapy has to be applied. Symptomatic treatment is based on anti-inflammatory, anti-eczematous, and immunomodulation approaches.

Topical corticosteroids (TCS) with diverse potency and formulation have been established as first-line therapy in every stage of disease. Immunosuppressive and immunomodulatory therapy with topical calcineurin inhibitors (TCI) can be applied for long-term treatment with similar anti-inflammatory efficacy. Combination therapies as TCS with antiseptics and astringents (for acute stadium) or with keratolytic ointments (chronic eczema) have shown good outcome.

In disseminated lesions, UV phototherapy (UVA and UVB) is used along with topical corticosteroids or tar preparations for its anti-inflammatory, immunosuppressive, and antipruritic effect.

In severe and resistant cases, systemic corticosteroid treatment in combination with antibiotics should be applied.

In severe pruritus, systemic antipruritic treatment with antihistamines is recommended; however the efficacy in patients with nummular eczema can be limited.

Psychosomatic counseling, relaxation techniques, or acupuncture can be beneficial as supportive approaches to minimize emotional stress.

Topical Treatments

Topical Corticosteroids (TCS)

Topical corticosteroids are used in the treatment of eczema lesions for their anti-inflammatory and immunosuppressive effects. According to their potency, there are four groups of TCS (group I: low potency to group IV: very potent), although

clinical effect can depend on formulation, duration of treatment, extent of the treated area, and stage of disease. Mostly once daily application is recommended.

In acute eczema corticoid cream (O/W) in combination with topical antiseptics and astringent dyes ensures faster exsiccation. In severe cases wet dressings applied over the treated area increase the penetration of the active agents and thereby contribute to accelerate healing. Limited treatment duration has to be considered with this approach, due to higher rate of side effects and possibility of systemic resorption of the corticosteroids.

Lipophilic corticosteroid ointments and creams are appropriate in chronic eczema for higher penetration.

In short-term treatment regiments, TCS have low rate of side effects. Most common are skin atrophy, hypertrichosis, and steroid acne or acute contact dermatitis due to preservative agents. To avoid possible side effects, mild TCS are applied once daily at the beginning of treatment (up to 14 days), potent TCS over 3–5 days with subsequent dose tapering (lower TCS potency or extension of application interval). In stable disease proactive therapy with once/twice weekly application of a low potent TCS can be offered in chronic recidivant cases as relapse prophylaxis.

Topical Calcineurin Inhibitors (TCI)

Tacrolimus (0.03 % and 0.1 %) ointment and pimecrolimus 1 % cream are immunomodulatory agents with suppressive activity on T cells. As an alternative nonsteroid topical treatment, these agents became an essential part of the eczema therapy during the last years. They are mostly applied in mild to moderate eczema and can be used in delicate skin areas such as the face, genital region, and intertrigines. Recent studies have shown that a long-term treatment on a daily basis over several months is well tolerated in children and adults. Most common side effects are burning or itching on the application side; in atopic patients skin infections (herpes simplex, molluscum contagiosum) can occur and have to be treated with temporary discontinuation of the TCI therapy. Sun protection and skin disinfection on the application sites are recommended during use of TCI.

Topical Antiseptics (TAS) and Astringents

Topical antiseptics have antimicrobial effect and help to reduce bacterial contamination in affected areas. Due to the compromised skin barrier in eczema lesions, the use of clioquinol, potassium permanganate (KMnO4), and diverse astringent solutions is recommended (Table 67.4) rather than alcoholic solutions (irritation).

This topical treatment is favored because of its broad antimicrobial spectrum and low risk of bacterial resistance.

Contact dermatitis can develop after sensitization; persistent skin and clothes coloration are seen in contact areas upon application.

Topical Antibiotics (TAB)

Due to the risk of emerging bacterial resistance, the use of topical antibiotics for nummular eczema is not recommended.

Tar Preparations

Tar mixtures cause antimicrobial, antipruritic, and photosensitizing effect. The last finds application in the therapy of chronic resistant eczema in combination with UVB phototherapy. Possible side effects are phototoxicity and long-term high risk of skin cancer. To minimize carcinogenic risk, the use of tar mixtures has been limited over the last years.

Table 67.4 Topical antiseptics and astringents for nummular eczema

Solution %	Coloration
Clioquinol	Yellow
KMnO4 aq. Sol.	Pink
Solutio pyoctanini (Gentian violet aqueous 1 %)	Ink blue
Solutio castellani aq.	Magenta
Eosin aq. solution 1 %	Red

Supportive Approaches and Treatment Regiments

Wet Wrap Dressings

Wet wrap dressing is a technique of topical treatment during the acute stage of eczema with vesicles, erosions, and exudation. Oozing lesions are creamed with corticosteroid cream and dressed with wet bandages for 20 min. This causes enhanced penetration of the cream with more potent effect and faster drying of the vesicles. Dressings can be applied once daily; mostly up to 3 days are sufficient to exsiccate the lesions. Caution is needed because of the higher penetration of corticosteroids with possible systemic side effects.

Proactive Treatment

Use of TCS or TCI in previously affected areas (once/twice weekly) to avoid exacerbation after clinical improvement.

Topical Treatments at a Glance

- *Acute nummular eczema*:
  Exsiccating agents with anti-inflammatory and antiseptic properties
  Wet dressings
  Glucocorticosteroid lotions and solutions in tapering dose
  Topical calcineurin inhibitors in delicate areas and for prolonged treatment
  (Phototherapy)
- *Subacute and chronic eczema*
  Lipophilic TCS ointments in tapering dose
  Topical calcineurin inhibitors
  Keratolysis in hyperkeratotic lesions with salicylic acid 3–5 % or urea 10 %
  Intensive basis therapy (lipophilic lotions and creams)
  Tar preparations in combination with UVB phototherapy
  UVA1 phototherapy

Systemic Treatments

Systemic treatment is indicated in severe cases with disseminated eczema lesions, superinfection, or in relapsing cases.

Systemic Antibiotics (SAB)

As in nummular eczema a sensitization to staphylococcal superantigens has been assumed as a trigger and *Staph. aureus* superinfection is common in eczema lesions, antibiotic treatment is mostly performed with anti-staphylococcal agents (penicillins, cephalosporins, lincosamides).

Beta-lactamase-resistant penicillins are recommended after performing an antibiogram. Possible adverse effects are intolerance reactions like allergic exanthema or urticaria. Another challenge is the increasing bacterial resistance to penicillins.

Cephalosporins and carbapenems are well tolerable and effective treatment alternative. A significant side effect of clindamycin is pseudomembranous colitis. In cases of acute onset of diarrhea, clindamycin should be withdrawn.

Due to the wide spread resistance to tetracyclines and macrolides, these are no longer recommended in the therapy of *Staph. aureus*.

Systemic antibiotic treatment is performed over 5–7 days; in case of an underlying infection (tonsillitis, urethritis, bronchitis), specific antimicrobial therapy is recommended.

Systemic Corticosteroids (SCS)

Systemic corticosteroids are indicated in severe cases of acute eczema with widespread affection of the body and extremities and in chronic recurrent eczema.

Daily administration of 0.5–1.0 mg/kg prednisolone equivalent is recommended for up to 7 days in tapering dose.

Side effects on the skin such as atrophy, telangiectasia, striae distensae, purpura, and hypertrichosis or systemic side effects as Cushing, osteoporosis, and suppression of the pituitary–adrenal-axis occur usually after long-term treatment but have to be reconsidered and monitored.

Contraindications represent severe systemic infections, peptic ulcer disease, psychiatric

disorders, glaucoma, hypertension, and osteoporosis. These should be ruled out.

Antihistamines (AH)

Antihistamines are indicated as supportive treatment in patients with severe pruritus. Parenteral application is more effective than oral administration. First-generation antihistamines have pronounced antipruritic effect, also causing sedation and fatigue. AH are generally well tolerated. Caution is indicated in patients with impaired renal function, cardiac diseases, or concomitant medication such as antidepressants. AH are mostly part of a combination therapy with local and systemic corticosteroids.

Ciclosporin (CyA)

Ciclosporin is a T cell immunosuppressive drug with broad application in the transplantation medicine and in the field of dermatology in refractory atopic eczema, psoriasis, pemphigus, and other autoimmune diseases. For severe nummular eczema in atopic patients, ciclosporin treatment can be reconsidered to achieve remission. Possible side effects are hypertension, impairment of the renal and liver function, hypertrichosis, gingival hyperplasia, and infections. Regular laboratory checkup (blood cell count, hepatic and renal function parameter, ESR, CRP) and blood pressure should be monitored every 4–6 weeks during the long-term treatment. Based on the potential epithelial carcinogen effect, ciclosporin should not be combined with phototherapy, and the duration of treatment should be limited (up to 1 year).

Methotrexate (MTX)

Methotrexate represents a cytostatic agent with immunosuppressive and antiproliferative effect, based on suppression of the folic acid synthesis. In autoimmune disorders, psoriasis, and rheumatic diseases, it has already found broad application. Recently, successful and well-tolerated treatment of refractory nummular eczema in children with MTX has been reported (Roberts et al.). Limitations of use are pregnancy and lactation, hepatic and renal diseases, bone marrow suppression, or systemic infections. Regular checkup of blood cell count, liver and renal function, as well as contraception are required. Men should be aware of potential impairment of spermiogenesis. Semen cryopreservation should be discussed with male patient before initiating therapy. In cases of cough and dyspnea under treatment, pulmonar toxicity and alveolitis should be ruled out.

Phototherapy (PT)

Phototherapy is used for its immunomodulatory and anti-inflammatory effects as whole body irradiation alone (UVA; 320–400 nm) or in combination with photosensitizing substances (psoralen UVA/PUVA) or with tar preparations (UVB; 280–320 nm). According to irradiation type and minimal erythema doses (MED) of the patient, procedures are performed three to five times per week over 3–4 weeks. Purpose of treatment is to maintain discrete erythema in order to achieve therapeutic effect. Depending on the individual skin reaction, UVB irradiation doses are increased on a daily basis with 15–30 %, beginning with the 80 % of the personal MED (25–70 mJ/cm^2). PUVA therapy starts usually with initial dose 0.5–1.0 J/cm^2.

Phototherapy should only be performed in patients without increased photosensitivity. Medications causing phototoxicity (diuretics, tetracyclines, quinolones, herbs) should be withdrawn over the treatment duration. Patients should wear protective glasses and cover face and genitalia during irradiation. Other side effects are acute dermatitis (overexposure), skin aging, and higher long-term risk for skin cancer (Fig. 67.7).

Systemic Treatment at a Glance

- Systemic treatment should be applied in severe and recurrent eczema.
- Therapy of first choice is systemic corticosteroids in combination with broad-spectrum antibiotics.
- Combination with phototherapy is effective in disseminated eczema.
- Systemic immunosuppressive agents as CyA and MTX can be considered in refractory cases to achieve remission. Immunosuppressive therapy should be performed over limited duration under regular laboratory checkups.

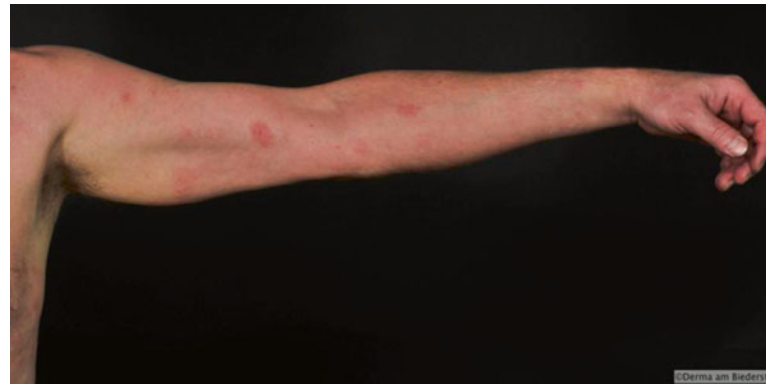

Fig. 67.7 Nummular eczema improved after UVB phototherapy

Complementary Treatments

Psychosomatic Counseling

As in many cases with chronic recurrent disease, significant impairment of quality of life has been reported in patients with nummular eczema. Severe pruritus seems to have essential impact on the limitations in patient's daily activities and social interactions. Psychological and psychosomatic techniques as behavioral therapy and autogenic training have shown significant supportive effect in controlling the itch–scratch behavior and eventually in improvement of the skin condition.

Prognosis

Nummular eczema is a chronic disease with relapsing and refractory course.

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Onychomycosis

68

Dimitris Rigopoulos and Stamatis Gregoriou

Key Points

- Onychomycosis is the most common nail disorder and has a severe impact on health-related quality of life.
- Onychomycosis is caused by dermatophytes, yeasts, and non-dermatophyte molds and is more common in immunosuppressed and patients with nail trauma.
- There are five major clinical presentations of onychomycosis: distal and lateral subungual onychomycosis (DLSO), proximal subungual onychomycosis (PSO), superficial white onychomycosis (SWO), endonyx, and total dystrophic onychomycosis (TDO).
- Topical treatment is recommended for restricted disease. The most effective agents are 8 % ciclopirox and 5 % amorolfine nail lacquers.
- Systemic treatment is recommended in extensive disease. Terbinafine is more effective in dermatophyte infections.
- Treatment through the use of devices includes lasers and photodynamic therapy, but more evidence-based data are needed to obtain strong recommendation.
- Chemical or surgical nail avulsion should not be used as monotherapy but rather in combination with topical or systemic treatment.
- Treatment of choice should be individualized and should take into account the type of fungi isolated through direct microscopy and culture, the age of the patient, and concomitant use of other systemic medications.

Definition

Onychomycosis is the most common nail disorder. Even though some consider it just a cosmetic problem, hand nail onychomycosis may lead to pain, discomfort, and impaired tactile functions, while toenail dystrophy can impair walking and exercise. Onychomycosis has significant impact in health-related quality of life with both emotional and social function affected in patients with onychomycosis (Belyayeva et al. 2013).

Epidemiology

Onychomycosis affects up to 6 % of the population and represents 20–40 % of all nail disorders (Baran et al. 2006). Onychomycosis is more common in aged populations and patients with HIV infection

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_68, © Springer-Verlag Berlin Heidelberg 2015

or under immunosuppressive therapy. Activities predisposing to onychomycosis include sports participation, swimming in swimming pools, and occlusive footwear. Toe nails are more frequently affected than fingernails probably due to slower growth rate. Other predisposing factors include nail trauma, peripheral vascular disease, smoking, and psoriasis (Sehgal et al. 2010). Epidemiology of fungi causing onychomycosis varies according to geography. Dermatophytes are the most frequently implicated causative agents in onychomycosis (approximately 90 % in toenail and 50 % in fingernail). *Trichophyton rubrum* (*T. rubrum*) is the most common causative agent followed by *T. mentagrophytes*. Nondermatophyte molds (NDM) mainly affect toenails and occasionally fingernails and include *Scytalidium dimidiatum* and *Scytalidium hyalinum*, *Scopulariopsis brevicaulis*, *Aspergillus* species, *Onychocola canadensis*, and *Acremonium* species (Singal and Khanna 2011). Molds are considered pathogens when the following criteria are fulfilled:

1. Nail features consistent with onychomycosis
2. Positive direct microscopy
3. Failure to isolate a dermatophyte in the culture
4. Growth of more than five colonies of the same mold in at least two consecutive nail samplings (Tosti et al. 2000)

Yeasts can be either contaminants or pathogens in fingernail infections. *Candida albicans* accounts for 70 % of cases, while *C. parapsilosis*, *C. tropicalis*, and *C. krusei* can also be isolated. Chronic exposure to moisture and chemicals, as seen in laundry workers, house and office cleaners, food handlers, cooks, dishwashers, bartenders, chefs, fishmongers, confectioners, nurses, and swimmers, contributes to chronic paronychia accompanied by *Candida* onychomycosis (Rigopoulos et al. 2008).

Clinical Presentation

There are five major clinical presentations of onychomycosis:

- Distal and lateral subungual onychomycosis (DLSO)
- Proximal subungual onychomycosis (PSO)
- Superficial white onychomycosis (SWO)
- Endonyx
- Total dystrophic onychomycosis (TDO)

DLSO is the commonest clinical variant affecting both fingernails and toenails. The fungus enters via the distal subungual and lateral nail groove and spreads proximally. Clinically, there is onycholysis and subungual hyperkeratosis.

PSO is uncommon and often associated with immunosuppression. It affects both fingernails and toenails. The fungus first invades the proximal nail fold, migrates to the underlying matrix, and then spreads distally under the nail plate. Clinically, there is subungual hyperkeratosis, transverse leukonychia, and proximal onycholysis and eventually destruction of the proximal nail plate.

SWO affects mostly toenails. Clinically, small opaque white spots of leukonychia are present on the dorsal nail plates. Baran et al. have proposed a classification of SWO as classical SWO, dual invasion of the nail plate, superficial and ventral, and the pseudo-SWO with deep fungal invasion of the nail plate (Baran et al. 2004).

In endonyx onychomycosis the infection starts from the free edge, and the fungus penetrates the distal nail keratin of the nail plate where it forms milky white patches without subungual hyperkeratosis or onycholysis (Figs. 68.1 and 68.2).

In TDO there is total destruction of the nail plate where the nail crumbles and disappears leaving a thickened abnormal nail bed.

Candida may cause onycholysis with distal subungual hyperkeratosis with a yellowish gray mass that lifts off the nail plate.

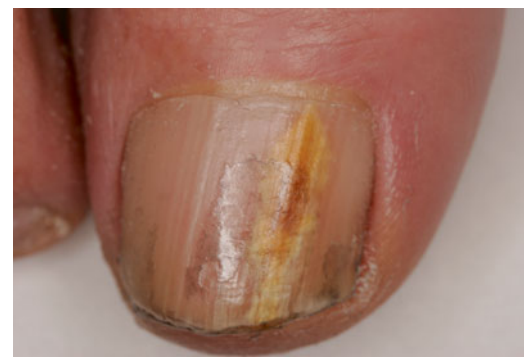

Fig. 68.1 Dermatophytoma

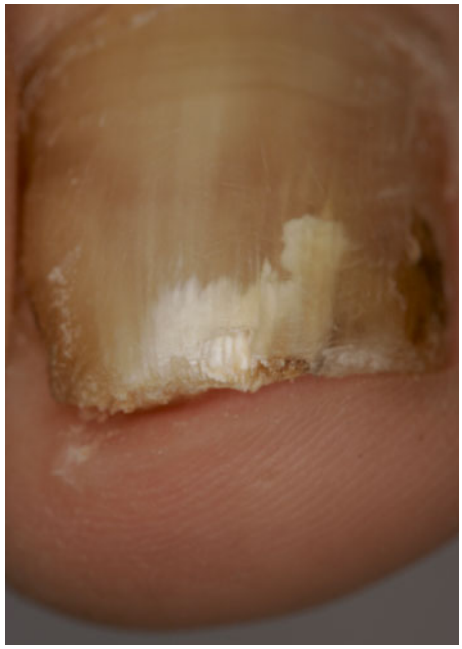

Fig. 68.2 Endonyx

Diagnosis

Identification of the pathogen before initiating treatment is important in order to select the appropriate therapeutic agent.

Samples should be obtained from affected nails. The patient should have discontinued topical and systemic antifungal drugs for an appropriate duration (Table 68.1). The nail should be thoroughly cleaned with alcohol, the onycholytic nail plate should be clipped, and then scrapings should be obtained from the nail bed. Subsequently, direct microscopy of the specimen in 10–30 % KOH should be performed. The nail is examined for fungal hyphae, spore, or yeast forms. Culture confirms the diagnosis and identifies the fungus. Specimens should be sent for culture even when direct microscopy is negative. Different media are used to grow different fungal species. Colonies of most dermatophytes are usually completely differentiated in 2 weeks. Absence of growth after 3–6 weeks should be considered as negative. False-negative results may be attributed to inappropriate nail sampling (Singal and Khanna 2011).

Table 68.1 Time needed to discontinue medication in order to obtain a nail sample for a credible direct microscopy and culture

Drug	
Topical agent	4 weeks
Itraconazole	9 months
Terbinafine	8 weeks
Fluconazole	1 week

Histopathology may be necessary when direct microscopy and culture are repeatedly negative in patients with clinical signs of onychomycosis. Nail plate clippings are stained with periodic acid-Schiff (PAS) staining to evaluate the presence or absence of fungi.

Other less frequently used tests to diagnose onychomycosis include immunohistochemistry and dual flow cytometry especially for identifying mixed infections and for quantification of fungal load in the nail. DNA-based methods such as PCR-RFLP assays have been used recently for detecting fungi (Bontems et al. 2009). The role of scanning electron microscopy and confocal microscopy at present is primarily for research.

General Principles of Treatment

Treatment options for onychomycosis include topical agents, systemic agents, chemical or surgical nail avulsion, and devices such as lasers and photodynamic therapy.

Topical Treatments

Topical agents are the mainstay of onychomycosis treatment. A recent study with 1,447 patients with onychomycosis showed that 89.1 % were prescribed a topical agent either as monotherapy or in addition to other treatment (Di Chiacchio et al. 2013). The 2005 consensus on treatment guidelines for onychomycosis suggests topical treatment if:

A. Nail surface involvement is less than 50 %
B. Number of nails involved are less than 5
C. Nail matrix is not affected
D. There is a contraindication for systemic treatment

In addition topical treatment can be used as adjuvant to systemic treatment and nail avulsion or as prophylaxis after systemic treatment. Immunosuppressed patients or patients with nail thickness more than 2 mm should be considered for systemic treatment regardless of other factors (Lecha and Effendy 2005).

Permeation of nail plate by water-soluble or lipophilic vehicles is poor. Nail plate shows a radically different biochemistry from the skin consisting of 15 % water and less than 5 % lipids (van de Kerkhof et al. 2005). Bovine hoofs often used as in vitro models for evaluating nail permeation have been reported to have 14-fold more permeation when compared to human nails (Monti et al. 2011). An ideal topical agent should be able to exhibit prolonged presence on the nail plate after application and increased concentration on the nail plate after evaporation of the vehicle. Treatment outcomes are also dependent on compliance which is known to be compromised for prolonged therapies. A study on compliance of patients using topical agents for onychomycosis reported an overall compliance of 23.9 %. Successful treatment was observed in 63 % of patients with adequate compliance; on the other hand only 2 % of patients with poor response achieved complete remission of onychomycosis (Zhou et al. 2011).

Ciclopirox 8 % Lacquer

Ciclopirox is a synthetic hydroxypyridone antifungal agent. Glucuronidation is the main metabolic pathway of ciclopirox; therefore, it does not normally interact with drugs metabolized via the cytochrome P450. Ciclopirox does not interfere with ergosterol biosynthesis. It chelates trivalent cations, inhibits metal-dependent enzymes that are responsible for degradation of toxic metabolites in the fungal cells, and targets metabolic and energy-producing processes in microbial cells. Ciclopirox is a broad-spectrum antimicrobial that includes dermatophytes, yeasts, and non-dermatophyte molds. It is also effective against some Gram-positive and Gram-negative bacteria including resistant strains of *Staphylococcus aureus*. After evaporation of volatile solvents in the lacquer, the concentration of ciclopirox in the remaining lacquer film reaches approximately 35 %, providing a high concentration gradient for penetration into the nail. It achieves fungicidal concentrations inside the nail plate for most pathogens. Although ciclopirox readily penetrates nails, very low levels of ciclopirox are recoverable systemically, even after chronic use. This unique and multilevel mechanism of action provides a very low potential for the development of resistance in pathogenic fungi, with cases of resistance rarely reported (Subissi et al. 2010). Mycological cure rates after daily application for 48 weeks (negative culture and negative light microscopy) have been reported to range between 29 % and 85.7 %, while complete cure rate (clinical cure plus mycological cure) has been reported to range between 5.5 % and 8.5 %. The most common adverse event is the appearance of mild erythema in 5 % of the treated population (Gupta et al. 2000).

Amorolfine 5 % Lacquer

Amorolfine is a structurally unique, topically active antifungal agent that belongs to morpholines. It inhibits ergosterol biosynthesis, modifies fungal cellular membrane permeation, and inhibits fungal metabolic pathways. It possesses both fungistatic and fungicidal activity in vitro. Its spectrum of in vitro activity includes dermatophyte, dimorphic, some dematiaceous and filamentous fungi, and some yeasts. The amorolfine concentration in the nail plate following application of 5 % nail lacquer is 25 %. In clinical trials, application of amorolfine 5 % nail lacquer once or twice weekly for up to 6 months produced mycological and clinical cure in approximately 40–55 % of patients with mild onychomycosis 3 months after cessation of therapy (Banerjee et al. 2011).

Tioconazole 28 % Nail Solution

Tioconazole is an imidazole antifungal agent. Percutaneous absorption of tioconazole is negligible suggesting it is unlikely to produce systemic side effects. It has been shown to have a broad spectrum of activity in vitro against dermatophytes and yeasts, as well as against some chlamydia, trichomonads, and Gram-positive

bacteria. It inhibits ergosterol synthesis and additionally has a toxic effect on fungal cellular membrane (Sobue and Sekiguchi 2004). Complete cure rates after twice daily application of tioconazole 28 % nail solution for 48 weeks has been reported to be 22 % (Hay et al. 1985).

Miconazole 2 % Tincture

There are scarce data in medical literature about the efficacy of miconazole 2 % tincture on the treatment of onychomycosis. The tincture leaves a brownish hue on the nail after multiple applications. A study reported 13 dropouts out of 23 patients using miconazole treatment. At least partial response was observed in 80 % after application for 32 weeks (Bentley-Phillips 1982).

Nail Avulsion

Nail avulsion can be performed either surgically or chemically. Application of urea 40 % formulation followed by ketoconazole, oxiconazole, or bifonazole cream results in 50–75 % mycological cure after 12 weeks (Grover et al. 2007; Tsuboi et al. 1998). Removal of the nail by itself has poor or no result in mycological cure (Malay et al. 2009). Compliance of therapy after nail avulsion could be compromised as all studies report a 50 % dropout rate.

Topical Agents for Prophylaxis

Topical application of amorolfine for 52 weeks after complete nail cure has been reported to decrease recurrence to 29.2 % compared to 50 % among those not using prophylactic application after 3 years (Sigurgeirsson et al. 2010).

Systemic Treatments

A clinician should always evaluate efficacy, safety, and cost when deciding on systemic treatment options for onychomycosis. Oral therapy is recommended in:

1. Moderate to severe onychomycosis
2. Multiple nail involved
3. Immunocompromised patients
4. Matrix involvement
5. Failure of previously used topical therapies

Oral antifungals used to treat onychomycosis include griseofulvin; azoles including ketoconazole, itraconazole, and fluconazole; and the allylamine terbinafine. Azoles inhibit ergosterol synthesis and increase fungal cell membrane permeability by reducing the activity of various enzymes. Ketoconazole is rarely used nowadays because of risk of severe hepatic side effects. Griseofulvin takes a long time to achieve therapeutical concentration in the nail and persists for just 2 weeks after stopping therapy. Consequently administration is prolonged (4–9 months for fingernails and 10–18 months for toenails,) and results in poor compliance. Mycological cure rates are low making griseofulvin the least preferred agent. The adult dose is 500 mg to 1 g daily to be administered after a fatty meal (Roberts et al. 2003).

Itraconazole

Itraconazole is a triazole with spectrum against dermatophytes, *Candida*, and NDM. It is highly lipophilic and bioavailability is increased if received after food intake. Itraconazole gets into the nail through both matrix and nail bed 7 days after starting therapy and remains for up to 6–9 months post-treatment. It achieves high concentrations even in subungual hyperkeratosis (567 ng/g). Itraconazole classical regimen is a dose of 200 mg once daily for 3 months. A pulse regimen with 200 mg twice daily for a week every month with two such pulses for fingernail onychomycosis and three for toenail disease has been reported to be as effective as the continuous (Gupta and Ryder 2003). Drug interaction may potentially occur because of binding of itraconazole to cytochrome P450 3A4 system in the liver. Common adverse reactions include headache and gastrointestinal adverse events. Less common adverse events include asymptomatic liver function abnormalities and hepatitis. Monitoring for hepatic functions is recommended only in patients with preexisting liver disorders or concomitant uptake of hepatotoxic drugs. It is contraindicated in patients with congestive cardiac failure due to increased risk of negative ino-

tropic effects and in patients receiving H1 and H2 inhibitors because it increases the risk for arrhythmia (Singal and Khanna 2011). Itraconazole is not approved for children less than 12 years old.

Fluconazole

Fluconazole does not have an on-label use in the treatment of onychomycosis. However, it is highly effective against both *Candida* and dermatophytes. It has been detected in nails within 7 days after initial dose and remains for 3–6 months after treatment. Weekly administration is sufficient and uptake should not necessarily be associated with meals. Dosage in published studies varies between 150 and 450 mg per week for 5–12 months. The common adverse effects include headache, skin rash, gastrointestinal complaints, insomnia, and palpitations. Fluconazole inhibits both CYP3A4 and CYP2C9, and close monitoring is required when prescribing drugs metabolized by these enzymes. Simultaneous use of fluconazole and terfenadine or cisapride is contraindicated (Singal and Khanna 2011).

Terbinafine

Terbinafine is an allylamine. It inhibits fungal squalene epoxidase, resulting in accumulation of squalene, dysfunction of fungal cell membrane, and death of the fungal cell. In vitro terbinafine is fungicidal against dermatophytes, NDM (*Aspergillus fumigatus* and *Scopulariopsis brevicaulis*), and *C. parapsilosis* and fungistatic against *C. albicans*. Terbinafine is well absorbed orally with >70 % bioavailability. It is detectable in the nail 7–21 days after initial dose and up to 9 months after treatment. Approved continuous treatment consists of 250 mg daily for 6 weeks for fingernail and 12 weeks for toenail onychomycosis. Pulse regimens of terbinafine have also been used with success in the treatment of onychomycosis. Gupta et al. employed two courses of terbinafine (250 mg daily for 4 weeks) alternating with 4 weeks interval without terbinafine and found it to be as effective as continuous terbinafine and more efficacious than pulse itraconazole for treatment of toe nail onychomycosis (Gupta et al. 2009). Common adverse reactions with terbinafine include gastrointestinal symptoms, skin rash, pruritus, urticaria, asymptomatic liver enzyme abnormalities, and taste disturbances. Severe adverse drug reactions are infrequent and include agranulocytosis, hepatitis, acute generalized exanthematous pustulosis, and lupus erythematosus. Terbinafine is metabolized by cytochrome P450 enzymes, and therefore, concentration is decreased by rifampicin and increased by cimetidine. It decreases cyclosporin levels and inhibits the cytochrome P450 enzyme CYP2D6 responsible for metabolism of tricyclic antidepressants, beta-blockers, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors type B (Singal and Khanna 2011).

Head on Comparative Studies

The LION study demonstrated superiority of the continuous terbinafine regimen over intermittent itraconazole regimen in both mycological and clinical cure and lower risk of recurrence (Sigurgeirsson et al. 1999). A meta-analysis of randomized controlled trials by Gupta et al. reported mycological cure rates of 73–79 % for terbinafine, 56–70 % for itraconazole pulse, and 54–64 % for pulse itraconazole regimens. The corresponding values for clinical response were as follows: terbinafine 61–71 %, pulse itraconazole 59–81 %, and continuous itraconazole 65–75 % (Gupta et al. 2004).

Device Treatment

Device treatment seeks to address some of the unmet needs of onychomycosis therapy such as high rates of relapse, drug adverse events, and fungal resistance. Currently there are four categories of device-based treatments: laser devices, photodynamic therapy, iontophoresis, and ultrasound.

Lasers

Fungi are heat sensitive above 55 °C, so absorption of laser energy is likely to result in fungicidal effects. However, heating dermal tissue to temperatures above 40 °C results in pain and necrosis; therefore, the laser energy format must either be pulsed to allow the dissipation of heat by the tissue through its superior thermal conduction or

delivered at a moderate energetic level to prevent tissue damage (Gupta and Simpson 2012).

Long-pulse Nd:YAG lasers have been used to treat the nail in a spiral pattern with 30–40 J/cm2 energy fluence with a spot size of 4 mm and a pulse duration of 35 ms. Treatment was repeated after 2 min. Participants received two treatments per session with a 2 min interval, four sessions at 1 week intervals, and they were followed after therapy from 12 to 30+ months. A completely clear nail plate was achieved by 93.5 % of participants (Kozarev and Vizintin 2010). Flashlamp pumped short pulse Nd:YAG 1,064 nm lasers have also been reported to be effective in the treatment of onychomycosis. Treatment protocol used was four sessions, at 1 week intervals with a pulse length of 0.3 ms, an energy fluence of 13 J/cm2, and a repetition rate of 6 Hz. Follow-up mycological culture was negative in 95 % of patients (Gupta and Simpson 2012). Q-switched lasers emit the highest peak power per pulse of all the Nd:YAG lasers. They have also been reported to have efficacy in the treatment of onychomycosis(Gupta and Simpson 2012). The diode lasers that are currently under investigation for onychomycosis operate at near-infrared wavelengths. Studies have shown that 870 and 930 nm wavelength treatment comprised of 4 min of dual wavelength therapy, followed by 2 min of 930 nm treatment showed an 85 % improvement of infection in 26 toes treated at 180 days (Landsman et al. 2010). However, more evidence-based data is needed.

Photodynamic Therapy

5-Aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) are precursors of heme. They cause a buildup of protoporphyrin IX (PpIX) that, in the presence of the correct spectrum of light, generates reactive oxygen species that initiate apoptosis. Case reports and two case series have reported controversial results regarding efficacy in the treatment of onychomycosis. The protocols developed for these studies indicate that the nail plate should be pretreated with urea ointment to soften the nail plate prior to application of the photosensitizer. Treatment length has been reported to be 3–5 h for each session with an irradiation source of 570–670 nm at 36–100 J/cm2 repeated for one to three sessions (Watanabe et al. 2008; Piraccini et al. 2008; Sotiriou et al. 2010; Gilaberte et al. 2011).

Iontophoresis

There are two iontophoresis devices currently in clinical trials. Iontophoresis has been reported to increase the amount of terbinafine accumulated in the nail plate. The nail plate then acts as a reservoir of terbinafine that is then released into the nail bed and matrix over 60–70 days. Mycological cure after three sessions of iontophoresis with terbinafine has been reported to reach 84 % (Amichai et al. 2010).

Special Populations

Children

Prevalence of onychomycosis in children is extremely low, possibly because of faster nail growth. Griseofulvin has an on-label use in children in a dosage of 10 mg/kg daily. Terbinafine is approved for use in children above 4 years of age. However, terbinafine, fluconazole, and itraconazole have been used safely with favorable outcome in children aged 2 years and above (Gupta et al. 1998).

Elderly

Treatment of onychomycosis in the elderly may include no therapy, mechanical or chemical debridement, topical and oral agents, or combination of these modalities. Debridement is more used more frequently than in younger patients because nail dystrophy is more common because of high prevalence of arthritis problems. Systemic treatment should be used with caution because the risk for drug interactions is increased due to multiple medications received.

Pregnancy and Lactation

Terbinafine is category B drug while itraconazole and fluconazole are in pregnancy category C. Use of all these drugs should be avoided in pregnancy. All oral antifungals are excreted in breast milk and therefore contraindicated in lactating mothers.

Future Options

Oxaboroles include tavaborole and benzoxaborole and have shown good efficacy against *Trichophyton rubrum* and *Trichophyton mentagrophytes* and excellent penetration of the nail plate (Alley et al. 2007). A lacquer employing 10 % eficonazole used once daily for 48 weeks has shown 15–18 % complete cure in patients with onychomycosis (Elewski et al. 2013). A solution of amphotericin B applied for 12 months resulted in 100 % mycological cure in eight patients with NDM (Lurati et al. 2011). Considerable resources have been allocated in the development of new permeation enhancers such transfersomes that release terbinafine and nanoemulsions (Sigurgeirsson and Ghannoum 2012). Systemic treatment with posaconazole has been reported to be as effective as treatment with terbinafine in patients with onychomycosis (Elewski et al. 2012). There are only case reports about the systemic use of voriconazole in the treatment of onychomycosis (Spriet et al. 2012).

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Pemphigus Foliaceus and Pemphigus Erythematosus

69

Christoph M. Hammers, Enno Schmidt, and Luca Borradori

Abbreviations

Abs	Antibodies
ACR	American College of Rheumatology
AZA	Azathioprine
CS	Corticosteroids
CYC	Cyclophosphamide
Dsg	Desmoglein
IA	Immunoadsorption
IF	Immunofluorescence
IVIg	Intravenous immunoglobulins
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MTX	Methotrexate
PE	Pemphigus erythematosus
PF	Pemphigus foliaceus
RCT	Randomized controlled clinical trials
RTX	Rituximab
TPMT	Thiopurine methyltransferase

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Key Points

- Pemphigus foliaceus and pemphigus erythematosus are autoimmune diseases of the skin associated with an autoantibody response directed against desmoglein-1, a component of desmosomes in human epidermis.
- Their incidences greatly vary in different countries and continents. In South America and North Africa, endemic forms of pemphigus foliaceus exist, the prevalence of which is relatively high.
- Clinical presentation is characterized by development of fragile bullae, which rapidly rupture, resulting in erosions, crusting, and scaling. Lesions may remain either localized to the seborrheic areas of the face, scalp, back, and chest or generalize.
- In patients affected by pemphigus erythematosus and the sporadic form of pemphigus foliaceus, drug triggering should always be considered and excluded.
- Management of pemphigus foliaceus does not greatly differ from that of pemphigus vulgaris. Systemic corticosteroids

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_69, © Springer-Verlag Berlin Heidelberg 2015

represent the mainstay of therapy and are usually combined with an immunosuppressive adjuvant. Dapsone and, in treatment-resistant cases, rituximab may be employed with substantial benefit.

Definition and Epidemiology

Pemphigus foliaceus (PF) is a chronic autoimmune blistering disease of the skin, characterized by autoantibodies against a structural component of the epidermal desmosome, desmoglein 1 (Dsg1). Binding of anti-Dsg1 antibodies to the antigen results in subcorneal split formation, dissociation of keratinocytes with loss of cell-cell adhesion (acantholysis) in the superficial epidermis and, clinically, flaccid bullae. The sporadic form of PF most commonly starts in adulthood, with equal distribution in both sexes. Its incidence is low, with 0.1–1/million new cases per year. In contrast, there is an endemic form of PF, which is relatively common in distinct subtropical areas of Brazil and Colombia, where the prevalence of the disease is up to 3–5 %. PF affects predominantly young women with painful erosions (*fogo selvagem*, Portuguese for *wild fire*). Further endemic forms exist in Northern Africa (e.g., Tunisia, Mali, Egypt). Pemphigus erythematosus (PE; syn. Senear-Usher syndrome) is a localized form of PF with lesions typically developing on the face and the upper trunk and back (Figs. 69.1 and 69.2).

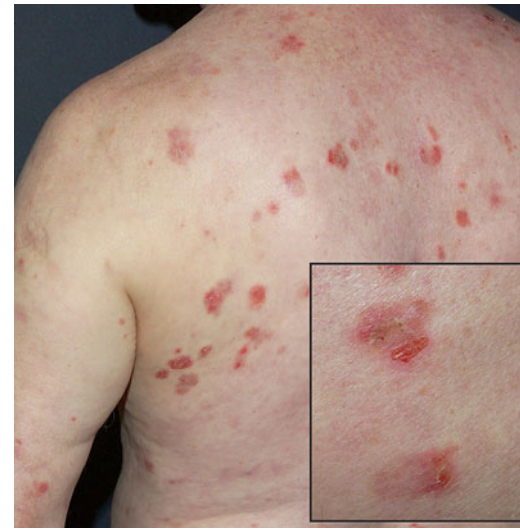

Fig. 69.1 Pemphigus foliaceus, localized disease. The presence of isolated erythematous, scaling lesions on the trunk. Superficial fragile blisters occur leaving eroded areas. Insert with close-up view of some lesions

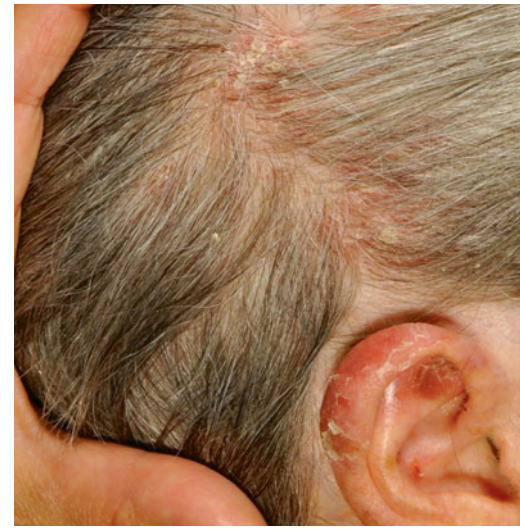

Fig. 69.2 Pemphigus foliaceus, localized disease with the presence of isolated erythematous and scaling lesions on the scalp, ear, and neck. Based on these features mimicking seborrheic eczema, the condition is also called seborrheic pemphigus

Basic Concepts of Pathogenesis

Pemphigus diseases are autoimmune in nature. The exact mechanisms leading the human immune system to react against normal skin components are far from being understood in detail. In PF, IgG antibodies (abs) against Dsg1 are formed (with involvement of both B and T cells), circulate in the bloodstream, and bind to their target skin antigen. The direct pathogenicity of these antibodies has been shown convincingly in vitro and in vivo. Even as monovalent cloned single-chain variable fragments, these abs can cause loss of cell-cell adhesion in the superficial epidermis where Dsg1 is highly and specifically expressed.

Interestingly, B cells from individuals without PF can potentially produce nonpathogenic antibodies against the precursor protein of Dsg1 (preDsg1), and ELISA screening of individuals from endemic areas frequently detects serum anti-preDsg1 IgG (which is not found in cohorts of US-American or Japanese individuals). As suggested by this geographical clustering of cases, the transition from nonpathogenic to pathogenic IgG abs, which finally bind the mature Dsg1 protein, might be triggered by environmental factors. In case of Brazilian *fogo selvagem*, anti-Dsg1-specific PF sera have been described to cross-react with a sand fly salivary antigen, implying a precipitating role for this vector.

When PE was first described by Senear and Usher in 1926, they suggested that the presentation with a lupus-like rash or seborrheic dermatitis was a combination of pemphigus and cutaneous lupus erythematosus. This hypothesis has been abandoned, as, in most cases, serum antinuclear abs are absent in PE and patients do not meet the American College of Rheumatology (ACR) criteria for systemic lupus erythematosus. In lieu thereof, the "lupus-band" phenomenon in PE patients may be apportioned to UV irradiation-induced basement membrane zone deposition of complexes of Dsg1 ectodomains and Dsg1-specific IgG abs, thus somehow resembling lupus bands found in patients with various cutaneous forms of lupus erythematosus.

Clinical Presentation

In contrast to pemphigus vulgaris, in PF there is only skin involvement, without mucosal lesions, although very rarely transitions from PF to pemphigus vulgaris and vice versa have been described (Figs. 69.3 and 69.4).

Whereas endemic PF also occurs in children and adolescents, sporadic PF frequently occurs in middle age. The seborrheic areas of the face, scalp, back, and chest are preferentially affected in both forms. Because of the localization of acantholysis in the upper epidermis, the resulting blisters are very fragile and rapidly rupture. The Nikolsky sign may be positive. In the course of disease, hyperkeratotic, crusting "puff pastry–like," psoriasiform, or seborrheic scales develop. Erosions heal without scarring but typically result in postinflammatory hyperpigmentations. In some cases, the extensive exfoliation may resemble erythroderma, a complication commonly seen in *fogo selvagem*. All erosions are subject to possible bacterial (and viral) superinfection, with rarely sepsis.

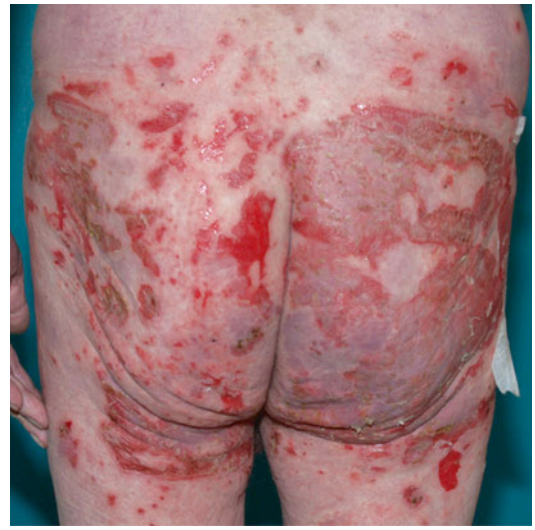

Fig. 69.3 Pemphigus foliaceus, extensive disease with widespread erythema, erosions, crusts, and scaling of the gluteal region

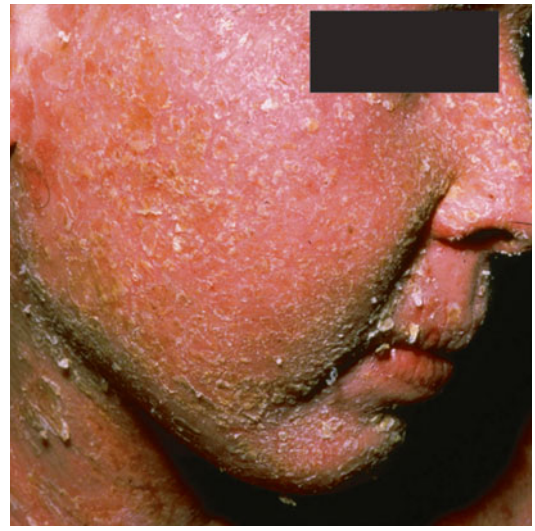

Fig. 69.4 Pemphigus foliaceus, extensive disease with erythrodermic involvement. Widespread erythematous psoriasiform lesions in a young woman living in North Africa

Clinical features of PE on the face, back, and trunk may closely resemble those of cutaneous lupus erythematosus with erythema and scaling. As most patients with PE do not meet the ACR criteria for systemic lupus erythematosus, PE should clearly be separated from the few cases in which PF coincide with cutaneous lupus erythematosus.

Drug-Induced Pemphigus Erythematous and Pemphigus Foliaceus

Association of disease onset with certain drugs is well recognized and should be actively excluded in all patients with PE and PF. Two groups of medication related to the occurrence of pemphigus have been identified, sulfur-containing drugs (thiol drugs) and drugs not containing sulfur. Penicillamine and captopril, both drugs that contain a thiol group, are the most frequently reported triggers. Among the other group, non-sulfhydryl angiotensin-converting enzyme inhibitors, pyrazolone derivatives, penicillin, and rifampicin have been frequently described. Thiol compounds have been particularly implicated in PF triggering. In these cases, pemphigus disease can remit spontaneously in up to 50 %, after drug withdrawal.

Diagnosis and Differential Diagnosis

Following the in 2013 validated European Guidelines for diagnosis and treatment of pemphigus, four criteria have to be considered to confirm the diagnosis (Hertl et al. 2013):

1. Clinical presentation (see above).
2. Histopathology: For histopathology a 4 mm punch biopsy should be taken of a fresh small vesicle or one third of the peripheral portion of a blister and two thirds perilesional skin. In PF, acantholysis at the granular layer is expected leading to subcorneal splitting.
3. Direct immunofluorescence (IF) microscopy of a perilesional skin biopsy: For this purpose, a skin biopsy of perilesional skin is taken and analyzed for IgG and/or C3 deposits in the epidermis. In PE, "lupus-band-like" deposits may be noted along the cutaneous basement membrane, in particular in sun-exposed areas.
4. Serological detection of serum antibodies that label, by indirect IF microscopy, the cytoplasmic cell membrane of typically used substrates such as monkey or guinea pig esophagus and anti-Dsg1 abs by ELISA: The pattern of indirect IF microscopy on monkey esophagus is expected to be reticular and "fishnet like." For ELISA, two commercial systems are available to test for anti-Dsg1 antibodies (Euroimmun, Lübeck, Germany; MBL, Nagoya, Japan). In general, ELISA values correlate well with the extent and activity of the disease.

Differential diagnoses of PF and PE include:

- Pemphigus vulgaris (mucosal lesions always present; histopathology with suprabasal "tombstone-like" acantholysis, ELISA for Dsg3-specific abs positive)
- Drug-triggered bullous eruptions (negative direct IF microscopy, negative Dsg1 ELISA)
- IgA pemphigus (intraepidermal neutrophilic dermatosis and subcorneal pustular dermatosis, IgA reactivity with desmocollin occasionally found)
- Bullous impetigo (microbiology) and staphylococcal scalded skin syndrome (negative IF microscopy/ELISA studies)
- Neutrophilic dermatoses (negative IF microscopy/ELISA studies)
- Cutaneous lupus erythematosus (histopathology, direct IF microscopy, ACR criteria)
- Other acantholytic dermatoses (Hailey-Hailey disease, Darier's disease, Grover's disease, here negative IF microscopy/ELISA studies)

General Principles of Treatment

Therapy aims at induction and maintenance of remission in patients, with reduction of pathologic autoantibodies, and prevention of further blistering, erosion of skin, or other complications (bacterial and viral infections).

Given the rarity of PF and PE, data from large, randomized controlled clinical trials (RCTs) are sparse, and the recent publication of *consensus statements* with common definitions and end points will help to conduct future studies.

However, the mainstay of therapy is general immunosuppression with corticosteroids (CS), and the use of adjuvant immunosuppressants has been shown to exert a steroid-sparing effect that is highly desirable in long-term CS administration. Treatments for pemphigus vulgaris and PF do not differ, except for the point that PF and PE are generally thought to be better responsive to therapy, although no comparative data are available.

Corticosteroid doses are generally being calculated with prednisone as reference; low doses equal to <7.5 mg/day of prednisone equivalent, 7.5–30 mg/day (or: 0.5 mg/kg/day) correspond to medium, and 30–100 mg/day (or: >0.5 mg/kg/day) to high doses. Pulsed therapy relates to >250 mg/day of prednisone equivalent for a few days.

Prior to initiation of CS and additional immunosuppressive therapy, serological tests for the following entities are indicated: complete blood count, blood electrolytes, creatinine, liver enzymes, and fasting serum glucose (complemented by an oral glucose tolerance test, where applicable). Depending on the treatment considered and on the individual patient situation, the authors recommend the following additional investigations: tuberculin skin test and/or interferon-gamma release assay (to prevent reactivation of latent or chronic TB), chest X-ray, serologies for HIV, hepatitis B and C, testing for serum IgA deficiency (if IVIg is considered), thiopurine methyltransferase (TPMT) activity (if azathioprine is considered), G6PD serum activity (if dapsone is considered), beta-HCG (to exclude pregnancy in females of childbearing age), bone density scan (prior to CS treatment, especially in postmenopausal women), and ocular examination (to exclude glaucoma or cataract).

First-Line Treatment as Recommended by the 2013 European Guideline and Overview of Selected Studies

Especially in initial control of newly diagnosed cases, CS represents the first-line choice of treatment (Table 69.1).

CS dosing in PF is largely empirical. The 2013 European S2 Guideline for diagnosis and treatment of pemphigus (Hertl et al. 2013) recommends initial systemic CS therapy at 0.5–1.5 mg/kg/day. If initial control is not reached within 2 weeks, a higher prednisone dose is advised.

Table 69.1 Algorithm for treatment of pemphigus

	Remarks
First line	
Corticosteroids (1.0–1.5 mg/kg/day initial dose; tapering by 25 % dose reduction every 2 weeks (more extended <20 mg day^{-1}))	Dose is given as prednisone equivalent; optimal dose not validated
Second line	(*In refractory disease, in addition to first-line therapy*)
Azathioprine (1–2.5 mg/kg/day), mycophenolates (2 g day^{-1}), or cyclophosphamide (500–750 mg i.v. as bolus or 50 mg/day p.o.)	Steroid-sparing effects are demonstrated for all immunosuppressants listed
Third line	(*In refractory disease, or in case of contraindications to immunosuppressive agents*)
Rituximab (2 × 1 g i.v. (2 weeks apart) or 4 × 375 mg m^{-2} (each 1 week apart)), IVIg (2 g/kg/month), immunoadsorption (on 3–4 consecutive days with 3–4-week intervals), dapsone (100 mg/day or up to 1.5 mg/kg/day), methotrexate (10–20 mg/week)	

Adapted from the 2013 European Guidelines, (Hertl et al. 2013)

As high-dose CS therapy did not differ from medium-dose usage (with regard to time to remission and relapse rates) in a prospective study with 22 pemphigus patients by Ratnam et al. (1990), moderate and individually adjusted CS use is advocated to prevent potentially severe side effects as hyperglycemia, osteoporosis, or iatrogenic Cushing's syndrome. When no new lesions appear and old ones begin to heal, CS are tapered by 25 % of the initial dose and, every 2 weeks, by another 25 % (with extended tapering at doses <20 mg/day). Nevertheless, there is little data supporting such a tapering regimen, which should be

always adjusted to the clinical context, response to therapy, clinical tolerance, and existing comorbidities. If lesions reappear during tapering of oral CS therapy, the dose should be increased again (and a change in adjuvant immunosuppression may be considered).

First-Line Adjuvants

Systemic CS are generally combined with an immunosuppressive adjuvant, although both the molecule of first choice and the best time for its introduction remain unclear (i.e., as early as possible vs. treatment-resistant cases or when contraindications to corticosteroid therapy exist). Following the 2013 European Guideline, first-line adjuvants are azathioprine (AZA) at doses of 1–3 mg kg/day and mycophenolate mofetil (MMF; 2 g/day) or mycophenolic acid (MPA; 1,440 mg day^{-1}).

In a large 4-arm RCT with 120 patients by Chams-Davatchi et al. (2007), the steroid-sparing effect of AZA has been shown to be superior to that of MMF. Beissert et al. (2006) compared two combination therapy protocols (CS plus AZA, both at 2 mg/kg/day, vs. CS plus MMF, at dosages of 2 mg kg/day and 2 g/day) and could not find differences regarding the clinical end points. In an intention-to-treat analysis, this study suggested that AZA had lower effectiveness than MMF in induction of disease control. In another RCT, Beissert et al. (2010) compared two protocols (CS [1–2 mg/kg/day] plus MMF [2–3 g/day] vs. CS [1–2 mg/kg/day] plus placebo). These authors were unable to demonstrate superiority of the combined regimen compared to CS alone as primary end point. As secondary end points, patients with adjuvant MMF appeared to have a shorter time to response and a more sustained duration of response. Nevertheless, the high dropout rate (>20 %), the side effects profile in the MMF group, and costs of MMF make any conclusion difficult. The most important side effects and peculiarities of the compounds discussed here are summarized in Table 69.2.

Second-Line Adjuvants

Options compliant with the 2013 guidelines are anti-CD20 monoclonal antibody (i.e., rituximab), intravenous immunoglobulins (IVIg), immunoadsorption, cyclophosphamide, methotrexate, and dapsone.

- Rituximab (RTX) is a chimeric IgG1 anti-CD20 monoclonal antibody that specifically binds the human CD20 antigen, expressed on the majority of B cells, except for early B-cell progenitors and plasma cells. RTX is usually given as either four weekly infusions of 375 mg m^{-2} (lymphoma protocol) or as two 1 g infusions, separated by 2 weeks (rheumatoid arthritis protocol). It is indicated in patients who remain dependent on more than 10 mg CS per day (combined with an immunosuppressive adjuvant). This treatment can be repeated with a single infusion of 1,000 mg (or even 500 mg) in case of clinical relapse and as early as 6 months after initial administration. So far, no RCT on RTX therapy in pemphigus has been published. Two uncontrolled prospective studies by Ahmed et al. (2006) and Joly et al. (2007) demonstrated initially high response rates: clinical remission after RTX administration (and, in one study, concomitant IVIg) was noted in 81–86 % of patients, which was, however, not sustained in every patient. In a recent retrospective study with 47 patients by Leshem et al. (2013), remission rates were 76 % after one cycle and 91 % after a second cycle. At a median follow-up time of 8 months, 22 % of patients experienced a relapse, and additional cycles led to remission in 75 % of those individuals. Of note, a retrospective study by Lunardon et al. (2012) underlined a higher efficacy in those patients treated earlier in the course of disease. A meta-analysis of 20 PF patients reported severe adverse events in only one (5 %) patient who developed a bacterial sepsis in contrast to severe adverse events (two of them fatal) in 14 (14 %) of 103 PV patients.

Table 69.2 Side effects of first- and second-line drugs in therapy of pemphigus, as mentioned in the text

Compound	Dosing	Peculiarities	Potential side effects
Corticosteroids, CS	1.0–1.5 mg/kg/day initial dose (prednisone equivalent)	Adjust dose to disease activity; combination with CS-sparing immunosuppressants often indicated	Hyperglycemia, osteoporosis, weight gain, Cushing's syndrome, fluid retention, immunosuppression, glaucoma, cataract, increased blood pressure, thinning of skin, mood changes
Azathioprine	1–2.5 mg/kg/day	Slow onset of efficacy; frequent controls of blood counts necessary; adjust dose to TPMT activity	Myelosuppression (usually manifested as neutropenia), nausea, immunosuppression, hepatotoxicity, increased risk for nonmelanoma skin cancers or lymphoma
Mycophenolates	2 g/day	Differences of bioactive MPA serum levels between patients; side effects profile more favorable compared to AZA but higher costs	Nausea, vomiting, reversible hematological adverse effects as leukopenia, thrombocytopenia; immunosuppression; rare cases of PML
Rituximab	2 × 1 g i.v. (2 weeks apart) or 4 × 375 mg m^{-2} (each 1 week apart)	Remarkable effect in treatment-resistant cases. Reinfusion may be necessary upon relapse; immunogenic potential of compound	Severe infections, deep venous thrombosis, sepsis, urticaria, arthralgia, anemia
Intravenous immunoglobulins	2 g/kg/month	May be cost-effective, although expensive; should be given in combination with other immunosuppressants; alternative for pregnant pemphigus patients	Infusion reaction (chills, pyrexia, tachycardia), aseptic meningitis, migraine, headache, renal insufficiency
Immunoadsorption	On 3–4 consecutive days with 3–4-week intervals	Fast removal of pathogenic serum antibodies; adsorption over 3–4 consecutive days; adjuvant treatment	Hypotension, bradycardia, sepsis (in particular with central venous line)
Cyclophosphamide	500–750 mg i.v. (as bolus) or 50 mg/day	Formation of metabolites, e.g., acrolein (needs to be antagonized with Mesna); prophylaxis of *Pneumocystis* (*carinii*) *jiroveci* pneumonia	Hematologic, gastrointestinal, pulmonary toxicities; risk of secondary malignancies after prolonged exposure (i.e., >20 g cumulative dose); gonadal toxicity and infertility after cumulative doses of >5 g
Methotrexate	10–20 mg/week	Anti-inflammatory properties	Myelosuppression, hepatic toxicity, pulmonary fibrosis
Dapsone	50–100 mg per day or up to 1.5 mg/kg/day	Anti-inflammatory properties; regular laboratory work-up with complete blood cell counts and liver enzymes required	Methemoglobinemia, hemolysis, agranulocytosis, very rare: hypersensitivity syndrome ("dapsone syndrome") with fever, rash, eosinophilia involvement of internal organs

- High-dose IVIg are clinically effective in pemphigus, as shown by a RCT in 61 Japanese patients. In this study, patients with PV and PF who did not respond to prednisolone doses of >20 mg day over at least 7 days received, over 5 consecutive days, a single cycle of 200 or 400 mg/kg/day or placebo. Lowering of disease activity and serum levels of anti-Dsg

antibodies in a dose-dependent manner was observed. The 2013 European Guidelines recommend combination of IVIg (2 g/kg/cycle^{-1}; applied monthly over 2–5 days) with systemic CS and immunosuppressive adjuvants, as IVIg alone may not lead to long-term suppression of autoantibody synthesis. Its favorable properties also render IVIg a very safe therapeutic alternative in pregnant pemphigus patients.

- Immunoadsorption (IA) allows for fast removal of circulating antibodies and is recommended as an option in patients who have not sufficiently responded to first-line treatment. Performed on 3 consecutive days, IA is capable of lowering anti-Dsg serum IgG by 95 % compared to initial measurements, and by combining IA with standard immunosuppressive therapy, reductions of about 90 % were maintained after 12 months (Schmidt et al. (2009)). Combination of IA with standard immunosuppressive therapy and the anti-CD20 monoclonal antibody RTX is reported with 80–96 % of patients in complete remission after 6–9 months of protocol treatment, and with 91 % overall complete remission rate after a mean follow-up of 33 months (Behzad et al. (2012), Kasperkiewicz et al. (2012a, b)). By this combination therapy, patients benefit from both the rapid reduction of serum autoantibody levels by IA and the excellent long-term effects of RTX.
- Cyclophosphamide (CYC) is an alkylating agent resulting in reduced lymphocyte counts, affecting both T and B cells. It shows the capacity to spare steroids, an effect, which was less attenuated that that of AZA and superior to that of MMF (Chams-Davatchi et al. (2007)). Oral administration at doses of 1–2 mg/kg/day may result in significant cumulative doses, and CYC-sparing pulsed monthly i.v. protocols were applied in pemphigus (Sethy et al. (2009)). Given the severe side effects (Table 69.2), safer therapeutic approaches such as rituximab, IVIg, and IA are currently replacing CYC in Europe and Northern America.
- Methotrexate (MTX) is a folic acid antagonist with antitumorigenic properties (at high concentrations) and anti-inflammatory properties (at low doses). Retrospective studies suggest clinical improvement at doses of 10–50 mg/week and a beneficial effect in control of less severe cases of pemphigus.
- Dapsone is a long-established sulfone derivative with both antibiotic and anti-inflammatory effects. In one placebo-controlled, randomized study in a small series of pemphigus vulgaris patients, Werth et al. (2008) investigated the efficacy of adjunct dapsone: the outcome was defined as the ability of tapering CS to at least 7.5 mg/day within 1 year of reaching the maximum dose of 200 mg/day dapsone, and, although not statistically significant, the trend favored the dapsone-treated group (8/11 patients reached the primary outcome measure, with no adverse effects, vs. 3/10 patients receiving placebo). The European Guideline recommends, if considered, 100 mg/day or doses up to 1.5 mg/kg/day.

Additional Supportive Treatments and Precautions

Besides systemic pharmacologic therapy, additional topical and external therapies have a place and are beneficial in management of the disease. According to the European Guideline, these measures include:

- Intralesional CS injections for isolated lesions of the skin (triamcinolone acetonide)
- Topical treatment of lesions with potent CS (clobetasol propionate) or calcineurin inhibitors
- Antiseptic baths
- Covering of erosive lesions with low-adhesive wound dressings or local emollients
- Analgesics

Prolonged CS therapy and immunosuppression require additional measures of precaution, including:

- Prophylaxis of osteoporosis (bone density scans, vitamin D and calcium supplementation)
- Ophthalmologic controls
- Use of antifungals, antivirals, and/or antibiotics, when clinically indicated

- Prevention of gastric/duodenal ulcers (H2-blockers, proton-pump inhibitors)
- Antithrombotic prophylaxis, when appropriate
- Vaccinations against seasonal influenza, tetanus, and pneumococcus (although the protection may be questionable during immunosuppressive therapy)
- Support from psychologists and physiotherapists
- Use of sunscreens and avoidance of bright sunlight

Follow-Up and Discontinuation of Therapy

Due to the potential side effects from therapy and the chronic course of disease, patients should be monitored closely, not for disease control only, but for tolerance to treatment and side effects. Based on the evolution of disease, serological monitoring by Dsg1-ELISA and/or IIF should be performed regularly. After discontinuation of systemic CS in patients with complete remission, adjuvant immunosuppression can also be reduced over 6–12 months. The discontinuation of therapy is primarily based on the clinical presentation with complete absence of active cutaneous lesions over several months. In these cases, negative or low ELISA-Dsg1 values or negative direct IF microscopy findings are useful markers to support discontinuation of therapy, but prospective studies are needed to assess their exact role in guiding management.

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Pemphigus Vegetans

70

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Abbreviations

CS	Corticosteroids
Dsg	Desmoglein
IF	Immunofluorescence
Pveg	Pemphigus vegetans

Key Points

- Pemphigus vegetans is a rare variant of pemphigus vulgaris that is predominantly associated with autoantibodies directed against desmogleins.
- Historically, two forms have been differentiated, the Hallopeau type and the Neumann variant. Nevertheless, there are overlaps between these two forms and with pemphigus vulgaris.
- Treatment options are essentially based on the guidelines proposed for pemphigus as well as case reports.

Definition and Epidemiology

Pemphigus vegetans (Pveg) is a rare (<5 %) variant of pemphigus vulgaris clinically characterized by chronic vegetating erosions. These affect primarily the intertriginous areas. Historically, two forms were described, the Hallopeau type and the Neumann type. Although clinical features may be distinctive, overlaps between these two types and with pemphigus vulgaris exist. It is therefore questionable to consider Pveg as a distinct entity but rather a clinical phenotype observed within the pemphigus vulgaris spectrum (Figs. 70.1, 70.2 and 70.3).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_70, © Springer-Verlag Berlin Heidelberg 2015

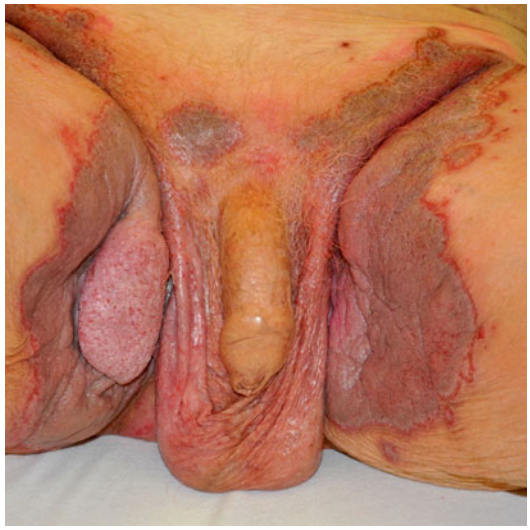

Fig. 70.1 Typical features of pemphigus vegetans, Hallopeau type. There are extensive vegetating, papillomatous, and eroded lesions in the inguinal folds. Pustules are observed at the periphery of the large plaques

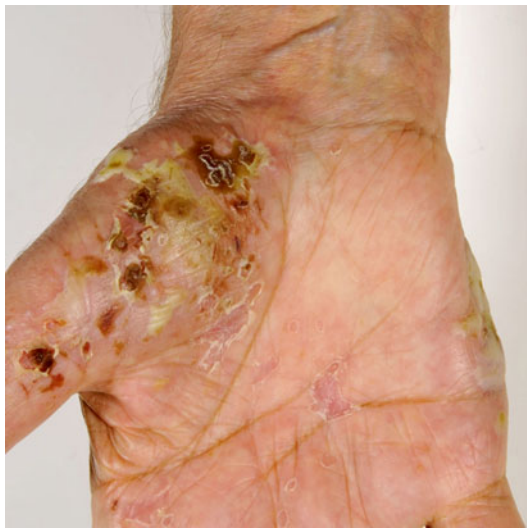

Fig. 70.2 Pemphigus vegetans, Hallopeau type. Grouped pustular lesions on the palm

Due to the rarity of Pveg, there is only little insight in the mechanisms responsible for the peculiar presentation and evolution of Pveg.

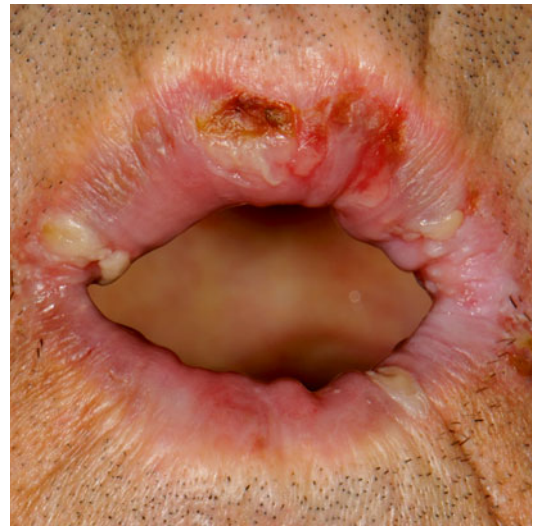

Fig. 70.3 Pemphigus vegetans, Hallopeau type. Perioral pustular lesions with involvement of the lips

Basic Concepts of Pathogenesis

Desmoglein 3 (Dsg3) has been found to be the main and preferential target antigen of Pveg, although a number of patients have anti-Dsg1 and, more rarely, anti-desmocollin 1 or 3 antibodies. It is likely that a different pathogenicity of the autoantibodies (specificity for distinct antigenic sites within the Dsg3 ectodomain, distinct IgG subclass profile) plays a role in the peculiar clinical presentation of affected patients. Other genetic and environmental factors may also be relevant. In case of the pustular Hallopeau form, the presence of distinct HLA loci also found in pustular psoriasis may contribute to the clinical picture. In some patients, intake of angiotensin-converting enzyme inhibitors, penicillamine, or other drugs was described as trigger.

Clinical Presentation

The Neumann type of Pveg was first described in 1886. It begins with extensive blistering and characteristically shows a tendency to heal

with papillomatous vegetations. The Hallopeau type, described in 1889, is rather associated with pustules having a grouped or annular distribution that subsequently develop into vegetating and eroded lesions with an unpleasant odor and without frank blister formation. The Nikolsky sign may be positive. Lesions can be restricted to a single site in the initial phase of the disease and then become multifocal. Although most lesions are typically located in intertriginous spaces (groins, axillae, intergluteal folds, etc.), any area of the integument can be affected. Involvement of the scalp, soles, genitalia, and nails has been described. Involvement of the lips, oral commissure, and oral mucosa also is possible. Oral lesions are usually few in number, rarely vegetating, and usually resemble those found in pemphigus vulgaris. Food intake may be disturbed by significant pain from oral lesions, and rarely, esophageal involvement leads to weight loss. In some cases, a presentation of Pveg is observed during the course and treatment of other forms of pemphigus, an observation arguing against the idea of Pveg being a separate entity. According to a retrospective study by Zaraa et al. (2011) including 17 patients, the Neumann subtype occurred in about two-thirds and the Hallopeau form in one-third of patients. In one patient, both clinical variants coexisted (simultaneously or serially). There is some controversy if the Hallopeau variant really has a more favorable course than the Neumann subtype, as often reported, since no large case series with follow-up are available.

Diagnosis and Differential Diagnosis

To confirm the clinical diagnosis suspected on clinical grounds of the aforesaid, the following investigations are essential: (1) lesional histopathology, (2) direct immunofluorescence (IF) microscopy of perilesional skin, and (3) serological detection of anti-epithelial cell-surface antibodies by indirect IF microscopy (using monkey esophagus or guinea pig esophagus as substrate) and Dsg3 ELISA. The number of circulating eosinophils may be increased in some patients.

- Lesional histopathology typically shows suprabasal intraepidermal acantholysis, papillomatosis, and/or eosinophilic abscesses. The formation of intraepidermal microabscesses and eosinophilic infiltration helps differentiate Pveg from pemphigus vulgaris.
- Direct IF microscopy findings, however, are indistinguishable from those in classical pemphigus vulgaris and reveal deposition of IgG/C3 at the intercellular space of keratinocytes. Labeling of IgA, isolated or combined with IgG/C3, is rarely observed.
- Circulating autoantibodies against Dsg3 are frequently detectable by commercially available ELISAs. In occasional cases, autoantibodies against Dsg1, desmocollins, and periplakin have also been detected.

Knowledge of the peculiar clinical presentation of Pveg is essential to consider the diagnosis, carry out the appropriate immunopathological and immunoserological studies, and start appropriate management of affected patients.

Differential diagnoses of Pveg include:

- IgA pemphigus
- Neutrophilic dermatoses (negative IF microscopy studies)
- Halogenoderma (intake of halogen-containing drugs, negative IF microscopy studies)
- Pyodermatitis-pyostomatitis vegetans (negative IF microscopy studies, presence of chronic inflammatory gastrointestinal diseases—ulcerative colitis, Crohn's disease)
- Acrodermatitis continua suppurativa Hallopeau (variant of pustular psoriasis; negative IF microscopy)
- Keratoderma blenorrhagicum of Reiter's syndrome (negative IF microscopy)
- Paraneoplastic pemphigus (association with lymphoproliferative disorders distinct

immunopathological profile with anti-plakin antibodies)
- Tinea capitis with kerion formation (positive mycology)
- Hailey-Hailey disease (negative IF microscopy, family history)

General Principles of Treatment

Given the rarity of Pveg, data from randomized controlled clinical trials are not available. As treatment regimens for Pveg do not differ significantly from those for pemphigus vulgaris (and pemphigus foliaceus), we refer to the corresponding chapters (see Chapter 71) and to the 2013 European Guidelines on treatment of pemphigus for more detailed information.

The overall aim of therapy is to induce remission from disease, to improve quality of life of affected patients, and to avoid complications related to both the skin disease and the introduced therapy.

Generally, systemic corticosteroids (CS) are the mainstay of therapy and should be combined with immunosuppressants (e.g., azathioprine, mycophenolates) in refractory cases. Due to the vegetating and verrucous lesions and their peculiar distribution in flexural areas, the use of topical medications in addition to systemic therapy has a more important role in controlling lesions compared to pemphigus vulgaris, and in IgA-related cases the use of dapsone may be beneficial. Here, we provide a short overview of anecdotic treatment regimens successfully used in Pveg patients:

- Dapsone, a sulfone derivative, may result in an excellent response (check first for G6PD serum activity and ensure laboratory follow-up).
- Single patients have been treated by combination of CS and etretinate (10–50 mg/day). The latter molecule has now been replaced by acitretin (a metabolite of etretinate).
- Extracorporeal photopheresis has successfully been used in a patient with recalcitrant Pveg who had severe side effects from long-term treatment with CS and azathioprine (Kaiser et al. (2007)).
- Combination therapy of CsA (300 mg/day) with CS induced full remission within 3 weeks in one report.
- In a case of Pveg with esophageal involvement, the combination of minocycline (100 mg/day) and nicotinamide was reported as successful (Sawai et al. (1995)).
- Etanercept, an inhibitor of TNF-α, has been used in a recalcitrant case of Pveg: Blistering was controlled by combining etanercept, CS, and azathioprine (Lin et al. (2005)).

Additional Supportive Treatments and Precautions

Besides systemic therapy, additional topical and external therapies are beneficial in the management of the disease, including intralesional CS injections, topical treatment of lesions with very potent CS, antiseptic baths, low-adhesive wound dressings, and analgesics. The use of skin grafting or laser vaporization seems questionable (Motomura et al. (2009)).

Follow-Up and Discontinuation of Therapy

Due to the potential side effects from CS therapy and immunosuppression and the chronic course of the disease, patients should be monitored closely. Discontinuation of therapy is primarily based on the clinical presentation with absence of lesions under minimal therapy (prednisolone equivalent at or below 10 mg/day) over several months. Negative direct IF microscopy studies and serum anti-Dsg3 ELISA reactivity may represent valuable prognostic markers.

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Pemphigus Vulgaris

71

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Abbreviations

6-MP	6-mercaptopurine
Ach	Acetylcholine
CS	Systemic corticosteroids
Dsg	Desmogleins
IIF	Indirect immunofluorescence
DIF	Direct immunofluorescence
ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
HPRT	Hypoxanthine guanine phosphoribosyltransferase
IA	Immunoadsorption
IV	Periodic Intravenous
IVIg	Intravenous immunoglobulin
LFT	Liver functions tests
MMF	Mycophenolate mofetil
MTX	Methotrexate
PV	Pemphigus vulgaris
RA	Rheumatoid arthritis
TPMT	Thiopurine methyltransferase

Key Points

- Pemphigus vulgaris (PV) is a potentially life-threatening blistering disorder due to autoantibody formation against a plethora of epithelial antigens (including both adhesion and nonadhesion molecules) characteristic of epidermis and other stratified squamous epithelia.
- Genetic predisposition, based on a complex polygenic basis ("the soil"), though essential, is not by itself sufficient to initiate the autoimmune mechanism. The intervention of many and various inducing or triggering environmental factors ("the seed") seems to be crucial to set off the disease.
- The clinician, who plans the therapy, cannot overlook the frequent association of PV with other preexisting or coexisting conditions (diabetes, hypertension, peptic ulcer, autoimmune diseases, and neoplasms), as well as the existence of wide clinical variations of the disease.
- Due to the lack of standard criteria of care, the management of PV cannot be based on large-scale randomized controlled trials, but is hinged more on expert opinion rather than on empirical evidence. For all these reasons, to indicate a standard treatment tailored to all

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_71, © Springer-Verlag Berlin Heidelberg 2015

forms of PV and to each patient's needs is a utopian task.
- Of note, the growing interest towards PV genetics and, in particular, a more complete knowledge of its complex polygenic basis may lead to the development of a genetic-based tailored therapy in the next future.
- In this chapter, therapeutic guidelines for cases of PV of average severity, along with grades of recommendation and levels of evidence that are associated to the proposed treatments, are indicated. Supportive measures, precautions, and suggestions for PV patients are also outlined.

Definition and Epidemiology

Pemphigus (from the Greek πέμφιξ-ίγος that means blister) vulgaris (from the Latin for common) (PV) is the most frequent and representative form of a group of mucocutaneous diseases (autoimmune pemphigus) characterized by intraepithelial blister formation.

PV is a potentially life-threatening blistering disorder sustained by autoantibody formation against a plethora of epithelial antigens including both adhesion and nonadhesion molecules characteristic of the epidermis and other stratified squamous epithelia. Its incidence is estimated at one to five cases per one million inhabitants per year but is much higher in some Ashkenazi Jewish populations and in Eastern countries, such as India, Malaysia, China, and Japan. The mean age at onset ranges from 40 to 60 years, although several cases have been reported in childhood, adolescence, and old age. PV shows equal or quite equal frequencies among males and females in the Northern countries (North America, UK, France) as well as Malaysia and India, while a female predominance (range M/F: 1/1.1–1/2.25) is reported in Mediterranean areas and at temperate latitude (Italy, Israel). Sex gender may play a role due to its influence on the immune system disclosed at many levels, such as sex chromosomes, hormonal makeup (sex steroids and prolactin), childbearing potential, pregnancy, sociological characteristics, and finally psychological makeup.

The existence of a complex polygenic basis, involving both HLA loci and non-HLA ones (desmoglein 3, immunoglobulin heavy chain constant region, tyrosine phosphatase N22 genes), seems to be established. To date, the association between HLA class II genes (DR4, DR14, DQ1, and DQ3) and PV is the strongest one. Recent molecular gene subtyping studies have revealed a significant increase of DRB1*0402, DRB1*1401, DRB1*1404, DRB1*1454, DQB1*0503, and DQB1*0302. Furthermore, some findings focus on the HLA class I A (A3, A10, A26, B15, B35, B38, B44, and B60) and HLA class I B (HLA-E*0103) antigens.

Basic Concepts of Pathogenesis

According to the recent "apoptolysis (apoptosis-acantholysis) theory," PV would be the consequence of simultaneous, synergistic, and cumulative effects of a constellation of autoantibodies targeting several keratinocyte cell membrane antigens, so disrupting the epidermis integrity through steric, immunological, and biochemical events ("multiple hit theory").

Cell-cell dishesion is depicted as a multistep mechanism initiating with the autoantibody binding to keratinocyte membrane and subsequent activation of the apoptotic machinery; continuing with basal cell shrinkage (early acantholysis) and internalization of extra-desmosomal desmogleins; and ending up with complete cell-cell detachment, formation of suprabasal clefts (advanced acantholysis), rounding up with apoptotic death of isolated parabasal keratinocytes (Tzanck cells), and "tombstoning" of the surviving basal cells.

Originally, desmogleins 1 and 3 (Dsg1 and Dsg3), both combined with plakoglobin, and belonging to the cadherin supergene family, have been representing the necessary and sufficient

targets of pemphigus antibodies, usually known as intercellular antibodies ("compensation theory" by Amagai and Stanley). In the last years, other autoantibodies directed towards non-Dsg antigens (desmocollins, plakoglobin, FcεRIα, annexins, PERP (a tetraspan membrane protein implicated in apoptosis and adhesion), and acetylcholine (Ach) receptors) have been found in PV sera. The presence of autoantibodies towards Ach receptors (nicotinic, muscarinic, the mixed muscarinic and nicotinic α9-AchR, and pemphaxin) outlines the involvement of a possible impairment in the keratinocyte acetylcholine axis, which plays a pivotal role in regulating proliferation, cell adhesion, motility, and desmosomal cell contact.

Genetic factors alone are essential but not enough to initiate the autoimmune response. Factors able to facilitate PV in genetically predisposed individuals are many and various. Most of them are exogenous and directly originating from the environment (e.g., drug intake, viral infections, physical agents, contact allergens, diet); however, also endogenous factors, such as emotional stress and hormonal imbalance, can be taken into account.

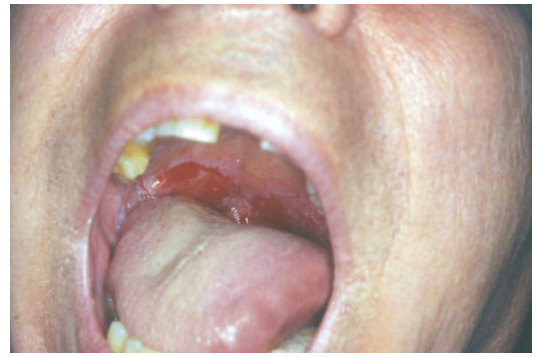

Fig. 71.1 Oral pemphigus

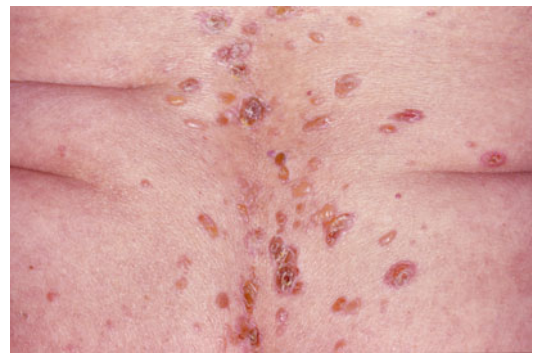

Fig. 71.2 Pemphigus vulgaris on the trunk

Clinical Presentation

The primary lesion is a flaccid bulla containing a serous fluid and occurring on apparently normal skin or mucosa (cold bulla). The duration of this bulla is ephemeral, particularly in mucous membranes, due to the fragility of the roof; their tearing produces serum-weeping erosions that reepithelialize gradually.

In nearly two-thirds of cases, PV begins in the oral mucosa, where the disease can remain confined for several months (oral pemphigus) (Fig. 71.1). Intact bullae are quite an uncommon finding in the mouth, where poorly healing erosions represent the hallmark lesions. They are typically painful, in particular to the contact with sour or salty foods and drinks. Salivation becomes abundant with frequent bloody streaks. It is almost constant a characteristic "fetor" of the mouth. With their spreading, the lesions then affect the epiglottis, pharynx, and larynx, not infrequently causing odynophagia and dysphonia. Lips are often covered by bloody crusts, which constantly detach and reappear.

Subsequently, PV affects the skin with a certain predilection for the trunk, intertriginous areas (axillae, submammary, umbilical, and inguinal regions), as well as the scalp (Fig. 71.2). The size of bullae can vary from a lentil to an egg; the content, initially serous and clear, becomes purulent or serohematic after a few days and characteristically does not fill the cavity, giving a typical flaccid appearance to the lesion. Some of the bullae wilt, so resulting into squamous crusts; others break, so evolving in serum-weeping erosions that heal slowly without scarring sequelae. In the most severe forms, oral and skin manifestations are associated to lesions affecting other mucous membranes (esophageal,

genital, urethral, anal, and less often conjunctival) and sometimes keratinized appendages (areas of alopecia, onychomadesis). If a treatment is not started, the disease becomes generalized (new crops of bullae appear everywhere, more and more areas of skin present eroded and crusted): there is a progressive loss of serum, blood proteins, and electrolytes, which, together with the considerable difficulty in eating and frequent opportunistic infections of the eroded areas, seriously compromises the overall condition of the patient, leading to death in 2–3 years. The use of systemic glucocorticoids and immunosuppressive drugs has completely modified the natural course and dramatically improved the prognosis of the disease. Currently, mortality from PV is low, but deaths from treatment complications are not a rare event.

Diagnosis

PV diagnosis is generally based on typical clinical findings (including Nikolski signs), histopathological as well as immunohistochemical examinations, and finally laboratory tests. Nikolski sign I is evoked when a lateral pressure is applied to the edge of a blister or to normal-appearing skin, with resultant enlargement of the preexisting bulla or formation of a new bulla. Peripheral extension of a bulla can also be obtained by exerting a direct pressure onto it (Nikolski sign II or Asboe-Hansen sign). Despite being significant, both these clinical signs lack an absolute diagnostic value. In our experience, Tzanck test is a useful diagnostic tool although it is not required by some experts as a key diagnostic finding: by scraping the floor of a skin or oral lesion of recent onset, typical acantholytic cells may be observed under light microscopy. Biopsy, performed on recent bulla including a small margin of healthy tissue, shows the presence of suprabasal cavities. Histological diagnosis should be confirmed by immunofluorescence. Direct immunofluorescence (DIF), performed on perilesional intact skin/mucosa or uninvolved skin, shows the deposition of intercellular antibodies and often C3 in the epidermis. Indirect immunofluorescence (IIF) on monkey esophageal epithelium both detects and determines pemphigus antibodies titers. Despite being less sensitive than DIF, IIF is more common in clinical practice, especially when biopsy is difficult to perform (uncooperative patients). Enzyme-linked immunosorbent assay (ELISA) is available for direct measurement of anti-Dsg3 and anti-Dsg1 serum antibodies, thus superseding IIF due to its higher sensitivity and specificity (particularly useful in detecting anti-Dsg3 in IIF negative PV patients). ELISA has shown a significant association between anti-Dsg1 as well as anti-Dsg3 titers and disease localization: mucosal dominant PV has a strong correlation with anti-Dsg3 positivity, while mucocutaneous PV type has high titers of both anti-Dsg1 and anti-Dsg3. However, the link between these titers and PV activity (severity, relapse) as well as response to treatment is still a controversial topic. Some authors claim that antibodies titers do not correlate with disease activity and therapeutic response, while others claim that anti-Dsg3 and anti-Dsg1 titers are reliable indicators of disease activity and severity, treatment status, and clinical course. In fact, both anti-Dsg1 and anti-Dsg3 titers (particularly the former compared with the latter) have been found to be significantly reduced after treatment and achievement of clinical remission. A strong association has recently been demonstrated between salivary anti-Dsg1 antibodies and mucosal severity of PV. When the diagnosis remains uncertain, immunoprecipitation and immunoblotting studies on serum are needed. In conclusion, expert opinion rather than empirical evidence still has a pivotal role in PV diagnosis, due to the lack of large-scale controlled trials, which can explain wide variations among diagnostic techniques. Although the desire of establishing common diagnostic criteria, through epidemiological studies, has been emerging, this goal is still far.

Differential Diagnosis

Recurrent aphthous stomatitis, Behcet's disease, erosive lichen planus, Stevens-Johnson syndrome, or cicatricial pemphigoid may simulate oral pemphigus: however, in all these conditions,

Tzanck test is always negative. Widespread skin erosions may evoke the diagnosis of bullous pemphigoid, glucagonoma syndrome, and epidermolysis bullosa: the findings of acantholytic cells (pathognomonic of pemphigus), of intercellular antibodies by immunofluorescence, and anti-Dsg 3 antibodies by ELISA (both hallmarks of PV), remove any doubt. In particular circumstances (e.g., suspicion of paraneoplastic pemphigus), immunoprecipitation or immunoblotting may help to establish the diagnosis.

General Principles of Treatment

The initial aim of treatment in PV is to halt blister formation, promote healing of blisters and erosions, and determine the minimal dose of medication necessary to control the disease, while the ultimate aim should be drug withdrawal.

Since the introduction of systemic corticosteroids (CS), in the 1950s, and immunosuppressive agents, in the 1960s, the prognosis of the disease has been dramatically improving.

However, mortality, although decreased, still remains at a relatively high level (12 %): in most cases, death is not related to PV itself but to the complications of long-term therapy. Along with treatment adverse effects, the clinician, who plans the therapy, cannot overlook the frequent association with other preexisting or coexisting conditions (diabetes, hypertension, peptic ulcer, autoimmune diseases, and neoplasms), as well as the existence of wide clinical variations of PV and the lack of standard criteria of care based upon large-scale randomized controlled trials. As a result, PV treatment has been hinged solely on expert opinion rather than on empirical evidence. For all these reasons, to indicate a standard treatment tailored to all forms of PV and to each patient's needs is a utopian task. Of note, the growing interest towards PV genetics and, in particular, a more complete knowledge of its complex polygenic basis may in the next future lead to the development of a genetic-based tailored therapy.

Therapeutic guidelines for cases of average severity, along with associated grades of recommendation and levels of evidence (Table 71.1), are given here. Supportive measures, precautions, and suggestions for PV patients are also outlined.

General Therapeutic Guidelines

The combination of CS and immunosuppressive drugs (used as adjuvant medications for their steroid-sparing effect) is the cornerstone of management in PV. As a rule, the impact of the initial treatment determines the therapeutic outcome. For this reason, we recommend a full steroid dosage even in less severe cases, although some Associations of Dermatologists suggest patients with mild disease should receive an initial prednisone or prednisolone dosage of 40–60 mg/day, while patients with severe disease a dosage of 60–100 mg/day.

There are two schedules of using this combination therapy depending on the disease severity: conventional therapy (orally given), in mild to moderate cases of PV, which uses continuous high dosage, and pulse therapy (intravenously given) in severe life-threatening or recalcitrant PV cases, that instead administers intermittent exceedingly high doses.

Concerning CS, it is worth noting that, in addition to their well-known immunosuppressive and anti-inflammatory activities, these drugs also exert a typical action in PV regulating adhesion and viability of keratinocytes, through a combination of genomic and nongenomic pathways. They upregulate the expression of several genes and block the post-transcriptional phosphorylation of some adhesion molecules, so interfering with the pathogenic mechanisms carried out by PV antibodies.

The immunosuppressive drug used in conventional therapy is usually azathioprine, claimed to be the most effective steroid-sparing agent: in the early stages, it is used in combination with oral CS to induce PV remission and then alone to maintain the achieved clinical remission after CS withdrawal. When contraindicated, it can be replaced by other drugs (oral cyclophosphamide,

Table 71.1 Grades of recommendation and levels of evidence associated to most of the treatments for PV discussed in the text

Drug or treatment	Strength of recommendation	Quality of evidence
Oral corticosteroids	A	II-iii
Azathioprine	B	II-iii
Oral cyclophosphamide	B	III
Mycophenolate mofetil	B	III
Methotrexate	C	III
Chlorambucil	C	IV
Cyclosporine	C	I
Dapsone	C	IV
Pulsed corticosteroids	C	IV
Pulsed cyclophosphamide and corticosteroids	B	II-iii
IVIg	B	III
Gold	B/C	III
Tetracyclines and nicotinamide	C	IV
Plasmapheresis	C	I
Immunoadsorption	Unreported	Unreported
Grades of recommendation		
A. There is good evidence to support the use of the procedure		
B. There is fair evidence to support the use of the procedure		
C. There is poor evidence to support the use of the procedure		
D. There is fair evidence to support the rejection of the use of the procedure		
E. There is good evidence to support the rejection of the use of the procedure		
Levels of evidence		
I: Evidence obtained from at least one properly designed, randomized controlled trial		
II–i: Evidence obtained from well-designed controlled trials without randomization		
II–ii: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group		
II–iii: Evidence obtained from multiple time series with or without the medical intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence		
III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees		
IV: Evidence inadequate owing to problems of methodology (e.g., sample size, or length or comprehensiveness of follow-up or conflicts of evidence)		

cyclosporine, mycophenolate mofetil, methotrexate, chlorambucil, and others).

The adjuvant drug used in pulse therapy is cyclophosphamide, first in combination with intravenous CS, and then alone.

Although PV is largely managed with systemic therapy, supplementary topical treatment may be of additional benefit: this is aimed at preventing local infections and stimulating reepithelialization of eroded areas.

Conventional Therapy

In our experience, associated *deflazacort* and *azathioprine* offer the best therapeutical results and the fewest side effects, except for the patients who carry a double low-activity allele for thiopurine methyltransferase (TPMT), being at risk of myelosuppression when long treated with azathioprine. The effect of azathioprine is exerted by active 6-thioguanine nucleotide metabolites,

I Attack treatment for 4 weeks

- Deflazacort 120 mg daily
- Azathioprine 100 mg daily

IIa Alternate day decrease in steroid dosage

Days	1	2	3	4	39	40
Deflazacort (mg)	120	114	120	108	120	0
Azathioprine		100 mg daily			100 mg daily	

IIb Weekly decrease in steroid dosage

Weeks	I							II							VI						
Days	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Deflazacort (mg)	120	0	120	0	120	0	120	105	0	105	0	105	0	105	45	0	45	0	45	0	45
Azathioprine							100 mg daily								100 mg daily						

III Maintenance treatment: spacing steroid administration

- Deflazacort 45 mg every other day for 2 months
  45 mg every third day for 2 months
  45 mg on Tuesday and Friday for 2 months
  45 mg weekly for 6 months to 2 years
- Azathioprine 100 mg daily

Fig. 71.3 Stages of conventional corticosteroid-immunosuppressive therapy for PV

generated by hypoxanthine guanine phosphoribosyltransferase (HPRT) once 6-mercaptopurine (6-MP) crosses cell membranes. These metabolites compete with their endogenous counterparts in several biochemical pathways (nucleotides are precursors of RNA and DNA as well as carriers of energy and second messengers). As a result, azathioprine has both immunosuppressive and cytotoxic properties.

The schedule of conventional treatment is organized in four stages (Fig. 71.3).

Front-Line Treatment

Therapy starts with an attack steroid dosage of about 2 mg/kg/day deflazacort (120–150 mg/die) and 1.5 mg/kg/day azathioprine (100 mg/die) until all active lesions disappear, which on average requires 4 weeks.

Decreasing Steroid Dosage on Alternate Days

The only steroid dosage is lowered by 6 mg on alternate days progressively down to zero: this requires at least 6–7 weeks. On the other days, the initial dose of deflazacort (120–150 mg/die) remains unchanged. Azathioprine dosage is not modified.

At the end of this period, esophagoscopic monitoring and ELISA test for anti-Dsg1-Ab should be performed, and the patient's condition should be carefully assessed.

Decreasing Steroid Dosage Weekly

If the therapeutical response is good, the alternate-day administration of deflazacort will be lowered by 15 mg weekly until it reaches

45 mg, while it seems wise not to reduce azathioprine dose in the mean time. Should mucosal lesions still persist or the antibody titer rise, the alternate-day full-dose deflazacort cannot be lowered, while the daily dose of azathioprine can be increased to 150 or 200 mg, until signs of active PV disappear. Only after that deflazacort decreasing can be accomplished as indicated above.

As a result, the duration of this last schedule strictly depends on the course of the disease.

Once 45 mg dosage is reached, deflazacort is continued for alternate days for 2 months.

Maintenance Treatment: Distancing Steroid Dosage

After the 2 months of deflazacort 45 mg on alternate days, its dosage is gradually spaced out to every third day (for a further 2 months), twice a week (for another 2 months), and subsequently once a week for a variable period (6 months to 2 years). The concomitant daily dose of azathioprine is maintained at 100 mg. There are no absolute criteria for when treatment can be stopped.

In most cases, if remission lasts 2 years, the weekly administration of deflazacort at 45 mg can be discontinued, thus giving the patient only azathioprine at an unmodified dosage (usually 100 mg/day) for another year. Then, even the azathioprine treatment may be stopped.

In case of relapses, the high-dosed combination may be taken into account, although less severe forms may reasonably be treated with immunosuppressive drugs alone.

Side Effects of CS and Azathioprine

The early unavoidable adverse effects of CS include enhanced appetite, changes in blood glucose levels and serum electrolytes, fluid and salt retention resulting in weight gain, neuropsychiatric disorders (emotional lability, insomnia, irritability, anxiety, depression, euphoria, hyperactivity, and manic episodes), infections, and transient hematological abnormalities. Delayed drawbacks include cushingoid appearance, hypothalamic-pituitary-adrenal suppression, hyperlipidemias, atherosclerosis, cardiovascular events, cataracts, growth retardation, osteoporosis, osteonecrosis, myopathy, muscle cramps, weakness, and skin bruising and thinning. Furthermore, CS treatment may aggravate concomitant acne vulgaris, diabetes mellitus, hypertension, and peptic ulcer disease.

As to azathioprine, nausea and myelosuppression are related to TPMT activity, while hepatotoxicity, hypersensitivity reactions, rash, pancreatitis, and increased susceptibility to infections are unrelated to TPMT status. Patients who are homozygotes for the low-activity allele encoding TPMT are at risk for severe myelosuppression if treated long term, due to the lack of its metabolism ability. Therefore, before starting the treatment, TPMT measurement should be performed in all patients prescribed azathioprine for dermatological conditions. As this enzymatic assay is not easy to perform, the evaluation of azathioprine toxicity is carried out through periodic monitoring of the full blood count (FBC) and liver functions tests (LFT), with a weekly frequency for the first 4 weeks or until maintenance dose is achieved. In the maintenance period, the monitoring frequency can be reduced to once every 3 months for the duration of therapy. A more frequent evaluation of FBC and LFT is advised in patients with hepatic or renal impairment, in the elderly, and in those treated with high doses of azathioprine.

Immunosuppressive Drugs Replacing Azathioprine

When contraindicated, azathioprine can be replaced by other immunosuppressants that proved to be effective in controlling PV patients if added to the basic steroid treatment (steroid-sparing agents).

Oral *cyclophosphamide* (1–3 mg/kg daily in two or three divided doses) can be an alternative to azathioprine if secondary infertility is not a concern. Long-term use of oral cyclophosphamide may cause sterilization with azoospermia

(this explains why this drug should be avoided in young patients), hematological abnormalities (lowering in platelets and leukocytes), hair loss, gastrointestinal disturbance, raised transaminases, potential risk of hemorrhagic cystitis, and carcinoma of the bladder.

Mycophenolate mofetil (MMF) at a daily dosage of 2–2.5 g, given in two divided doses with CS, is a relatively new drug in PV treatment, to be considered in recalcitrant cases or when azathioprine or cyclophosphamide are unsuitable. MMF is believed to have a favorable safety profile compared with other immunosuppressive drugs (including azathioprine) because of its selective inhibitory action on inosine monophosphate dehydrogenase affecting "de novo" purine synthesis of mainly T and B lymphocytes. Compared with azathioprine, despite having an inferior steroid-sparing activity, MMF is more effective in inducing disease control. MMF should be preferred to azathioprine not only in the homozygotes for the low-activity allele for TPMT (see above) but also when treating PV patients with a coexistent herpetic infection, since the former markedly potentiates the antiherpes virus activities of acyclovir, ganciclovir, and penciclovir, while the latter can undermine the host's antiviral defenses. Although MMF has a better safety profile, it may evoke the same adverse effects associated to immunosuppressive drugs (gastrointestinal disturbances, hematologic alterations, and increased risk of opportunistic infections): their incidence is relatively lower if compared to that reported with other immunosuppressive agents. MMF has been used with good results even in monotherapy. As experience increases, it may supersede other agents as the immunosuppressant of choice due to its efficacy and more favorable safety profile.

Methotrexate (2.5 mg every 12 h × 3 doses each week) (MTX) can be considered as adjuvant treatment if more established drugs cannot be used. Methotrexate has been recently reevaluated after early reports of high mortality and morbidity rates. Its drawbacks include myelosuppression, hepatotoxicity, and pneumonitis.

Oral *chlorambucil* (4–6 mg once daily) is another adjuvant drug that can be considered when more established options cannot be used. To date, there are still limited data to support its administration.

Cyclosporine (5 mg/kg daily) in association with CS offers no advantage over treatment with CS alone in PV patients. Thus, on the basis of the current evidence, it cannot be recommended as an adjuvant drug.

Dapsone (50–200 mg daily) has been suggested as a steroid-sparing agent in the maintenance phase of PV treatment or as a first-line agent. However, little evidence to recommend the use of dapsone in PV is available. The untoward effects occurring with high/protracted doses of this drug include methemoglobinemia and hemolytic anemia, which often force the reduction of the dosage or the discontinuation of dapsone. Glucose-6-phospate dehydrogenase deficiency (G6PD) is an absolute contraindication to its administration. A combination of CS and dapsone may be used in childhood PV to avoid severe effects of immunosuppressants in the growing age.

Pulse Therapy

Pulse therapy entails the periodic intravenous (IV) administration of massive doses of CS (dexamethasone or methylprednisolone) and of the immunosuppressive drug (megadoses or boluses), interspersed by the oral assumption of low doses of the immunosuppressant only. This schedule may be considered in patients with very severe forms of PV and with high antibody titers, particularly if unresponsive to high oral doses.

On the first day, *dexamethasone* (100 mg) or, alternatively, *methylprednisolone* (500 mg) is associated with *cyclophosphamide* (500 mg) and dissolved in 500 mL of 5 % glucose solution given by slow IV drip (1–2 h); on the second and third day, 100 mg dexamethasone (or, alternatively, 500 mg methylprednisolone) alone (without cyclophosphamide) is administered again by IV drip; from the fourth to the 14th day, only 50 mg/day of cyclophosphamide is given orally. Subsequently, the previous cycle is resumed. The interval between boluses, initially 2 weeks, is then increased to 4 weeks

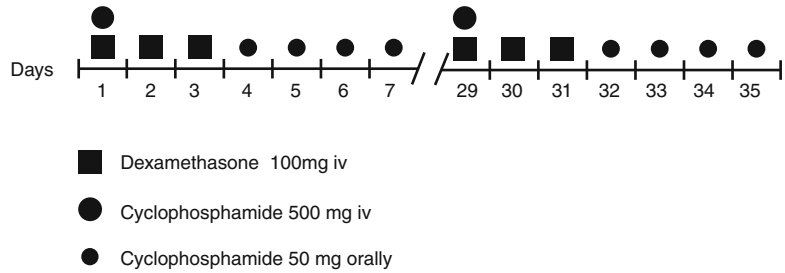

Fig. 71.4 Pulse therapy: IV megadoses of corticosteroid and immunosuppressive drugs are given over a short time (3 days and 1 day, respectively) every fourth week; in between these pulses, a low-dosed immunosuppressive treatment is given orally

until clinical remission (Fig. 71.4). Once this aim is achieved, the treatment is usually continued for 4–6 months. The number of pulses required to induce disease remission ranges from 6 to 30 weeks. After the pulses interruption, oral 50 mg cyclophosphamide is continued alone for at least 1 year as maintenance management, if there are no relapses. A variant of the classical pulse therapy (50 mg/kg/day of cyclophosphamide alone per 4 days) has been successfully used in recalcitrant patients (Hayag et al. 2000).

Side effects of pulse therapy encompass rare mild acute events (nausea, facial flushing, mood change, sleep disturbance) and severe drawbacks (aseptic osteonecrosis, seizures, cardiac arrhythmias, and even sudden death), which are more frequent among patients with concomitant risk factors. Paradoxically, long-term treatment with oral cyclophosphamide may cause several drawbacks (see above) which are more common than those reported with IV high-dosed administration of the same drug.

Biologic Agents

They include essentially IVIg and rituximab. The use of TNF-α antagonists (infliximab, etanercept) in PV has been emerging in the recent years, and therefore it still belongs to innovative nonconventional therapies.

Intravenous Immunoglobulin (IVIg) Therapy

IVIg is a purified blood product deriving from the plasma of between 1,000 and 15,000 healthy donors, containing IgG antibodies directed against pathogens, foreign antigens, and even self-antigens. It has demonstrated to be an effective, although expensive, treatment exerting its action through several postulated mechanisms. In PV, it may directly neutralize circulating antibodies (mimicking anti-idiotypic mechanism) and indirectly slow down their production through immunomodulatory effects. Repeated courses of IVIg could be considered as an adjuvant maintenance agent for recalcitrant PV become unresponsive to conventional regimens (CS and immunosuppressive drugs), or when high doses of CS are relatively contraindicated (diabetes, gastrointestinal diseases, osteoporosis, infections, or immunodeficiency). In addition, in view of report of a faster action in some cases, it could be used to help the induction of immediate remission in patients with severe recalcitrant PV, if necessary associated with slower-acting drugs.

Patients are given a daily dose of 400–600 mg/kg of IgG for three to five consecutive days. The infusion is administered slowly over 4–5 h. The cycles are initially spaced 2–3 weeks apart; thereafter, the interval is increased to 4 weeks, and the treatment is continued until the disease is successfully controlled. Past studies suggested that the efficacy of IVIg for PV treatment involved multiple cycles. However, recent studies demon-

strate that a single cycle may be sufficient to suppress disease activity.

To date, IVIg is one of the safest agents available: the incidence of long-term adverse effects requiring medical treatment has been reported to be relatively low with IVIg therapy compared with other treatments. Potential common early complications reported include chills, dyspnea, tachycardia, hypertension, muscle pains, abdominal pain, pyrexia, nausea, and headache. These drawbacks are self-limited and generally respond to slowing the infusion. Moreover, they may be prevented by premedication with oral diphenhydramine and acetaminophen. Rare side effects reported include anaphylaxis, increased creatinine and transaminases, hepatic dysfunction, hepatic encephalopathy, hematological alterations (lowering in white blood cell, red blood cell, and platelets count), bleeding tendency (particularly in the digestive tract), hypoalbuminemia, and aseptic meningitis (incidence ranging from 11 to 17 %). Of note, there is a theoretical risk of blood-borne virus infections.

Conversely, local or systemic infections facilitated by conventional immunosuppressants may be better controlled by IVIg. This firmly supports the recent use of this therapy in association with rituximab: in this schedule, IVIg role is more than a prophylaxis due to its both synergistic and immunomodulatory effects.

Other benefits of IVIg therapy include a corticosteroid-sparing effect, the possible use as monotherapy and, in addition to controlling PV, the ability to induce sustained clinical remission.

On the other hand, further multicenter trials, with large groups of patients, are needed, and some practical considerations along with the high cost may be a deterrent to IVIg use. However, the cost of treating present and future adverse effects of long-term therapy with high-dose systemic CS and immunosuppressive agents would also be high, and probably comparable.

Rituximab

In PV patients who do not enter into remission despite the use of high-dose steroid therapy and immunosuppressive treatments, a chimeric IgG1 monoclonal anti-CD 20 antibody, rituximab, has been recently employed as adjuvant with promising results. According to the latest findings, rituximab may be the first-choice treatment in PV due to some characteristics: a good safety and tolerability profile as well as a positive and long-lasting response in patients after a single course. Altogether these elements make rituximab a therapy that is potentially able to modify the natural history of PV.

This antibody targets the B cell differentiation antigen CD 20, a membrane protein that participates in B cell activation and proliferation. By eliminating CD 20+ B cells (essentially through complement and antibody dependent cytotoxicity) in their evolutive stages (pre-B cells, immature B cells, mature B cells, and immature plasma cells), rituximab affects both the humoral- and cell-mediated responses in patients with PV because of the close interaction between B and T cells: circulating B cells are reduced so preventing their maturation into antibody-producing plasma cells. Rituximab is administered intravenously at a dosage of 375 mg/m^2 by slow infusion (4–6 h) once weekly for 4 weeks per course, with a premedication of oral paracetamol (500 mg) and chlorpheniramine maleate (10 mg).

The clinical response usually occurs only after several weeks. In most of the cases, clinical improvement goes parallel to the serum decrease of autoantibodies measured by indirect immunofluorescence. Conversely, in some patients, it was not accompanied by a simultaneous decrease of antidesmoglein titers. Once control of the disease has been achieved, low doses of steroids and immunosuppressants can suffice for the subsequent management. Rituximab is able to induce a prolonged clinical remission after a single course of four treatments.

In previously reported cases, a variety of immunosuppressive drugs were used as adjuvant therapy after rituximab administration with a frequent complicated course due to the onset of systemic infections. Recent studies using no drugs or only steroids after rituximab administration showed an uncomplicated follow-up as well as long-lasting clinical remission. Thus, we may assume that, after rituximab administration, the use of an immunosuppressant other than a steroid

does not result in much difference in the rate of response, period of remission, or incidence of relapses, but it is responsible for higher risk of systemic infections.

Side effects of rituximab include infusion-related toxicity (fever and chills), generally occurring only during the first infusion, serious infections, deep venous thrombosis, long-term hypogammaglobulinemia, and neutropenia.

Particularly, some researchers believe that the use of rituximab in severe PV does not increase significantly the infection rates, but only the addition of immunosuppressive drugs other than steroids could increase this risk: sepsis from *Pseudomonas aeruginosa* and *Staphylococcus aureus*, hip arthritis caused by *Pseudomonas aeruginosa*, a community-acquired pneumonia, and pneumonia from *Pneumocystis carinii* have been reported in PV.

Being rituximab a chimeric murine-human molecule, there are some concerns about the long-term adverse effects of infusion of a foreign protein. A prior sensitivity to murine proteins has to be ruled out before administering this drug. As rituximab is very expensive, its use should be limited to selected patients with treatment-resistant or life-threatening disease.

Rituximab and IVIg

This association has been used in PV patients who had inadequate responses to long-term, high-dose CS plus at least three or more immunosuppressants, or a minimal response to IVIg, or who experienced acute relapses whenever intervals between IVIg infusions were increased, or finally who experienced a failure of immunosuppressive drugs used in combination with IVIg therapy. The proposed schedule includes two cycles of rituximab (375 mg/m^2 of body surface area) once weekly for 3 weeks and IVIg (2 g /kg) administered in the fourth week, then followed by a single monthly infusion of rituximab and IVIg for 4 consecutive months (consolidation therapy). Along with a dramatic clinical response, patients treated with this combination have not shown the side effects generally associated with rituximab.

Second-Line Treatments

Numerous side effects of a prolonged administration of CS and immunosuppressive drugs have spurred on a continued search for other therapies that might be used alone as sole systemic alternative treatment, or in combination with a low-dose conventional cure, as an adjuvant management.

The use of *gold salts*, which have long been used in the treatment of rheumatoid arthritis (RA) and lupus erythematosus, has waned with the introduction of other immunosuppressive agents. The mechanism of action is probably linked with the T-mediated immunosuppressive properties of gold salts. Intramuscular injections of either gold sodium thiomalate or aurothioglucose are given once weekly, in single doses of 50 mg to a total dose of 1 g. The treatment can be continued with fortnightly doses to 2 g, then monthly doses up to 3 g. Adverse side effects, such as pruritus, allergic reactions, nausea, renal toxicity, and bone marrow suppression, are frequent, up to 42 % of cases. Auranofin is an oral preparation (3 mg twice daily) that seems to be less toxic but also less effective. As a rule, we do not favor the use of gold compounds in patients with PV because of the reported onset of pemphigus lesions in patients treated with chrysotherapy for RA.

The association of oral *tetracycline* (2 g/day) or *minocycline* (200 mg/day) with *nicotinamide* (1.5 g/day), jointly with topical steroids, has proven to be a beneficial adjunct to the conventional treatments, allowing a reduction in steroid or immunosuppressive doses required to maintain remission. It has been used in some cases of PV in order to protect the patient, for a certain period, from untoward effects that occurred with the conventional treatment. On the whole, tetracycline-nicotinamide association exhibits a good safety profile (reversible minocycline-induced hyperpigmentation is a possible mucocutaneous side effect), and it may be helpful in mild forms of the disease. Even if the mechanism of action of tetracyclines remains obscure, though presumably based on anti-inflammatory properties, it is likely that nicotinamide, being a cholin-

ergic agonist, can act as a protective factor against acantholysis by interfering with acetylcholine receptor-reactive autoantibodies.

Topical Treatment

In PV, topical treatment is considered supplementary to the systemic therapy and aimed primarily at preventing infections and stimulating reepithelialization of the abraded areas. Intact bullae should be incised, and the resulting erosions should be treated with *spray*, *lotions*, or *creams containing CS* and *antibiotics* or *nonirritant antiseptics* (potassium permanganate, chlorhexidine).

Oral lesions, often stubbornly resistant to systemic therapy, are treated with *potent topical CS* (clobetasol propionate) in a special *adhesive paste*, which keeps the drug in place longer. For gums and hard palate mucosa, the local therapeutic activity of topical steroids can be enhanced by an *occlusive dressing of acrylic trays*. This method can achieve a prolonged remission phase in about half of the patients adopting it (stabilized oral PV with few lesions), without needing systemic therapy. Under these circumstances, similar results and benefits have been reported with *intralesional injections of triamcinolone acetonide* diluted to 10 mg/mL. Finally, to alleviate the pain that hampers food intake, *anesthetic nebulizers* (benzocaine) are used immediately before meals. In case of extensive erosive lesions on nasal, laryngeal, and upper respiratory tract mucosae, it may be useful nebulizing *steroid aerosols* with appropriate masks thrice a day.

Innovative topical treatments include *epidermal growth factor* (10 μg/g), *nicotinamide* gel 4 %, and *pimecrolimus* 1 % cream. The topical treatment with a *proteomics-derived desmoglein peptide* (Dsg349-60REWVKFAKPCRE) appears promising because it halted disease progression and persistently decreased desmoglein-reactive antibody titer, without adverse effects, in a patient with severe PV (Angelini et al. 2006; Ruocco et al. 2013).

Interventional Treatments

They include plasmapheresis and its derivative immunoadsorption.

Plasmapheresis

In 1978, our group introduced the technique of plasma exchanges for problem cases of PV as a logical consequence of the proven pathogenicity of pemphigus autoantibodies. The rationale of this method was removing harmful antibodies from the patient's circulation, although the effectiveness of the intervention showed to be temporary. It was soon clear that, being the antibody level in the circulation regulated by a feedback mechanism, a massive antibody depletion triggers a burst of new antibody production ("rebound" to the antibody "vacuum"). Thus, if every plasma exchange is followed by short cycles ("pulses") of conventional treatment with high doses of steroids and immunosuppressants (in particular cyclophosphamide), the therapeutic effect is increased and stabilized, as these "pulses" target B cells during their peak of autoantibody synthesis thus destroying them.

The regimen is scheduled with daily large-volume (60 mL/kg) plasma exchanges on days 1, 2, 3, and 7, intravenous *prednisolone* (2 mg/kg/day) and *cyclophosphamide* (12 mg/kg/day) on days 4, 5, and 6 during the first week (Fig. 71.5). The number of cycles necessary to achieve clinical control may vary from 3 to 12 over a period between 2 weeks and 10 months. The interval between two cycles is generally fixed at 4 weeks, but in most cases the treatment protocol is determined by the clinical severity of the disease and by patients' response to treatment following each cycle. The steroid dosage is gradually reduced to zero within 11 months, while oral cyclophosphamide (100–150 mg/day) is given for 6 months and then tapered to 50 mg/day for a further 4 months.

Plasmapheresis cannot be recommended as a routine treatment option in newly presenting

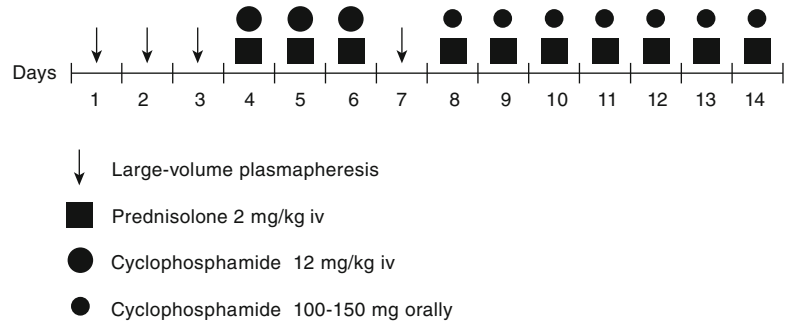

Fig. 71.5 Synchronization of plasmapheresis and pulse corticosteroid-immunosuppressive therapy: the pharmacological treatment is given soon after the antibody depletion caused by plasma exchanges to best hinder the "rebound" antibody production

patients with PV, while it caters for patients who are not responding to standard therapy, life-threatening cases of PV, and whenever the conventional therapy is contraindicated. This is the case of severe flare-ups of PV in pregnancy, which specifically call for plasmapheresis (plus CS and without cyclophosphamide), because this interventional treatment reduces the risk of intrauterine or neonatal pemphigus and obviates the serious side effects that conventional immunosuppressive therapy may cause to the fetus.

Plasmapheresis complications can be divided into minor ones (chills, fever, allergic reactions, transient hypotension) and major ones, which include fluid and electrolyte imbalance (rarely resulting in pulmonary edema or shock), depletion of platelets and other clotting factors with consequent bleeding diathesis, and systemic infections (pneumonia).

Working better than cyclophosphamide to prevent the risk of opportunistic infections due to its prophylaxis effect, high-dose IVIg infusion may be administered instead of cyclophosphamide to face the "rebound" antibody burst. Thus, IVIg use partly compensates the global immunosuppression induced by repeated plasma exchanges.

Plasmapheresis should always be conducted in immunohematology centers by a specialized staff.

Immunoadsorption

The main side effect of plasma exchange is removing a wide range of protective immunoglobulins, albumin, and clotting factors along with the pathogenic pemphigus antibodies. To overcome this drawback, one of us (V. R.) in the far 1984 theorized the possibility of selectively trapping the pathogenic autoantibodies out of the body by means of filtering membranes rich in sulfhydryls (-SH groups), thereby returning protective antibodies and plasma components to the patient. Unfortunately, technical problems, linked with difficulty in preventing air oxidation of -SH groups to disulfide bonds (S-S), stopped the fulfillment of the project. The original idea was accomplished 10 years later by Amagai et al. with the extracorporeal immunoadsorption (IA) of desmoglein-reactive autoantibodies using the extracellular domain of baculovirus-produced desmoglein 3. Interestingly, the molecular structure of desmoglein 3 is rich in -SH groups, which denotes the correct rationale of the original idea. Subsequently, different IA devices (protein A immunoadsorption columns, a tryptophan-linked polyvinyl alcohol gel adsorber) have been used. High-affinity reusable systems are preferably employed, but, in selected patients, IA with single-use systems can be chosen. The usual protocol entails one treatment cycle of four IA procedures on consecutive days. Further cycles with free intervals of 3–4 weeks are carried out depending on disease activity until clinical improvement is obtained. IA is a significant improvement over plasmapheresis also because it does not require reconstitution with fresh frozen plasma or human albumin; moreover, infections and allergic reactions are

less frequent. The clinical results can be rapidly observed: progressive reepithelialization of mucous and skin lesions is usually paralleled by an average of 50–70 % decrease in desmoglein-reactive autoantibodies titers. The incidence of adverse events (deep venous thrombosis, hypotension, bradycardia) is relatively low. However, despite undergoing a rapid remission, the disease usually recurs once the treatment is discontinued.

On the whole, extracorporeal IA is a candidate treatment of choice for patients with severe, life-threatening pemphigus and high levels of pathogenic autoantibodies, a circumstance where the immediate clinical response required is hard to achieve with the pharmacological therapy alone. Recently, due to the high incidence of relapses when the treatment is stopped, IA has also been associated to rituximab in a new treatment protocol. The aim is to combine the rapid remission induced by IA with the favorable positive longer-term effects of rituximab therapy. In fact, IA acts more rapidly than rituximab, but achieves a shorter disease remission than the latter when treatment is discontinued. This new protocol has been well tolerated.

Innovative Therapies

TNF-α antagonists (*infliximab* and *etanercept*) have also been used in PV, showing good results probably due to the role TNF-α exerts in the acantholytic process.

Cholinergic drug employment, ensuing from the recent acquirement on the role of keratinocyte acetylcholine axis imbalance in PV pathogenesis, has also been considered. The first cholinergic drug used was *pyridostigmine bromide* (Mestinon), an acetylcholinesterase inhibitor that also exerts an underrated direct nicotinergic action. As to muscarinic agonists, the topical application of *pilocarpine* gel 4 % showed a significantly higher reepithelialization index compared with placebo. Pilocarpine exerts its action by binding to M1 receptor, which is specifically targeted by PV antibodies, thus blocking the phosphorylation they induce.

Intravenous *desmoglein 3 peptides* have been used to suppress the production of anti-Dsg3 antibodies through inactivation or deletion of disease-associated CD4+ T cells.

A clinical trial is currently underway on *sirolimus*, which is an inhibitor of the *m*ammalian *T*arget *O*f *R*apamycin (mTOR), a serine/threonine protein kinase that regulates cell growth, proliferation, survival, protein synthesis, and transcription and that is overexpressed in keratinocytes exposed to PV antibodies.

Behavioral and Dietary Suggestions

Patients suffering from PV should avoid the abuse and indiscriminate use of drugs, even during the remission phase or if clinically healed, because of the risk for a drug-induced relapse of the disease. In particular, the medications often implicated in inducing or triggering PV (e.g., thiol drugs, phenol drugs, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, vaccines, interferons, and other cytokines) should be forbidden or limited as much as possible. When needed, the drug suspected of favoring PV can be replaced by others with similar therapeutic action but of a different category and with no inducing potential. Even the use of contraceptives and progestogens calls for caution in patients with PV. Women with PV should be informed that pregnancy may reactivate the disease due to a physiological steroid hormone imbalance.

Exposure to the sun and other ultraviolet sources requires special caution because of the risk for photoinduced relapses. The same can be said for intensive and prolonged emotional stress, which may interfere with the immune system.

Patients with PV should be advised to have a balanced diet and to avoid foods spiced with garlic, onion, and leek as these culinary plants, belonging to the genus *Allium*, contain thiol allyl compounds with a proven acantholytic potential. Patients should also be warned against the ingestion of very hot foods and beverages because of the possible acantholytic effect that excessive

heat may exert on oral and esophageal mucosae. Milk is among the foods to recommend, because of its high protein content, its easy intake even in the presence of painful oral erosions, and its high level of an oxidative enzyme (sulfhydryl oxidase) that has the potential to neutralize the acantholytic effect of thiol allyl derivatives found in the vegetarian diet.

Finally, even if it seems contrary to good sense, cigarette smoking is not contraindicated in patients with PV because nicotine can attenuate the acantholytic effect of pemphigus pathogenic autoantibodies both directly due to a cholinergic agonism and indirectly by inducing T cell-mediated immunosuppression.

Acknowledgements We are grateful to Dr Stefano Caccavale, a talented resident doctor, and Luigi Pio Guerrera, a keen medical student, who helped us to update this chapter.

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Drug-Induced Pemphigus

72

Olga Golberg and Karen Elizabeth Harman

Abbreviations

HLA	Human leukocyte antigen
IL-1	Interleukin-1
TNF-α	Tumour necrosis factor alpha

Key Points

- Drug-induced pemphigus is a rare variant of pemphigus.
- Multiple drugs are reported to induce pemphigus, most commonly thiol drugs. The mechanisms include autoantibody formation and direct acantholysis.
- The diagnosis requires an accurate drug history, a skin or mucosal biopsy for histology and direct immunofluorescence and may be supplemented by serological tests including indirect immunofluorescence and enzyme-linked immunosorbent assay.
- The clinical, histological and immunopathological features of drug-induced pemphigus are similar to those of idiopathic disease, and there may be a long latent period between starting a drug trigger and disease onset, making the diagnosis challenging.
- Patients in whom the disease persists after removal of the drug require treatment with systemic corticosteroids and/or immunosuppressive therapy, as for idiopathic pemphigus.

Definition and Epidemiology

Pemphigus comprises a group of autoimmune bullous diseases characterized by acantholysis (loss of adhesion between keratinocytes) that results in the formation of intraepithelial blisters in skin and mucous membranes. Drug-induced pemphigus (DIP) is a rare but well-established type of pemphigus, which was first recognized in the 1950s. Epidemiological data on DIP is very limited. It is estimated that approximately 10 % of cases of pemphigus are drug related. DIP affects all races and both sexes and can occur at any age. A number of reports from Israel may suggest an increased incidence of the condition in Ashkenazi Jews (Brenner et al. 1998).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_72, © Springer-Verlag Berlin Heidelberg 2015

Basic Concepts of Pathogenesis

While in the past most cases of DIP were associated with penicillamine, a variety of other drugs have been implicated in recent decades (see Table 72.1). Some of these drugs are thought to induce pemphigus via the same immunological mechanisms that are found in idiopathic pemphigus. Other drugs are postulated to cause acantholysis directly, through biochemical processes. A combination of both mechanisms may be involved in many cases of DIP. Pemphigus-inducing drugs can be broadly divided in two categories: thiol and non-thiol drugs.

Thiol drugs contain a sulfhydryl group (-SH) in their chemical structure and are the commonest cause of DIP. Examples of thiol drugs include penicillamine and captopril. About 7 % of patients treated with penicillamine for at least 6 months develop pemphigus. The sulfhydryl groups have been speculated to interact with desmogleins, enhancing their antigenicity and leading to autoantibody production. Thiol drugs have also been shown to induce acantholysis in vitro without antibody formation. The potential mechanisms for thiol-induced direct acantholysis include inhibition of enzymes of keratinocyte aggregation, disruption of cell adhesion by thiol–cysteine bonds and activation of proteolytic enzymes such as plasminogen activators.

Non-thiol drugs associated with pemphigus include penicillins, cephalosporins and ACE inhibitors other than captopril. Additional drugs have been recently reported to induce pemphigus, for instance, angiotensin II receptor blockers, anticonvulsants and glibenclamide. Some non-thiol drugs, such as penicillins and piroxicam, have sulphur in their chemical structure, which may be metabolized in vivo to form thiols. These are termed masked thiols, and their mechanism of acantholysis may be similar to thiol drugs. Other non-thiol drugs contain phenol groups, for example, levodopa and rifampicin. Phenol drugs have been postulated to induce acantholysis by causing release of cytokines (TNF-α, IL-1) from keratinocytes, which participate in the regulation and synthesis of complement and proteases. An active amide group is also found in the structure of many non-thiol drugs, and its role in the pathogenesis of DIP has been questioned.

Table 72.1 Drugs implicated in pemphigus

	Non-thiol drugs		
Thiol (SH) drugs	Phenol drugs	Pyrazolone derivatives	Miscellaneous drugs
D-penicillamine	Rifampicin	Oxyphenbutazone	Penicillins[b]
Bucillamine	Cephalosporins[a]	Aminopyrine	Quinolones
Captopril	Aspirin	Azapropazone	ACE inhibitors
Gold sodium thiomalate	Levodopa	Phenylbutazone	ARBs
Thiopronine	Progesterone	Aminophenazone	Phenytoin
Piroxicam[b]	Heroin		Carbamazepine
Carbimazole	Phenobarbital		NSAIDS
Methimazole	Pentachlorophenol		Chloroquine/hydroxychloroquine
5-Thiopyridoxine[a]			Montelukast
Pyritinol[a]			Interferon-α, β
Mercaptopropionylglycine			Nifedipine
			Propranolol
			Glibenclamide[b]
			Isotretinoin
			Imiquimod

ACE angiotensin-converting enzyme, *ARBs* angiotensin II receptor blockers, *NSAIDS* nonsteroidal anti-inflammatory drugs

[a]Both thiol and phenol drugs

[b]Drugs containing sulphur in their molecules (masked thiols)

Non-thiol drugs are more likely to induce pemphigus via immunological mechanisms. Studies have shown the presence of antibodies to pemphigus antigens, desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1), in most cases of thiol- and non-thiol-induced pemphigus. However, 4–5 % of rheumatoid arthritis patients treated with thiol compounds produce antibodies to non-conformational epitopes of Dsg1 or Dsg3 without developing pemphigus, suggesting that such antibodies alone are not sufficient to induce acantholysis (Yamamoto et al. 2010).

Patients with DIP have been found to carry the same susceptibility alleles HLA-DR4 that are thought to predispose to idiopathic pemphigus vulgaris (PV). Therefore, perhaps drugs are capable of triggering pemphigus in genetically susceptible individuals.

Clinical Presentation

DIP usually begins a few weeks to several months after initiation of an offending agent, although the onset of pemphigus after 6 years of anticonvulsant therapy has been described (Tang and Zhang 2012). The latency period may be much shorter on repeat exposure to the culprit drug. The clinical features of DIP are similar to idiopathic disease although pruritus is more common. Pemphigus foliaceus (PF) is the most common pattern of DIP, observed in up to 70 % of thiol-induced cases. It is characterized by multiple, superficial, fragile blisters over the seborrhoeic areas of the body, which easily rupture, evolving into erythematous, crusted and scaly erosions and plaques. The scalp, face and upper trunk are the common sites of involvement. Skin lesions may coalesce to cover large areas of the body and occasionally progress to an exfoliative erythroderma. The cutaneous lesions are often associated with itching and burning. The mucous membranes are typically spared. DIP may also present as pemphigus erythematosus (PE), which is a variant of PF localized to the malar region of the face and sometimes associated with the laboratory features of systemic lupus erythematosus.

Pemphigus induced by non-thiol drugs tends to manifest as PV. Most patients develop mucosal lesions, with painful erosions of the oral cavity being the commonest presenting feature. Other mucous membranes can be affected, in particular the conjunctiva, oesophagus and genitalia. Cutaneous involvement manifests with flaccid blisters, which soon rupture, producing painful erosions that tend to ooze and bleed. The Nikolsky sign can usually be elicited.

The prognosis seems to be more favourable in DIP caused by thiol drugs. Withdrawal of the drug results in remission in up to 50 % of thiol-induced cases of pemphigus compared with only 15 % of patients with pemphigus induced by non-thiols. This observation led some authors to term thiol- and non-thiol-related disease "drug-induced" and "drug-triggered" pemphigus, respectively. In patients who do not remit upon drug withdrawal, the course and prognosis of DIP is similar to that of idiopathic pemphigus.

Diagnosis

The diagnosis of DIP is challenging because it resembles idiopathic pemphigus, cannot conclusively be distinguished with investigations, and the latency between drug initiation and disease onset may be long. Furthermore, disease may persist despite cessation of the suspected agent. In most published reports, the diagnosis of DIP was based on the history, resolution of disease after withdrawal of the drug (with or without treatment) and recurrence/worsening of pemphigus after re-exposure to the same or similar drug. Some authors have also noticed a poor response to standard systemic treatment before stopping the culprit agent. A thorough drug history is therefore crucial for the diagnosis of DIP and should be obtained in all cases of pemphigus. The patient's medications should be cross checked against a list of those drugs reported to induce pemphigus (Table 72.1), and any potential triggers should be stopped, taking into account that there may be a prolonged latency period between starting the drug and the onset of pemphigus.

In addition to a clinical assessment, the diagnosis of DIP always requires laboratory investigations. These must include a lesional skin or mucosal biopsy for histopathology and a biopsy of perilesional skin or mucosa for direct immunofluorescence (DIF). The histological findings in DIP are identical to those in idiopathic disease and correlate with the clinical variant of pemphigus. In drug-induced PF, superficial intraepidermal cleavage is found, with acantholysis beneath the stratum corneum or within the granular layer. In drug-induced PV, there is a suprabasal acantholysis and retention of basal keratinocytes along the basement membrane, known as a "row of tombstones". Other findings in DIP include a mixed inflammatory infiltrate in the dermis, with possible eosinophil predominance, and eosinophilic spongiosis. DIF demonstrates intercellular epidermal deposition of IgG, with or without C3, in up to 90 % of patients with DIP.

Serological studies, indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA), are often used to further support the diagnosis of pemphigus. IIF detects circulating antibodies to PF or PV antigens (Dsg1 and Dsg3, respectively), or both, in about 70 % of patients with DIP and usually at low titre. DIF and IIF are negative in some patients, particularly in thiol-induced cases. ELISA is a very sensitive and specific test for the diagnosis of pemphigus and may be useful when IF studies are negative. In a small series of DIP, ELISA was positive for Dsg1 or Dsg3 in all six patients, while DIF and IIF were negative in one and two patients, respectively.

Unfortunately, the distinction between drug-induced and idiopathic pemphigus is not possible based on the histological features, nor routine immunopathology. However, novel tests have been proposed as adjuncts in the diagnosis of DIP. One study has shown differences in the pattern of immunostaining with the monoclonal antibody 32-2B which binds desmogleins 1 and 3 (Maruani et al. 2008). A normal pattern of immunostaining with 32-2B demonstrated a 70 % sensitivity and 84 % specificity for the diagnosis of DIP. In comparison, 84 % of idiopathic pemphigus cases showed a patchy pattern of immunostaining with 32-2B. The normal pattern of immunostaining in DIP was also associated with a better prognosis. Another potential diagnostic tool is the in vitro interferon-gamma release test, performed by culturing lymphocytes of PV patients with and without suspected drugs and considered positive if interferon-gamma secretion is at least 30 % higher from lymphocytes cultured with the drug compared with those cultured in medium alone (Goldberg et al. 2008). This assay was positive in 10 out of 14 patients with suspected DIP and may be useful for identifying culprit drugs in pemphigus patients. However, neither 32-2B immunostaining nor the interferon release assays are widely available and at present represent research tools rather than routine diagnostic tests.

Differential Diagnosis

The histopathology and immunopathology usually readily distinguishes pemphigus from other diseases but the differential diagnosis of DIP includes:

- All other forms of pemphigus
- Mucous membrane pemphigoid
- Bullous pemphigoid
- Linear IgA disease
- Subcorneal pustular dermatosis
- Erythema multiforme and Stevens–Johnson syndrome
- Bullous impetigo and staphylococcal scalded skin syndrome (in children)
- Lupus erythematosus (subacute, bullous or systemic)
- Severe seborrhoeic dermatitis (for drug-induced PF)
- Hailey–Hailey disease
- Other causes of mucosal ulceration

General Principles of Treatment

The first and crucial step in the treatment of DIP is to identify and stop the offending drug. If the patient is taking any implicated drug, consider stopping it even if there has been a delay between drug initiation and disease onset. This may result

in remission in many, but not all, patients and reduced disease severity in others. A rapid decline in circulating anti-desmoglein antibodies, associated with clinical improvement, has been observed after withdrawal of the offending drug (Nagao et al. 2005).

Patients in whom the disease persists after cessation of the implicated agent require therapy with systemic corticosteroids (CS) and/or immunosuppressants as for idiopathic pemphigus. Appropriate skin care is also an important part of management.

CS are the mainstay of treatment and the dosing regimens are similar to those used for idiopathic pemphigus. The most common approach is to initiate prednisolone with doses ranging from 0.5 mg/kg/day for mild disease to 1–1.5 mg/kg/day for more severe cases. If the clinical response is insufficient after 1 week, the dose could be increased up to 2–2.5 mg/kg. Once the disease activity is under control, tapering of CS should begin, with the aim of reaching the lowest dose needed for remission maintenance. One approach is to reduce the dose of prednisolone by 5–10 mg/day weekly and more slowly below the dose of 20 mg/day.

In severe DIP or if doses greater than 100 mg/day of prednisolone are required for disease control, pulsed intravenous CS should be considered. Intravenous methylprednisolone 250–1,000 mg or equivalent doses of dexamethasone are given on one to five consecutive days and can be repeated.

Adjuvant drugs are commonly prescribed in conjunction with CS in order to allow tapering of steroids to reduce their risks. Azathioprine is the most common immunosuppressive drug used for pemphigus, and its steroid-sparing effect in PV treatment has been supported by clinical trials (Chams-Davatchi et al. 2007). The dose of azathioprine is 1–3 mg/kg per day, but patients with low levels of thiopurine methyltransferase (TPMT) should receive reduced doses, e.g. 0.5 mg/kg.

Mycophenolate mofetil (MMF) may be useful in the treatment of DIP and has a more favourable side effect profile. The typical dose is 2 g per day (taken in two divided doses), prescribed in addition to systemic CS. In recent trials, MMF failed to show a significant steroid-sparing effect in pemphigus but was associated with a longer remission (Ioannides et al. 2012).

Methotrexate, ciclosporin and dapsone have also been utilized as adjuvants for the treatment of pemphigus, but there is little evidence to support their use in DIP.

For refractory disease and patients who cannot tolerate the first-line regimens, therapeutic options include cyclophosphamide, intravenous immunoglobulin (IVIG), rituximab, immunoadsorption and plasmapheresis.

Cyclophosphamide is usually prescribed as an adjuvant to CS and its dosing schedules vary. A well-established treatment regimen consists of monthly intravenous pulses of dexamethasone (100 mg for 3 days) and cyclophosphamide (500 mg on day 2), followed by oral cyclophosphamide 50 mg daily in between the pulsed therapy. Another approach is to combine conventional daily oral CS with monthly intravenous cyclophosphamide pulses (15 mg/kg).

IVIG is commonly given at a dose of 2 g/kg/cycle over two to four consecutive days, with cycles repeated every 4–6 weeks. A high dose of IVIG (400 mg/kg/day for 5 days) administered in a single cycle has proven to be safe and efficient for steroid-resistant pemphigus.

Rituximab, a monoclonal antibody against CD20 on B-lymphocytes, has shown efficacy in paraneoplastic pemphigus and severe PV and PF. Two dosage schedules are used: the lymphoma schedule of 375 mg/m^2 intravenously once weekly for 4 weeks and the rheumatoid arthritis schedule of 1 g IV given on two occasions, 2 weeks apart. Lower doses of rituximab (e.g. two 500 mg infusions 2 weeks apart) may also be effective.

Immunoadsorption works by removing circulating IgG antibodies and is typically administered as an adjuvant to immunosuppressive therapy (3–4 day cycles repeated every 3–4 weeks). In comparison, plasmapheresis non-selectively removes plasma proteins from the circulation and is more widely available.

Combination therapy with rituximab, IVIG, immunoadsorption and immunosuppressants has been tried but requires further evaluation.

The response to treatment is assessed clinically and characterized by cessation of new blisters and healing of old lesions. ELISA titres for anti-desmoglein antibodies may assist clinical assessment as they sometimes correlate with disease activity.

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Paraneoplastic Pemphigus

73

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Abbreviations

A2ML1	Alpha-2-macroglobulin-like-1 antigen
BMZ	Basement membrane zone
BPAG1	Bullous pemphigoid antigen 1
DIF	Direct immunofluorescence
Dsg	Desmoglein
ELISA	Enzyme-linked immunosorbent assay
IIF	Indirect immunofluorescence
PAMS	Paraneoplastic autoimmune multiorgan syndrome
PNP	Paraneoplastic pemphigus
TEN	Toxic epidermal necrolysis

Key Points

- Paraneoplastic pemphigus (PNP) or paraneoplastic autoimmune multiorgan syndrome (PAMS) is a rare autoimmune blistering disease associated with neoplasia, most commonly lymphoproliferative disorders.
- The pathogenesis of PNP is not fully understood. Multiple antibodies, mainly directed against proteins of the plakin family, are detected in the sera of patients with this disease. Antibodies to periplakin and envoplakin are strongly associated with PNP.
- Clinical manifestations include severe oral ulceration and a polymorphous cutaneous eruption. Pulmonary disease consistent with bronchiolitis obliterans may occur and is often fatal.
- Diagnosis is based on clinical, histopathological and immunological findings. Immunological investigations, including indirect immunofluorescence on rat bladder, ELISA, immunoblotting and immunoprecipitation, have high sensitivity and specificity for the diagnosis of PNP.
- Treatment includes systemic corticosteroids, rituximab and other immunosuppressive therapies. The response to treatment and prognosis in PNP is generally poor.

Definition and Epidemiology

Paraneoplastic pemphigus (PNP) is a life-threatening autoimmune blistering disease associated with neoplasia, most commonly lymphoproliferative disorders. An alternative term for PNP, which has been increasingly used in the literature, is paraneoplastic autoimmune multiorgan syndrome (PAMS). The latter term reflects the diversity of the cutaneous manifestations and

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_73, © Springer-Verlag Berlin Heidelberg 2015

systemic involvement that may occur in this disorder. The incidence and prevalence of PNP are unknown, but it is a rare disease. Anhalt et al. first described PNP in 1990, and by 2011, over 450 cases had been reported in the literature (Czernik et al. 2011). PNP occurs worldwide and affects both sexes, with possible male predominance. The disorder can occur at any age but appears to be most common in the 45–70 years age group.

Basic Concepts of Pathogenesis

PNP is associated with a variety of neoplasms, both malignant and, less commonly, benign. Lymphoproliferative disorders account for the vast majority of PNP cases. The most frequently associated neoplasms are non-Hodgkin lymphoma (40 %), chronic lymphocytic leuchemia (CLL) (18–30 %) and Castleman's disease (10–18 %), followed by carcinoma (9 %), thymoma (6 %), sarcoma (6 %) and Waldenström's macroglobulinaemia (1 %). Monoclonal gammopathy and malignant melanoma each account for fewer than 1 % of cases (Kaplan et al. 2004). Castleman's disease is the leading cause of PNP in children, and it has been reported with a higher frequency in Chinese patients. The most common non-haematological malignancy associated with PNP is carcinoma, with an increasing variety of adenocarcinomas and squamous cell carcinomas reported in the recent years (Webster et al. 2013). Sarcomas are less commonly implicated and include leiomyosarcoma and follicular dendritic cell sarcoma.

PNP is an autoimmune disorder induced by an underlying neoplastic process. The pathogenesis of PNP is not entirely understood, but thought to involve both humoral and cell-mediated immune mechanisms. The humoral response is characterized by production of antibodies mainly directed against intracellular proteins of the plakin family, which are essential components of desmosomes and play a key role in epidermal cell adhesion. Antibodies directed against two of these proteins, periplakin and envoplakin, are the most characteristic of PNP, and their detection is a highly sensitive and specific laboratory feature of the disease. Other commonly associated antibodies include those to desmoplakins I and II, bullous pemphigoid antigen 1 (BPAG1), plectin and a recently identified alpha-2-macroglobulin-like-1 antigen (A2ML1). Desmoglein 3 and 1 (Dsg 3, 1) antibodies are present in some cases, and antibodies to desmocollins, laminin-332 and plakophilin-3 have also been reported (Yashiro et al. 2013). In addition to circulating autoantibodies and tissue-bound antibodies in skin and mucous membranes, deposits of autoantibodies have been found in many internal organs of the affected patients. The role of most antibodies in the pathogenesis of PNP is uncertain, but those to periplakin and envoplakin may be pathogenic. The mechanism by which neoplasms induce antibodies to plakins and other antigens is unknown. Proposed mechanisms include dysregulation of the immune system, cross-reactivity between tumour and epidermal antigens and epitope spreading (increased exposure of multiple antigens to the immune system, as a result of tissue injury). The latter theory may explain the variety of antibodies found in PNP.

There is growing evidence that cell-mediated immunity is involved in the pathophysiology of PNP. Apoptosis of keratinocytes, mediated by cytotoxic T-lymphocytes, along with an increased local production of interferon-γ (IFN-γ) and TNF-α, has been demonstrated in PNP (Billet et al. 2006). In addition, CD8+ cytotoxic T-lymphocytes, CD56+ natural killer cells and CD68 + monocytes/macrophages have been found at the dermal–epidermal junction of affected patients. These inflammatory infiltrates are similar to the ones present in other diseases characterized by cell-mediated cytotoxic reactions, such as erythema multiforme and lichen planus. Therefore, it is possible that lichenoid variants of PNP predominantly involve cellular immunity, whereas vesiculobullous eruptions are mainly mediated by humoral responses.

Clinical Presentation

Approximately two-thirds of patients are known to have neoplasia at the time of onset of PNP. All PNP patients develop mucosal erosions, with

severe, painful stomatitis being the most constant feature and the first manifestation of the disease in about 45 % of patients. The oral erosions are typically widespread, involving the tongue (particularly lateral borders), oropharynx and vermilion border of the lips. The erosions tend to appear more necrotic than those observed in pemphigus vulgaris (PV). Multiple other mucosal surfaces can be affected, including the conjunctiva, larynx, anogenital region and gastrointestinal tract.

The cutaneous involvement in PNP is characterized by polymorphous eruptions that significantly overlap with other dermatological diseases. The spectrum of cutaneous lesions includes vesicles and bullae, which may be flaccid or tense, erythematous/violaceous scaly papules and plaques, targetoid lesions and erosions. Based on the morphology and histological findings, five clinical variants of PNP have been described: pemphigus-like, bullous pemphigoid-like, lichen planus-like, graft-versus-host-disease (GVHD)-like and erythema multiforme-like. Pustules and vegetative lesions can occur, and a combination of various lesion types is often present in PNP patients. Involvement of the palms, soles and periungual skin is common, unlike PV in which it is rare. Extensive epidermal detachment, resembling toxic epidermal necrolysis (TEN), has also been described. Pulmonary involvement is increasingly recognized in PNP and manifests with a bronchiolitis obliterans-like disease. It is thought to occur in about 30–40 % of patients. Clinically it is characterized by dyspnoea in the presence of a relatively normal chest X-ray and an obstructive pattern on pulmonary function testing. High-resolution CT may demonstrate features of bronchiolitis obliterans, such as expiratory air trapping and bronchial wall thickening. The pulmonary disease is usually progressive and often leads to fatal respiratory failure. The mechanisms of respiratory involvement in PNP are not fully understood, but it has been shown that respiratory epithelial cells express the plakin proteins which are recognized by PNP antibodies, and their reactivity against pulmonary epithelial antigens may cause sloughing of epithelial cells with subsequent obstruction of small airways. In addition, T-cell-mediated cytotoxicity appears to play an important role in pulmonary disease.

The prognosis in PNP is poor, with mortality rates approaching 90 %. However, a recent study of 53 patients showed a 5-year survival rate of 38 %, suggesting that better outcomes may be possible (Leger et al. 2012). The main causes of death include sepsis, multiorgan failure, respiratory failure due to bronchiolitis obliterans and progression of an underlying malignancy. Erythema multiforme-like eruptions and keratinocyte necrosis have been shown to be predictors of fatal outcome. The prognosis is better in PNP associated with Castleman's disease and thymoma, after resection of the tumours.

Diagnosis

The diagnosis of PNP is based on the combination of clinical and laboratory findings. There are no generally accepted diagnostic criteria, but the following mandatory criteria have been suggested: severe stomatitis, positive indirect immunofluorescence (IIF) on rat/monkey bladder epithelium, positive direct immunofluorescence (DIF) if negative IIF, detection of antibodies against envoplakin or periplakin and a concurrent neoplasm.

The laboratory tests used in PNP include histopathology, DIF and serological studies. The most common histopathological findings are suprabasal acantholysis, lichenoid interface dermatitis and keratinocyte necrosis. However, the histological features in PNP are not diagnostic as they are highly variable and may overlap with many other conditions.

DIF findings in PNP include epithelial intercellular and/or basement membrane zone (BMZ) IgG and/or C3. Combined intercellular and BMZ binding is unusual and should prompt suspicion about PNP. The sensitivity of DIF for PNP ranges from 41 to 79 %. IIF labelling of rat bladder epithelium has a high sensitivity and specificity for PNP of up to 86 and 99 %, respectively (Joly et al. 2000). IIF performed on rat bladder epithelium is positive exclusively in PNP, whereas IIF on monkey oesophagus detects antibodies in both

PV and PNP. Enzyme-linked immunosorbent assay (ELISA) for circulating antibodies against envoplakin and periplakin has a high diagnostic accuracy in PNP, with a sensitivity and specificity around 80 and 96 %, respectively (Probst et al. 2009). Immunoblotting and immunoprecipitation are additional serological tests for the diagnosis of PNP. They detect antibodies directed to periplakin (190 kD), envoplakin and desmoplakin II (210 kD double band), desmoplakin I (250 kD), BPAG1 (230 kD), plectin (>400 kD), A2ML1 antigen (170 kD) and other proteins found in PNP. Immunoblotting and immunoprecipitation are highly sensitive specific tests, but their availability may be limited.

Once the diagnosis of PNP is established, evaluation for an underlying malignancy is necessary.

Differential Diagnosis

- Oral mucositis due to chemotherapy and other causes of severe oral ulceration
- Pemphigus (vulgaris, drug-induced)
- Bullous pemphigoid and other autoimmune blistering disorders
- Mucous membrane pemphigoid
- Drug eruptions
- Lichen planus
- GVHD
- Erythema multiforme
- Stevens–Johnson syndrome and TEN

General Principles of Treatment

Treatment of PNP requires close collaboration between oncology, dermatology and respiratory physicians. Response to treatment in PNP is variable and generally poor. The cutaneous lesions are more responsive to therapy than the stomatitis, which is often refractory. Treatment of an underlying malignancy may be beneficial, but PNP commonly progresses despite controlling the neoplastic disease. In cases associated with thymoma and Castleman's disease, complete tumour resection sometimes results in remission of PNP. Supportive measures and adequate analgesia play an essential role in the management of PNP. In terms of specific treatment, this is similar to that of PV both in terms of the drugs used and doses. Systemic corticosteroids (typically prednisolone 1 mg/kg/day) are usually the first-line therapy for patients with PNP. Pulsed intravenous steroids (e.g. methylprednisolone 500–1,000 mg on 1–5 consecutive days) can also be used as initial therapy. Prednisolone is slowly tapered over months and often combined with other immunosuppressive agents, such as azathioprine, ciclosporin, mycophenolate mofetil and cyclophosphamide (→see Pemphigus chapter). Due to the rarity of PNP, there is insufficient evidence to date to support any particular treatment modality or therapeutic regime. In case reports and small case series, the following doses of immunosuppressive agents have been used, alongside steroids: azathioprine 100 mg/day, ciclosporin 5–7 mg/kg/day and mycophenolate mofetil 1–2 g/day. Several treatment regimens have been described for cyclophosphamide, for instance, cyclophosphamide 500 mg intravenously on days 1–3 every 3 weeks with dexamethasone 100 mg intravenously at 3-week intervals (Frew and Murrell 2011). Rituximab, a monoclonal antibody against CD20, expressed on B-lymphocytes, has shown efficacy for PNP in case reports, albeit inconsistently (Frew and Murrell 2011). The main dosage schedule used is 375 mg/m^2 intravenously once weekly for 4 weeks with (or without) subsequent doses at the intervals of several weeks to months. Alemtuzumab, a monoclonal antibody to CD52, expressed on T- and B-lymphocytes, has recently been reported to be effective in PNP associated with CLL. Other therapeutic options, such as plasmapheresis and intravenous immunoglobulin (e.g. 2 g/kg/cycle over 2–4 consecutive days, with cycles repeated every 4–6 weeks), have been used as adjuncts to immunosuppressive therapy.

Treatment should continue until disease control is achieved (as defined by the absence of new and healing of existing cutaneous and mucosal lesions), lack of efficacy is apparent or serious side effects occur. Careful monitoring and close liaison with oncologists are essential when using

immunosuppressive therapy in the context of an underlying malignancy. A particular caution should be taken in the setting of an undiagnosed neoplasm, as empirical immunosuppression in such circumstances can be detrimental.

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Pityriasis Lichenoides Acuta

74

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Pityriasis Lichenoides Acuta (PLEVA)

Key Points

- PLEVA includes a wide spectrum of clinical situations, ranging from cases with modest expressions to forms with high fever, malaise, intense myalgias, and multiple ulcero-necrotic lesions.
- In most cases, PLEVA is a self-healing process that resolves in a few months. Sometimes, the disease changes to pityriasis lichenoides chronica and may persist for years.
- The course of febrile ulcero-necrotic variant can last from 1 month to 2 years with recurrent acute episodes. Some cases can have a fatal outcome.
- The therapeutic strategy must be adapted to cope with the characteristics of clinical presentation.
- In cases with fever, an antibiotic treatment is always useful. In children, erythromycin is the antibiotic of choice, whereas tetracycline is preferable in adults.
- In cases without fever with moderate cutaneous lesions, in addition to topical treatment with steroid creams, it may be appropriate to start immediately the phototherapy. In adults, NB-UVB or PUVA may be preferable.
- In highly febrile patients with severe general condition and multiple ulcero-necrotic lesions, in addition to an antibiotic, it is advisable to administer a systemic steroid or methotrexate. Systemic steroids are suitable for adults and children, whereas methotrexate should be reserved for adult patients.
- Once an attenuation of clinical severity is obtained, it may be appropriate to begin a phototherapy session following the above criteria.

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Definition

Pityriasis lichenoides et varioliformis acuta (PLEVA), or acute guttate parapsoriasis, or Mucha-Habermann disease, is the acute form of a papulosquamous cutaneous disorder, whose chronic form is also known as pityriasis lichenoides chronica (PLC) or chronic guttate parapsoriasis. A rare severe ulcero-necrotic form, which is a febrile variant of PLEVA, is also known. Lymphomatoid papulosis, formerly considered

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_74, © Springer-Verlag Berlin Heidelberg 2015

as a possible persistent variant of PLEVA, is now classified as a primary cutaneous CD30(+) lymphoproliferative disorder, but the description of PLEVA variant, characterized in the conspicuous CD30 component, suggests the existence of intermediate forms between the classical PLEVA and lymphomatoid papulosis.

Epidemiology

The incidence and prevalence of PLEVA are unknown. Racial predisposition or special geographical frequency has not been reported. The disease has been observed mainly in adolescents and in young adults, less frequently in infancy, and rarely in old age.

Basic Concepts of Pathogenesis

Pityriasis lichenoides acuta is a disease of unknown etiology. It is debated if it is an inflammatory reaction triggered by various infectious agents, or an immune complex-mediated vasculitis, or a genuine lymphoproliferative process that is part of the cutaneous T-cell lymphoproliferative spectrum, possibly related to lymphomatoid papulosis. Attempts to isolate bacterial or viral agents have given controversial results, but the hypothesis of a reaction to an infective organism is largely accepted. The elevated incidence in young patients and the self-limited course support such a hypothesis. Pathogens that have been supposed to cause PLEVA include adenoviruses, Epstein-Barr virus, *Toxoplasma gondii*, parvovirus B19, as well as gram-positive cocci.

Clinical Presentation

The lesions of PLEVA usually appear on the anterior trunk and flexor surfaces of the extremities (Figs. 74.1 and 74.2). The onset is sudden with reddish-brown macules and edematous pink papules that undergo central vesiculation and hemorrhagic necrosis. Occasionally, headache, malaise, and fever may precede or accompany the onset of the disease. Lesions tend to be more numerous on the proximal than the distal parts of the extremities. The face, scalp, and palmoplantar surface are usually spared, but in some cases, the lesions may involve the entire body surface. In most cases, PLEVA is a self-healing process that resolves in a few months. Sometimes, however, the disease changes to pityriasis lichenoides chronica and may persist for years with a course characterized by remissions and exacerbations.

The febrile ulcero-necrotic Mucha-Habermann disease is characterized by necrotic cutaneous ulcerations associated with systemic manifestations. The disease begins with high fever, asthenia, malaise, intense myalgias, neuropsychiatric alterations, and multiple cutaneous lesions. Older lesions progress to large painful ulcers with central necrosis and raised borders. The course of febrile ulcero-necrotic variant can last from 1 month to 2 years with recurrent acute episodes. Some cases can have a fatal outcome.

Diagnosis and Differential Diagnosis

PLEVA histopathology has several aspects similar to PLC, confirming that the two clinical features, as well as their variants, belong to a common clinicopathological spectrum. In early stages, the most typical histological changes are represented by focal necrosis, occasional vesicles, and vacuolization of the basal layer. In advanced stages, the epidermis can be invaded by a dense infiltrate, while the necrotic phenomena are more pronounced and may involve the entire epidermis. A lymphohistiocytic infiltrate is present in the dermis with a predominantly perivascular arrangement and extends from the dermoepidermal junction until the reticular dermis. The vessels are dilated, sometimes occluded, and often surrounded or invaded by inflammatory cells with possible leukocytoclasis.

A number of laboratory abnormalities have been shown in patients with PLEVA, but they are not significant for the diagnosis. Immunofluorescence techniques have shown

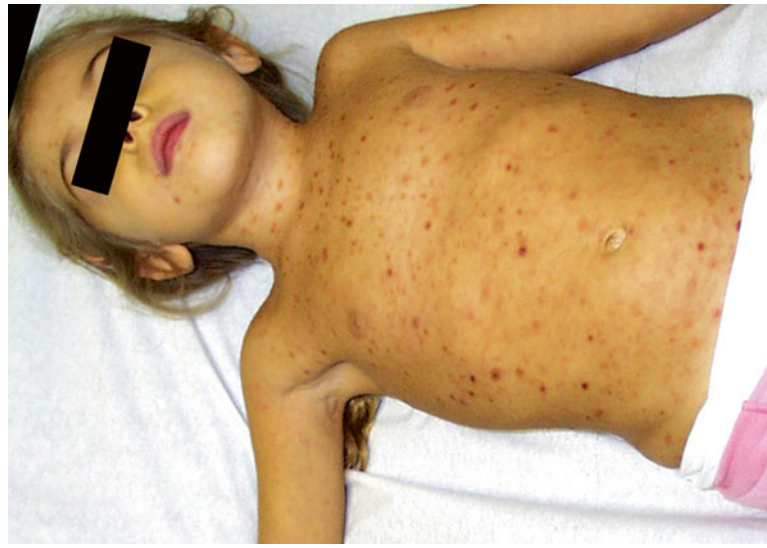

Fig. 74.1 PLEVA in a 6-year-old child

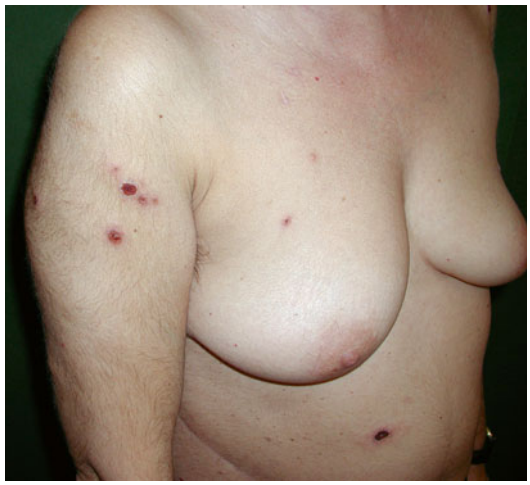

Fig. 74.2 PLEVA in a 52-year-old woman

slight vascular deposits of IgM and C3 in most lesions. Perivascular deposits of fibrin have been observed in early lesions; more extensive perivascular and interstitial deposits of fibrin have been detected in advanced lesions.

Clinical differential diagnosis of PLEVA includes conditions reported in Table 74.1.

Table 74.1 Conditions which must be clinically differentiated from PLEVA

Disease	Main clinical features
Pityriasis lichenoides chronica	Discrete papules and macules with micaceous scales
Lymphomatoid papulosis	Erythematous papules, rapidly evolving into red-brown, or hemorrhagic, or vesicular, or pustular, or necrotic lesions; occasional noduloulcerative lesions; in later phase, possible large plaques or nodules showing slow regression
Varicella	Small, erythematous macules on the scalp, face, and trunk, rapidly progressing into papules, vesicles, pustules with subsequent central umbilication and crust formation
Guttate psoriasis	Monomorphic lesions completely covered with stratified scales; bright underlying erythema; Auspitz's sign positive
Gianotti-Crosti disease	Lack of necrosis; acral distribution of the lesions
Erythema multiforme	Involvement of mucous membranes; target lesions

General Principles of Treatment

Most patients with PLEVA are in good general health and symptom-free except low-grade fever and mild pruritus. For these subjects, considering that the disease is often a self-healing process, treatment is not always necessary. A couple of weeks are usually sufficient to determine whether the disease may be a self-limiting condition without treatment. In any case, therapy is required in more severe forms, particularly in febrile patients with ulcero-necrotic nodules and plaques, evolving in ulcerated lesions.

Since the clinical evidence suggests that an infectious agent may be involved in the pathogenesis of PLEVA, an antibiotic treatment is recommended at least at the onset of the disease.

The patient's age is another important criterion to be considered in defining the therapeutic strategy. In fact, although PLEVA displays similar characteristics in adults and children, the latter cannot benefit by all available therapeutic procedures.

Topical Treatments

Steroid creams are largely used in the treatment of PLEVA, but there are no controlled studies demonstrating their effectiveness. Topical tacrolimus, a calcineurin inhibitor, mostly used in the treatment of atopic dermatitis, has been reported to work in some patients. Topical creams, with antiseptics or antibiotics, may be necessary in the forms with ulcerated lesions.

Systemic Treatments

Antihistamines are the most common and safe treatment and can be used both in adults and in children. They may relieve pruritus but have little influence on the course of the disease.

Antibiotics are largely used in the treatment of PLEVA, especially in the febrile forms. *Tetracycline* is mainly used in adults, whereas *erythromycin* is the first-line drug in childhood.

In a study of 15 children (11 suffering from PLEVA and 4 from PLC) treated with 200 mg of erythromycin 3 or 4 times a day, 2 PCL patients and 11 PLEVA patients had remission (Truhan et al. 1986). In another study including 22 children (72 % suffering from PLEVA and the remainder from PLC), erythromycin was administered to 8 subjects with moderate results (Romani et al. 1998). In a retrospective review of 124 patients, erythromycin was the initial treatment option in 79.7 % of patients. Andrea Andreassi observed a response to erythromycin in 66.6 % of patients with a median response time of 2 months; of those, 61 % cleared completely (Ersoy-Evans et al. 2007). More recently, a retrospective study on 24 children (15 affected by PCL, 6 from PLEVA, and 3 from PLEVA-PLC overlap) showed that oral erythromycin, at a dosage of 30–50 mg/kg/day in three to four divided dosages for 1–4 months, is an effective and well-tolerated therapeutic option (Hapa et al. 2012).

Patients with PLEVA are responsive to tetracycline given at the initial dose of 2 g daily for 2–4 weeks, followed by treatment of 1 g daily. According to our experience, minocycline and doxycycline at a dosage of 100 mg daily can be alternative options. Since tetracyclines are effective even if no infection signs are evident, a possible inhibition of neutrophil chemotaxis is hypothesized.

Corticosteroids have been reported fully effective in sporadic cases. In our experience, they are able to reduce the intensity of the disease. A short treatment with prednisolone at 0.5 mg/kg daily induces the regression of general symptoms, permitting other treatments to be performed, particularly phototherapy in patients with severe clinical lesions.

Methotrexate is effective in patients with PLEVA and in some cases it has been administered in association with corticosteroids. In one of the first studies, six patients with PLC were treated with methotrexate at doses ranging from 7.5 to 20 mg/week, with good final results. In subsequent studies, the use of methotrexate was extended to PLEVA with good results, but its potential side effects, as well as the tendency of the disease to recur after treatment, suggest restricting the use of this drug only to selected patients.

Other systemic drugs for the treatment of PLEVA include dapsone, cyclosporine, and high-dose immunoglobulins. All showed good efficacy, but the number of cases is small and does not allow a reliable assessment.

Phototherapy

UV treatment has been widely used with varying success both in patients with PLEVA and in those with PLC. It has been used as simple solar exposure, psoralen plus ultraviolet A (PUVA), UVA or UVA1 without psoralen, UVA/B, and UVB narrowband. All these procedures, except PUVA, can be used in adults and in children; however, some clarifications are necessary.

Treatment with UVB is performed two or three times a week, starting with doses of 20–40 mJ/cm^2 in relation to skin type. Twenty to thirty sessions are usually required to get the clearance of the lesions. UVA/B therapy is performed with modalities similar to those used for UVB alone. Narrowband UVB therapy with TL01 lamps provides further advantages. In a study performed on 31 patients (23 PLEVA, 8 PLC) treated with NB-UVB phototherapy, a complete response was observed in 15 out of 23 PLEVA patients (65.2 %) with a mean cumulative dose of 23 J/cm^2 after a mean number of 43.4 exposures (Aydogan et al. 2008). Particularly interesting are the results obtained with the UVA1 radiation, between 340 and 400 nm. In a study carried out on eight patients (three with PLEVA and five with PLC), each subject received 60 J/cm^2 UVA1 daily until remission. UVA1 therapy was an effective and well-tolerated treatment for PLEVA and PLC. The therapeutic activity seems to be related to direct effects on cutaneous inflammatory infiltrates because the lesions in unexposed cutaneous areas did not respond (Calzavara-Pinton et al. 2002). In a recent study, 15 subjects suffering from pityriasis lichenoides were divided in two groups, respectively, treated with PUVA or NB-UVB. As the difference between the two groups was insignificant, it was concluded that both options are acceptable for treating this disorder (Farnaghi et al. 2011).

The regression of PLEVA after UV radiation is not always permanent. Possible recurrences can be treated with further UV treatments. How UV radiation works in the treatment of PLEVA is not known. A possible hypothesis is that UV radiation inhibits the release of some inflammation mediators and therefore is able to interfere with lymphocyte infiltrate.

Practical Suggestions at Glance

Before starting the treatment of a patient suffering from PLEVA, it is necessary to accurately assess the case to be treated. This is because PLEVA includes a wide spectrum of clinical situations, ranging from cases with modest expressions to forms with high fever, asthenia, malaise, intense myalgias, neuropsychiatric alterations, and multiple ulcero-necrotic lesions. The therapeutic strategy must be adapted to cope with the characteristics of clinical presentation (Table 74.2).

Table 74.2 Treatment levels depending on the severity of disease

Severity of disease	Step-by-step treatment
Moderate and sporadic lesions, without fever	Topical steroids, possible phototherapy
Intense and disseminated lesions, with moderate fever	1. An antibiotic treatment is always useful: erythromycin in children, tetracycline in adults
	2. Phototherapy may begin when patients become afebrile
Highly febrile patients with severe general condition and multiple ulcero-necrotic lesions	1. In addition to an antibiotic, it is advisable to administer a systemic steroid (children and adults) or methotrexate (only adults)
	2. Phototherapy can be performed when patients are in good general condition

Several modalities of phototherapy are available: in *adults* NB-UVB or PUVA may be preferable. In *children*, the most suitable options are UVA or UVA/B or UVA1

In cases without fever with moderate cutaneous lesions, in addition to topical treatment with steroid creams, it may be appropriate to start immediately the phototherapy. In adults, NB-UVB or PUVA may be preferable.

In cases with fever, an antibiotic treatment is always useful. In children, erythromycin is the antibiotic of choice, whereas tetracycline is preferable in adults. Once the fever has disappeared, it is appropriate to begin phototherapy following the above indications.

In highly febrile patients with severe general condition and multiple ulcero-necrotic lesions, in addition to an antibiotic, it is advisable to administer a systemic steroid or methotrexate. Systemic steroids are suitable for adults and children, whereas methotrexate should be reserved for adult patients. Once an attenuation of clinical severity is obtained, it may be appropriate to begin a phototherapy session following the above criteria. Large ulcerations, typical of the febrile ulcero-necrotic variant, require local wound care. Infected lesions may be treated with topical antibiotic.

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Pityriasis Lichenoides Chronica

75

Paloma Borregón and Agustín España

Key Points

- Pityriasis lichenoides (PL) represents a unique group of inflammatory and acquired skin disorders that include pityriasis lichenoides et varioliformis acuta (PLEVA or Mucha-Habermann disease) and pityriasis lichenoides chronica (PLC).
- PLEVA and PLC are two ends of a disease spectrum. The prevalence, incidence and risk factors of PL in the general population are still unclear.
- PLC is distinguished by gradually developing, small, dim, erythematous-to-brown flattened maculopapules with fine centrally attached shiny scales. These crops of lesions are usually scattered across the trunk and proximal extremities and fade with minor hypo-/hyperpigmentation in the absence of scarring. PLC histopathology shows superficial perivascular interface dermatitis.
- PLC must be differentiated mainly from parapsoriasis, guttate psoriasis and lichen planus.
- There are no diagnostic or therapeutic guidelines for PLC.
- Topical corticosteroids, phototherapy and oral tetracycline or erythromycin are the most recommended treatments.

Definition

Pityriasis lichenoides (PL) is an uncommon, acquired skin condition. It represents a unique group of inflammatory skin disorders that include pityriasis lichenoides et varioliformis acuta (PLEVA or Mucha-Habermann disease) and pityriasis lichenoides chronica (PLC). PLEVA and PLC are two ends of a disease spectrum.

History

PL was first described between 1894 and 1925. Neisser and Jadassohn described what would now be considered the acute and chronic forms, respectively. In 1899, Juliusberg described pityriasis lichenoides in a chronic form and thus coined the term pityriasis lichenoides chronica (PLC).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_75, © Springer-Verlag Berlin Heidelberg 2015

In 1902, Brocq described pityriasis lichenoides as a form of parapsoriasis under the category of parapsoriasis en gouttes. This classification lasted for several years, and it was not until 1926 that PL was first distinguished on clinical grounds as an entity separate from parapsoriasis.

Mucha separated the acute form of pityriasis lichenoides from PLC in 1916. But it was in 1925 when this acute form was given the name pityriasis lichenoides et varioliformis acuta (PLEVA) by Habermann.

Epidemiology

The prevalence, incidence and risk factors of PL in the general population are still unclear. Some investigators estimate the incidence to be around 1 in 2,000 people. Neither an ethnic nor a geographic predisposition has been reported. However, PL does maintain a slight male predisposition and tends to present in late childhood and early adulthood.

Basic Concepts of Pathogenesis

The aetiology of PL is unknown. There are three major pathogenic theories: an inflammatory reaction triggered by infectious agents or drugs, an inflammatory response secondary to a T-cell dyscrasia and an immune complex-mediated hypersensitivity vasculitis. Both PLEVA and PLC contain lesion T-cell infiltrates, with a general predominance of CD8+ cells in PLEVA and CD4+ cells in PLC. Both types of lesions can exhibit dominant T-cell clonality, easily seen in PLEVA, where the infiltrate is denser. This clonality indicates that PL is a T-cell lymphoproliferative disorder like lymphomatoid papulosis and some forms of T-cell cutaneous hyperplasia. This concept may help to explain the occasional association of PL with other lymphoproliferative disorders such as cutaneous T-cell lymphoma, Hodgkin's disease and other lymphomas.

Clinical Presentation

The most common and subtle form of PL is PLC, which presents sequentially or concomitantly and, eventually, may overtake PLEVA. PLC is distinguished by gradually developing, small, dim, erythematous-to-brown flattened maculopapules with fine centrally attached shiny scales (Figs. 75.1 and 75.2). These crops of lesions are usually scattered across the trunk and proximal extremities and fade with minor hypo-/hyperpigmentation in the absence of scarring. Palms, soles, face and scalp can be also affected. This rash may resolve in months or wax and wane for years with extended lengths of remission. Irregular erythema and superficial ulcerations on the oral mucosa and palate have been reported. In dark-skinned people, PLC may rarely present with widespread hypopigmentation rather than the typical papular morphology, especially common in children.

PLC generally manifests a more indolent course than PLEVA. The distribution of PLC lesions may predict its prognosis; a generalized rash may last months but peripheral lesions can take years to resolve.

The diagnosis of PLC is made by clinical evaluation of the skin and a biopsy with histopathologic examination as a confirmatory tool.

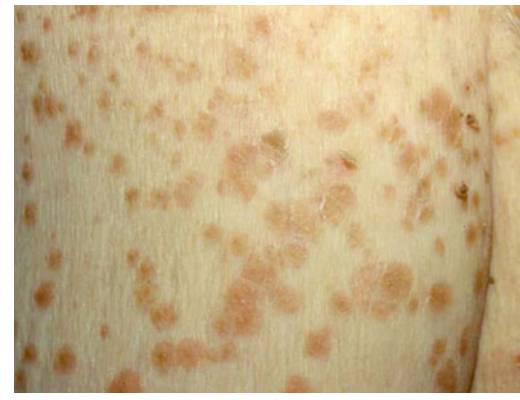

Fig. 75.1 Old patient with diffuse scaly papules and plaques

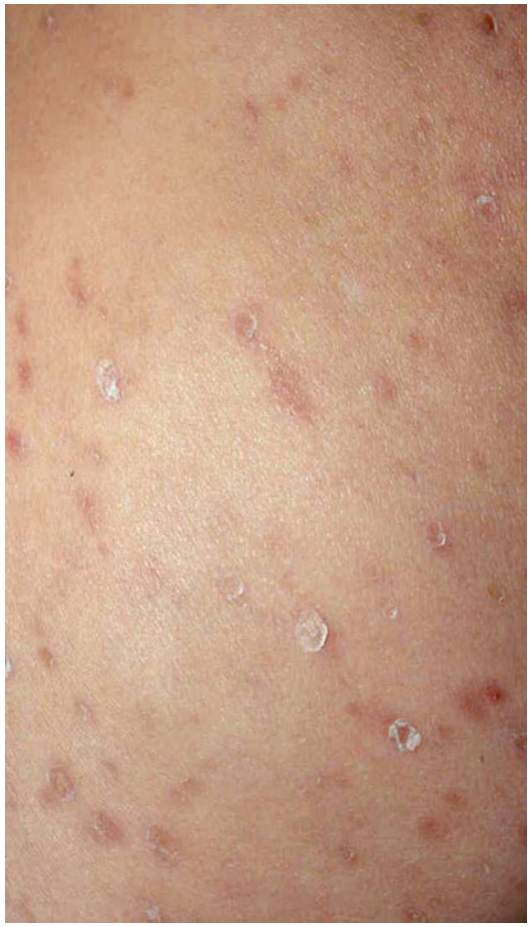

Fig. 75.2 Pityriasis lichenoides chronica in a 14-year-old boy: red scaly papules on the trunk

Diagnosis

PLC histopathology shows superficial perivascular interface dermatitis. The principal microscopic features are parakeratosis and mild lymphocytic infiltrate accompanied by focal keratinocyte necrosis and mild erythrocyte extravasation. They are similar changes to that observed in PLEVA but milder. While some observers allow occasional atypical lymphocytes, others regard this as a sign of lymphomatoid papulosis.

Immunohistochemical studies have shown that T cells predominate in both the dermal and epidermal inflammatory infiltrates. Most studies indicate that CD4+ T cells predominate in PLC. Admixed in the infiltrate are variable numbers of macrophages and CD1a + epidermal dendritic cells (Langerhans or indeterminate cells).

Differential Diagnosis

The differential diagnosis of the PLC is extensive and encompasses guttate psoriasis, lichen planus, papular eczematous dermatitis, tinea versicolor, Gianotti-Crosti syndrome, pityriasis rosea, drug or viral exanthemas (varicella), generalized arthropod bite reaction, erythema multiforme, cutaneous small vessel vasculitis, secondary syphilis, papulonecrotic tuberculid, polymorphous light reaction, generalized folliculitis, dermatitis herpetiformis, toxic epidermal necrolysis, graft-versus-host disease and mycosis fungoides. PLC must be differentiated mainly from parapsoriasis, guttate psoriasis and lichen planus. A thorough history and clinical, pathologic and laboratory examinations are strongly recommended to distinguish PL from other diagnoses.

An important skin entity to recognize and isolate from PLC is lymphomatoid papulosis, which is very similar clinically so that a biopsy is mandatory to make differential diagnosis by histopathology. The presence of atypical lymphocytes and CD30 positivity for most of these cells are seen in lymphomatoid papulosis but not in PL.

General Principles of Treatment

There are no diagnostic or therapeutic guidelines for PLC. Dozens of different treatments are advocated for this disorder. PLC can regress spontaneously, and due to the low frequency of the disease, its unknown aetiology and the unpredictability of its course, it is difficult to evaluate the effectiveness of the recommended therapies.

Phototherapy

For some authors, phototherapy is by far the most successful therapy and is the first-line therapy for PLC. It is used for a variety of modalities (e.g. UVB, narrowband UVB, psoralen plus UVA and

UVA) and is well tolerated. The total amount of energy used has varied from 10 to 370.5 J/cm^2. Ultraviolet light therapy, especially UVB, has even shown therapeutic value and safety in the paediatric population. Recurrences after cessation of therapy or after long periods of remission are not uncommon, although complete clearing has also been documented.

Topical Treatments

Topical corticosteroids are a good option for PLC, though no studies have specifically compared the efficacy of such agents with that of either placebo or other treatments. However, concerns about their side-effect profile have led to the increased utilization of nonsteroidal topical immune-modulating therapies. Topical tacrolimus has been reported to work in some patients with PLC, both 0.03 % ointment and 0.1 % ointment twice daily, probably because of its anti-inflammatory ability to affect T cells. Topical coal tar preparations could be also helpful.

Systemic Treatments

Oral agents most often used for treatment of PLC include antibiotics and methotrexate. The most common antibiotics include tetracycline and erythromycin.

If a foreign antigen is the suspected trigger (as drug or infectious agent), cessation of the implicated drug or anti-pathogen therapy must be the treatment used. Oral *tetracycline and erythromycin* are used for their anti-inflammatory rather than antibiotic effect, with erythromycin favoured in children younger than 12 years of age (to avoid possible adverse effects in dentition). Especially in the treatment of children, a long-term (4–8 weeks) high-dose treatment with erythromycin (30–50 mg/kg per day) can be effective. For adults, tetracyclines in high doses of about 2 g/day for at least 4 weeks have shown favourable results. Depending on the response, the dosage can be tapered over the course of several months to minimize the risk of relapses.

Antihistamines may be helpful in cases with significant pruritus.

Methotrexate is an effective treatment in some patients with severe forms of PLC in dosages of 7.5–20 mg/week. Recommended initial test dose of 5–10 mg/week can be gradually increased by 2.5–5 mg/week. Reduction of the dose can lead to recurrence. It is not recommended in children. Laboratory control of the treatment is essential. Before it, renal, hepatic and bone marrow function have to be monitored.

Systemic corticosteroids (e.g. prednisone 0.5–1.0 mg/kg of body weight per day with a slow taper) should be considered in PL cases with concurrent and chronic constitutional symptoms such as fever, arthritis and myalgias (more frequent in PLEVA).

Cyclosporine can be considered an alternative in refractory cases. The initial dose is 5 mg/kg per day over a period of about 6–8 weeks. Once the response is achieved, the dose should be slowly tapered. Blood pressure and renal function must be monitored every 2–4 weeks.

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Pityriasis Rosea

76

Milos Nikolic

Key Points

- Pityriasis rosea (PR) is a common, acute, or subacute self-limited papulosquamous skin disease.
- Approximately 1–2 % of new dermatological patients are affected by PR.
- PR affects mainly children, adolescents, and young adults.
- PR usually remits within 3–6 weeks.
- Viral etiology of PR is probable.
- Asymptomatic and mild cases may be left untreated.
- If itch is important, topical corticosteroids are indicated.
- Phototherapy (UVB or UVA_1) may be useful in the treatment.
- High-dose oral acyclovir, if introduced early in the course of PR, may reduce the disease duration.

Definition and Epidemiology

Pityriasis rosea is a very common papulosquamous skin disease. Most frequently, PR is mild, with an acute or subacute course, usually lasting 3–6 weeks. In some cases, the eruption may disappear in 1 week, but in rare cases PR may persist even 5 months or longer. The recurrence rate of PR is only 2 %.

Basic Concepts of Pathogenesis

The etiology of PR remains unelucidated. Many clinical and epidemiological characteristics suggest an infective agent as the etiologic factor. True epidemics have not been documented, but family outbreaks have been reported. Seasonal variations have been found: in Europe and North America, most cases have been diagnosed in winter months. The course of PR includes herald patch/patches as sites of inoculation, disseminated lesions that appear after a certain period, mild constitutional symptoms, self-limited course, and relatively rare relapses are the characteristics compatible with an infectious disease. Worsening of the eruption that may appear in patients treated with systemic corticosteroids is also an argument that favors infective etiology.

Investigations of many microorganisms as possible causative agents in PR were fruitless for many years. Recently, systemic active infection with human herpes viruses 6 (HHV-6) and/or 7

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_76, © Springer-Verlag Berlin Heidelberg 2015

(HHV-7) has been implicated in PR pathogenesis. HHV-8 has also been found as a possible etiologic agent of PR. Unfortunately, not all authors have been able to confirm the causative role of these viruses in PR.

Clinical Presentation

PR has been reported in all races and equally affects males and females. It may occur at any age, but most patients are between 10 and 35 years old. In temperate climate zones, the incidence is highest in winter and lowest in summer months. The prevalence of PR in the United States has been estimated to be 0.13 % in men and 0.14 % in women.

Prodromal symptoms are uncommon, and the first manifestation is the herald patch, present (or at least noticed) in 70–80 % of patients. Herald patch is usually a solitary, oval, erythematous, and scaly plaque, measuring 2–6 cm in diameter. Within 2–3 days to 2 weeks, smaller, erythematous (Fig. 76.3), round to oval macules and/or slightly infiltrated plaques with crinkly surface and a rim of fine scale (collarette scale – free at the center of the lesion and attached at the periphery), measuring 1–3 cm in diameter, appear in crops on the trunk and proximal extremities. The long axes of the lesions are oriented along the skin tension lines, running parallel to the ribs, forming the classical "Christmas-tree-like pattern." The face, hands, and feet are usually spared. Especially in children, these areas may be involved. New lesions continue to appear over a few weeks, persist for a few weeks, and then gradually resolve over another few weeks. The entire course of PR usually lasts 3–6 weeks. Most frequently, the lesions are asymptomatic, but mild to severe itch may be present. In some cases, the lesions may persist up to 3 months and very rarely more than 5–6 months. Upon resolution of the inflammatory lesions, residual hyper- or hypopigmented macules, lasting for another several weeks to months, may be found.

There are several clinical variants of PR, and the variants may be as frequent as the "classical" cases. The herald patch may be absent, or there may be more than one herald patch. In children, the lesions are often papular or purpuric. Vesicular (Fig. 76.2) or bullous lesions may be seen. Inverse PR affects predominantly skinfolds (Fig. 76.3). Urticarial lesions are rarely reported. In patients with darker skin, the lesions may have lichenoid aspect. The extent of the eruption in PR may be variable – in some patients the lesions are very numerous and disseminated, and in other cases, there may be only several lesions. Oral, palmar, or plantar lesions are rare but described in the literature.

The recurrence rate is low; approximately 2 % of patients will have a second attack, while multiple recurrences are even rarer.

Diagnosis

There are no specific laboratory tests that could help in the diagnosis. Biopsy is relatively rarely performed in routine practice, and most frequently, it is not necessary for the diagnosis. The histopathological characteristics are not diagnostic but may be suggestive. In the epidermis, spongiosis, vesicles, and focal parakeratosis are usually present. Also, exocytosis of mononuclear cells into the epidermis is frequently seen. In the upper dermis, edema and mild perivascular mononuclear cell infiltrate can be present, sometimes with extravasation of red blood cells (Figs. 76.1, 76.2, and 76.3).

Differential Diagnosis

The differential diagnosis includes secondary syphilis, viral exanthems, guttate psoriasis, seborrheic dermatitis, pityriasis lichenoides ("guttate parapsoriasis"), small plaque parapsoriasis, disseminated nummular eczema, PR-like drug eruptions (induced by captopril, gold salts, ketotifen, barbiturates, metronidazole, isotretinoin, lamotrigine, adalimumab, rituximab, etc.), and disseminated tinea corporis. Herald patch(es) may mimic psoriasis, tinea corporis, or nummular eczema.

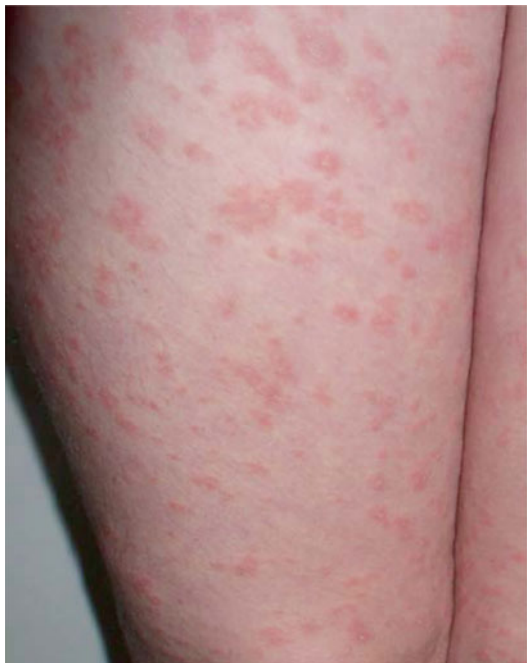

Fig. 76.1 Disseminated small oval plaques with characteristic collarette scale

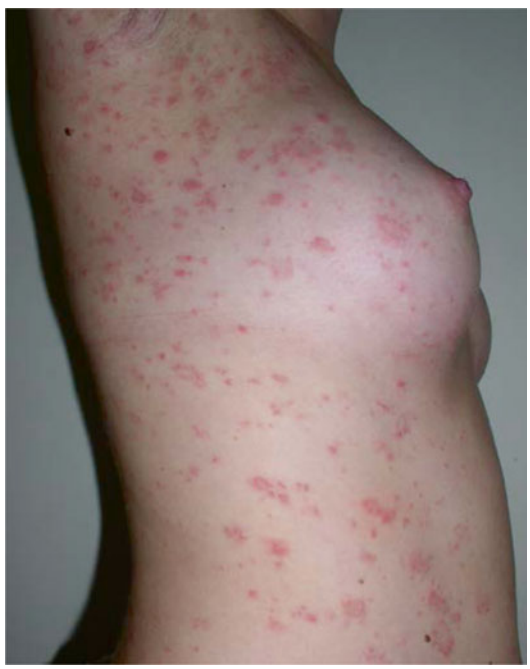

Fig. 76.2 One of the atypical variants of PR: disseminated, somewhere annular oval plaques with edge papulovesicles

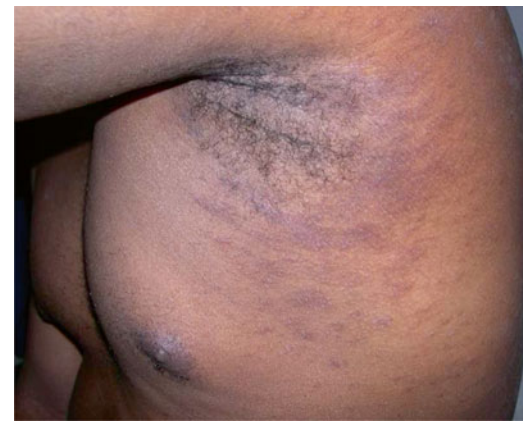

Fig. 76.3 Inverse PR in darkly pigmented skin (Courtesy of Dr. V. Petronic-Rosic, University of Chicago, Chicago, IL, USA)

General Principles of Treatment

The patients should be reassured about the nature and the benign course of the disease. Many patients, especially those with mild and asymptomatic disease, will not need any treatment.

Topical Treatments

If any treatment is necessary, most patients will benefit from mid-potency topical corticosteroids, applied twice a day. This approach will alleviate the itch and will hasten the regression of individual lesions. Pruritus can be also controlled using the topical antipruritics such as calamine lotion and lotions with menthol, camphor, or pramoxine. In disseminated forms, UVB phototherapy (both broadband and narrowband) may be helpful. Also, UVA_1 phototherapy (30 J/cm^2, three times weekly, for 3 weeks) has been found effective in the treatment of PR. In summer months, cautious exposure to sunshine can also be recommended. Phototherapy of PR may increase the risk of post-inflammatory hyperpigmentation.

Topical Treatments at a Glance

- Patients with itch will benefit from topical mid-potency corticosteroids.
- Patients with disseminated PR may be treated with UVB or UVA_1.

Systemic Treatments

If a patient with disseminated PR is seen early in the disease (first 7–10 days), oral acyclovir (based on the concept that HHV-6 and HHV-7 are causative agents) can significantly shorten the disease duration. Acyclovir tablets, 800 mg, should be given five times daily, for 7 days (the mean time for skin clearance in the acyclovir group was 18.5 days and in the placebo group, 37.9 days).

In some studies, oral erythromycin (given for its anti-inflammatory and immunomodulating effects) was successfully used in the treatment of PR: 1 g in four equally divided doses for 2 weeks in adults and 25–40 mg/kg in four divided doses in children. In some subsequent studies, erythromycin and azithromycin turned out to be ineffective in the treatment of PR.

Oral corticosteroids have been given for disseminated forms of PR, but in some cases this treatment even provoked a worsening of the eruption.

Patients with pruritus might benefit from oral H1 antihistamines.

Systemic Treatments at a Glance

- For patients diagnosed early, oral high-dose acyclovir may be given for 7 days.
- Oral erythromycin can be given for 14 days.

Overview of Pityriasis Rosea Treatment at a Glance

- For cases with limited number of lesions, topical mid-potency corticosteroid, twice a day.
- If disseminated PR is diagnosed early, oral high-dose acyclovir can be given for 7 days.
- If a patient with disseminated PR is diagnosed with a delay, UVB or UVA1 phototherapy can be recommended.

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Pityriasis Rubra Pilaris

77

Andrej Petrov and Vesna Pljakoska

Key Points

- Pityriasis rubra pilaris (PRP) is a chronic papulosquamous disorder of keratinization. The etiology is unknown. PRP shows similarities with psoriasis, but it is a distinct disease.
- According to Griffiths, there are six types of PRP. It appears in adults but also in a juvenile form. It typically affects extensor parts of the body, starting usually from the face. Typical lesion is hyperkeratotic papule. Spearing islands of the non-affected skin are a pathognomonic sign. After some time, salmon-like discoloration of the skin occurs. Palmoplantar keratoderma is almost always present.
- Histology is not confirmatory.
- PRP should be distinguished from psoriasis and other papulosquamous disorders.
- Treatment is topical or systemic. Retinoids are first-line treatment. Biologics are a new class of available medications for the treatment of PRP, basically used with success in psoriasis.

Definition and Epidemiology

Pityriasis rubra pilaris (PRP) is a chronic, inflammatory, papulosquamous disorder of keratinization with unknown etiology, characterized with affection of the body and palmoplantar ("sandal") affection. It appears both in hereditary and in acquired form. The first description of PRP is described by Claudius Tarral who, in 1835, published a case report in Rayer's *A Theoretical and Practical Treatise on the Diseases of the Skin* of a patient he had seen 7 years earlier. Tarral did not recognize the dermatosis as a distinct entity, and it was listed under the title of "general psoriasis."

It affects both sex male and female equally without sexual predilection. The highest incidence is in the first and sixth decade. Incidence is around 1:5,000. There may be racial variation as the incidence of classical PRP was reported to be closer to 1 in 50,000 in India.

The etiology is unknown. There are some similarities with psoriasis, but it is a distinct disease, which is more of a disorder of keratinization than an inflammatory disease. There are some clinical and histological evidence as well about vitamin A deficiency. Infective etiology and familial distribution are also suggested. PRP could appear also after drug therapy and the influence of some triggering factors, such as severe infection, especially in juvenile form. Simultaneously PRP may appear with other immunological disorders, like rheumatoid

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_77, © Springer-Verlag Berlin Heidelberg 2015

Table 77.1 Classification of pityriasis rubra pilaris. Griffiths' six types of PRP

Type	% of cases	Distribution	Prognosis
I. Classical adult	55	Generalized	Most clear in 3 years
II. Atypical adult	5	Generalized	Chronic
III. Classical juvenile	10	Generalized	Most clear in 1 year
IV. Circumscribed juvenile	25	Focal	Uncertain
V. Atypical juvenile	5	Generalized	Chronic

From Albert and Mackool (1999) modified

arthritis, and some malignancies like leukemia or Sezary syndrome, which indicates association with immunosuppression.

6. HIV related. Symmetrical, pruritic eruption composed of erythematous papules is associated with late-onset acne conglobata.

Classification

According to Griffiths there are six types of PRP (Table 77.1) and the classical adult type is the most common, and it has the best prognosis. Remission is appearing after several years. Type 2 PRP is the atypical adult form with a tendency to become chronic. The type 3 classical inherited variant seems to have also good prognosis. Type 6 is described recently in which PRP is associated with HIV and this type has a poor prognosis.

1. Classical adult. Commonest type (50 % of cases). Spreads caudally. The patient is usually erythrodermic with diffuse thickening of the palms and soles. Ectropion often is present.
2. Atypical adult. Long duration. Involves a more ichthyosiform pattern in association with hair loss and areas of eczematous changes.
3. Classical juvenile. Similar to type 1 but affects children in the first decade.
4. Circumscribed juvenile. Affects children, with sharply demarcated areas of follicular hyperkeratosis and erythema on the knees and elbows. Usually does not progress.
5. Atypical juvenile. Appears in the first few years of life and is chronic. Characterized by follicular hyperkeratosis, whereas erythema is not a prominent feature. The skin on the hands and feet can appear scleroderma-like.

Clinical Presentation

Clinical picture is the basis for establishing the diagnosis of PRP.

Classical disease begins on the face, with scaling and erythema, and on lateral parts of the neck and trunk. Also, the disease may appear on extensor surface of the extremities and especially on the back of the first and second phalange. PRP is starting with small plaque lesions which spread all over the body. Typical lesion is follicular hyperkeratotic papule. Spearing "islands" of not affected skin are a pathognomonic sign. In 20 % of the patients, mild pruritus and burning sensation are present. Also Koebner phenomenon may appear like in psoriasis. After some time orange-red "salmon-like" discoloration of the skin is present. This is the hallmark for PRP.

Palms and soles are almost always involved, often showing an orange color. Palmoplantar waxy keratoderma appears after some period, with typical side spreading, producing the so-called sandal pattern. Changes of the nails, thickened nails with a distal discoloration, and subungual hyperkeratosis are often present, but pitting of the nail and dystrophy like in psoriasis do not exist.

Erythroderma can occur after 2–3 months. Erythroderma is a very serious development of the disease and should be monitored carefully. However, usually PRP remains static and disappears after 12 months. Mild pruritus is present.

Histology

Histopathological examination is showing hyperkeratosis, acanthosis, and parakeratosis, both horizontal and vertical, and superficial perivascular lymphocytic infiltrate. There is prominent follicular plugging with dense keratotic material. Histopathological findings are not pathognomonic; they can exclude other papulosquamous diseases.

Differential Diagnosis

PRP has to be distinguished from psoriasis (which is sometimes very difficult) and other papulosquamous disorders in adults and atopic dermatitis in childhood. Other reasons of erythroderma should be excluded. Cutaneous T-cell lymphoma and drug skin reactions should be taken in consideration.

There is no diagnostic laboratory test to confirm PRP. Distinguishing clinical features of PRP include islands of normal, non-affected skin, follicular keratotic plugs, and orange-red discoloration of affected skin.

General Principles of Treatment

Because of the variable clinical course and low incidence, assessment of the treatment modalities is difficult. Treatment modalities should include topical application of medications and systemic therapy.

Topical Treatments

Emollients are effective treatments for pityriasis rubra pilaris. Conservative approach is advised in juvenile cases. Keratolytics, like salicylic acid and tar, are important in the treatment. Calcipotriol can also be effective in children. Urea is very helpful. Topical corticosteroids are not very effective. All irritating factors should be avoided. Palmoplantar keratoderma is difficult to treat. Keratolytics and corticosteroids under occlusion are advised. Calcipotriene should be considered. Tazarotene is also available in the treatment of PRP.

Systemic Treatments

Oral synthetic retinoids are currently the treatment of choice for PRP and have largely replaced vitamin A therapy. Oral retinoids are the first choice in the treatment of widespread disease. Acitretin 0.5–1 mg/kg (in adults) or isotretinoin 0.5–2 mg/kg is advised. Duration of treatment is from 3 to 6 months. The main disadvantage of retinoids is teratogenesis in females. Appropriate contraceptive measures are mandatory and pregnancy is absolutely contraindicated during treatment with acitretin and for 2–3 years after discontinuation of acitretin and during treatment with isotretinoin and for 1 month after discontinuation of isotretinoin. So, oral acitretin is not indicated for the treatment of women of reproductive potential.

Methotrexate is an alternative agent for refractory PRP. Methotrexate is a second line of treatment given orally 15–25 mg/weekly.

Use of cyclosporine in the treatment of pityriasis rubra pilaris is still controversial.

UV-light treatment uses the ultraviolet light spectrum of 290–400 nm to treat a variety of skin diseases. It can be used alone or in combination with other medications applied directly to the skin or taken orally. PUVA, Re-PUVA, is also applied in PRP with less success than in psoriasis vulgaris. UVB therapy used in psoriasis vulgaris could have negative influence and aggravate pityriasis rubra pilaris.

Oral antihistamines can be successful to decrease itching.

Oral megadoses of vitamin seem to be not so effective.

Biologics are new classes of medications that target immune system responses. The beneficial use of biologics in psoriasis is evidence based and tumor necrosis factor alpha (TNF-α) has a central role in psoriasis. There are some data emphasizing that blockade of tumor necrosis factor alpha with antagonists of TNF-α also could

have positive effects in PRP. They are administered by subcutaneous injection (adalimumab, ustekinumab, etanercept) or by intravenous infusion (infliximab).

In case of erythroderma, intensive supportive therapy is imperative.

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Polymorphic Light Eruption

78

Robert S. Dawe

Key Points

- Polymorphic light eruption is a common condition characterised by a recurrent abnormal reaction to sunlight (or artificial source ultraviolet radiation) that occurs with a delay following exposure and heals without scarring.
- There are several morphological variants (papular, 'pinpoint papular', vesicular, papular with vesicles, plaque, erythema multiforme-like, insect bite-like, haemorrhagic and even 'sine eruptione' [typical time course but no visible eruption]), hence the term 'polymorphic'.
- In those who are only affected a few times each year, such as on holidays, first-line photoprotection measures, if necessary supplemented by occasional use of prophylactic topical or systemic corticosteroids, can be enough.
- For those more severely affected, one of the second-line phototherapy approaches is indicated.
- For those who remain severely affected, third-line systemic immunosuppression is rarely necessary.

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Definition and Epidemiology

This is a recurrent abnormal reaction to sunlight (or artificial source ultraviolet radiation) that occurs with a delay following exposure and heals without scarring. There are several morphological variants (papular, 'pinpoint papular', vesicular, papular with vesicles, plaque, erythema multiforme-like, insect bite-like, haemorrhagic and even 'sine eruptione' [typical time course but no visible eruption]), hence the term 'polymorphic'. In many parts of the world, polymorphic light eruption (PLE) is the commonest cause of abnormal cutaneous photosensitivity. This condition is also sometimes termed polymorphous light eruption (PMLE), although the term PMLE has historically been used to include what are now recognised to be distinct conditions such as actinic prurigo (Addo and Frain-Bell 1984). Juvenile springtime eruption is considered by some to be a variant of PLE. 'Spring and summer eruption of the elbows' (Molina-Ruiz et al. 2013), 'benign summer light eruption' (Guarrera et al. 2011) and Taiwanese 'solar dermatitis' (Chen and Lee 2013) probably are variants of PLE.

PLE is common, affecting as many as 10–20 % of some populations (Rhodes et al. 2010). As such there is a broad range of severity. At least amongst those severely enough affected to attend tertiary referral dermatology services, the effects on quality of life can be pronounced. The diagnosis is usually straightforward and based on history taking. It typically starts before the age of 30

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_78, © Springer-Verlag Berlin Heidelberg 2015

years old and is more common amongst females than men. Investigations to look for alternative and relevant concomitant diagnoses (such as solar urticaria or photoallergy) are rarely required. Management is through advice on photoprotection measures (behavioural, environmental, clothing and topical sunscreen), prophylactic topical or systemic corticosteroid therapy if only problematic a few times each year (such as during annual holidays) and, when more severe, prophylactic phototherapy. Systemic immunosuppressive therapy is rarely required.

Basic Concepts of Pathogenesis

The mechanism behind PLE is probably a delayed-type hypersensitivity response to an ultraviolet-induced photoallergen. There is some evidence that PLE is associated with reduced ultraviolet suppression of the induction phase of delayed hypersensitivity responses than in those without PLE (Palmer et al. 2005). This may be a factor predisposing some people to development of the presumed autosensitisation of PLE. This could fit with the fact that people with PLE appear less prone to skin cancers and that this might not simply be due to sunlight avoidance measures alone (Lembo et al. 2008). Possibly those who show better recognition of skin antigens after ultraviolet exposure are better protected against skin cancers but more prone to PLE.

Diagnosis

Once PLE has been diagnosed (usually on history alone), sometimes with investigations in case of concomitant problems such as sunscreen photoallergy, the condition should be discussed with the patient.

General Principles of Treatment

What treatments are needed depend on the severity of the condition and the patient's wishes. In those who are only affected a few times each year, such as on holidays, first-line photoprotection measures, if necessary supplemented by occasional use of prophylactic topical or systemic corticosteroids, can be enough. For those more severely affected, one of the second-line phototherapy approaches is indicated. Other second-line approaches, such as the fern *Polypodium leuco*tomos extract, which has antioxidant and anti-inflammatory properties, remain experimental (Tanew et al. 2012). For those who remain severely affected, third-line systemic immunosuppression is rarely necessary.

First-Line Sun Avoidance and Protective Measures

- When practicable (and often it is not, as the wishes and needs of the patient's family are important), avoidance of extra environmental sunlight exposure such as vacations in sunnier climes should be avoided. Sometimes advice on the use of UV-absorbing 'museum film' (Dawe et al. 1996) to car and house windows is appropriate.
- Appropriate clothing (tightly woven fabrics).
- Broad-spectrum high-factor sunscreens, applied correctly (thickly, evenly and frequently).
- Avoidance of middle of the day (11 a.m. to 3 p.m.) sunlight.

Second-Line Prophylactic Phototherapy/Photochemotherapy

A randomised controlled study did not detect any difference in efficacy between narrowband ultraviolet B phototherapy and psoralen plus ultraviolet A (PUVA) (Bilsland et al. 1993). PUVA has been shown to be more effective than broadband UVB (Murphy et al. 1987a, b). Because of ease of use and greater safety, narrowband ultraviolet B should generally be the first-line phototherapy for PLE.

Although often termed 'desensitisation', phototherapy for PLE is not considered to work as an immunological desensitisation therapy but rather is thought to work through inducing photoprotection effects and its suppressive effects on the skin immune responses. Factors important in giving it

the best chance of working well include carefully selecting the time of year of administration (too early treatment may lead to loss of effect before it can be 'topped up' by natural UV exposure); treating normally exposed sites only (to avoid limiting treatment through treatment-induced PLE on other sites); methods of preventing, or at least reducing the severity of, PLE provoked during therapy (such as applying a potent topical corticosteroid immediately after treatments); and how many exposures are given (a typical approach is to give a course of 15 treatments, administered three times weekly) (Ferguson 1996; Man et al. 1999).

Prednisolone tablets taken at first onset of the rash of PLE slightly, but significantly, shortened the duration of the eruption (Patel et al. 2000). Use of a potent to very potent topical corticosteroid applied daily from the day before to the third day of a holiday also appears helpful for some with 'holiday only' PLE (Man et al. 2000).

Other Second-Line Treatments for PLE

Various approaches have been tried but overall have failed to enter widespread usage as overall not consistently adequately effective. These include ß-carotene, antimalarial drugs, omega-3 polyunsaturated fatty acids (from fish oil), a non-viable *Escherichia coli* filtrate and a strain of viable *E. coli*. An extract of the tropical fern *Polypodium leucotomos* may according to uncontrolled studies be of value. A recent randomised controlled study suggested that the prophylactic application of a vitamin D analogue can be useful (Gruber-Wackernagel et al. 2011).

For exceptionally severe and refractory cases, systemic immunosuppressive drugs, including azathioprine and cyclosporin, have been used.

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The Cutaneous Porphyrias

79

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Key Points

- Porphyrias are caused by defects in the haem biosynthesis pathway.
- Not all porphyrias cause skin disease.
- Porphyrias can only be diagnosed by laboratory porphyrin analyses.
- Porphyrias are generally hereditary diseases, except for porphyria cutanea tarda.
- Porphyria cutanea tarda is often caused by other systemic diseases.
- Photoprotection in the porphyrias must be against visible light.
- Porphyria cutanea tarda and erythropoietic protoporphyria can be associated with liver disease.
- Variegate porphyria can cause dangerous acute porphyric attacks.

Definition and Epidemiology

The porphyrias all result from a partial deficiency of one of the enzymes required for the biosynthesis of haem, thus causing accumulation of the enzyme's substrate. The toxicity profile of the accumulated molecule determines the clinical features of the resulting porphyria.

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The Biosynthesis of Haem

Haem is synthesized from simple biochemicals (glycine and succinyl CoA) via an eight-step pathway, each step being catalysed by an enzyme. Synthesis of the pyrrole ring (porphobilinogen (PBG)) is followed by assembly of the tetrapyrrole structure (hydroxymethylbilane). The carboxylic acid side chains of uroporphyrinogen III are progressively decarboxylated via coproporphyrinogen III to protoporphyrinogen, which is then oxidized to protoporphyrin IX. Finally, ferrous iron is chelated into the protoporphyrin's central cavity to form haem. Around 80 % of haem is synthesized in erythroid cell precursors in the bone marrow (for haemoglobin production) (Elder 1999a).

Classification

Porphyrias present with either skin disease or acute attacks or both.

In any porphyria, a partial enzyme deficiency causes the accumulation of porphyrins. The porphyrias may be classified, according to the predominant site of porphyrin accumulation, into erythropoietic (congenital erythropoietic porphyria and erythropoietic protoporphyria) and hepatic (all the others) types (Elder 1999a) (Fig. 79.1). For the clinician, the key division is between porphyrias that cause acute attacks and those that cause skin disease:

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_79, © Springer-Verlag Berlin Heidelberg 2015

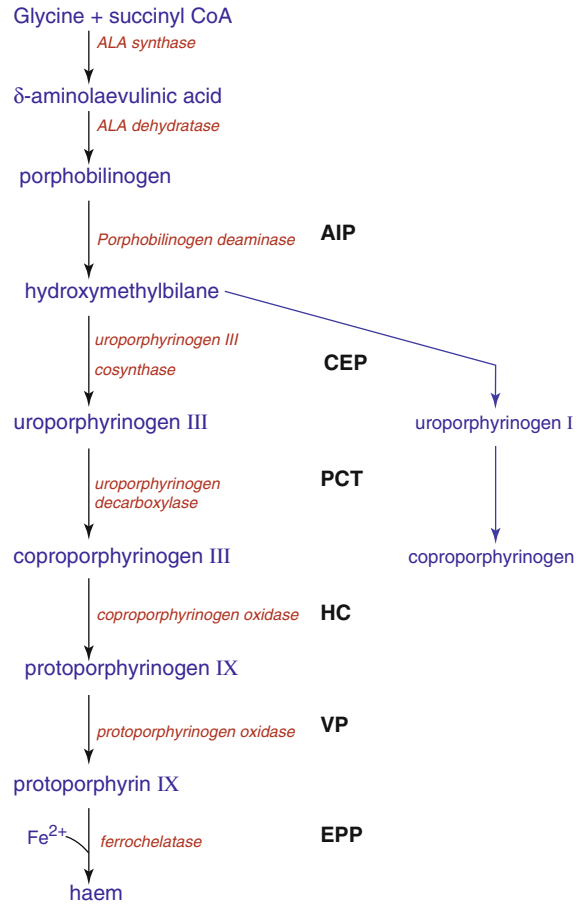

Fig. 79.1 The pathway of haem biosynthesis and the diseases caused by deficiency of each enzyme. *Abbreviations*: *AIP* acute intermittent porphyria, *CEP* congenital erythropoietic porphyria, *PCT* porphyria cutanea tarda, *HC* hereditary coproporphyria, *VP* variegate porphyria, *EPP* erythropoietic protoporphyria

1. Cutaneous disease only:
   - Porphyria cutanea tarda (PCT)
   - Congenital erythropoietic porphyria (CEP)
   - Erythropoietic protoporphyria (EPP)
2. Cutaneous disease and acute attacks:
   - Hereditary coproporphyria (HC)
   - Variegate porphyria (VP)
3. Acute attacks only:
   - Acute intermittent porphyria (AIP)

Basic Concepts of Pathogenesis

Photons of violet light (wavelength peak 408 nm) transform the porphyrin molecule into an excited singlet state. This may revert to the unexcited ground state by emission of characteristic red fluorescence, but intersystem crossing can convert it to an excited triplet state, which interacts with other molecules, particularly molecular oxygen, converting it to excited singlet oxygen in the process. The singlet oxygen stimulates production of hydroxyl radicals which damage tissue directly and indirectly by stimulating complement activation (Lim et al. 1984), mast cell degranulation (Glover et al. 1990) and matrix metalloproteinase activity (Herrmann et al. 1996). The histological site of this phototoxic reaction in the skin determines the clinical characteristics of the porphyria (Brun and Sandberg 1991; Takeshita et al. 2004).

General Principles of Treatment

The management of the skin disease involves preventing violet (Soret wavelength) light penetrating the epidermis. The connection between sun exposure and symptoms is obvious in EPP but is not obvious in the bullous porphyrias where

fragility and blistering are not related to individual episodes of sun exposure. Basic measures include sun avoidance behaviour, sun-protective clothing and hats. Most sunscreens do not protect against violet light. Sunscreens containing reflectant particles, particularly large particle-size titanium dioxide (pigmentary grade), zinc oxide and iron oxide, can effectively protect against violet light (e.g. Dundee sunscreen (Tayside Pharmaceuticals, Dundee, UK)) (Moseley et al. 2001; Kaye et al. 1991). Some window films can absorb violet light, and are useful on car or home windows, particularly in EPP and CEP.

Acute Attacks of Porphyria

AIP, HC and VP can all cause acute attacks, and HC and VP may also cause cutaneous disease. Acute attacks are potentially fatal episodes of an acute systemic neurotoxic reaction, which are frequently triggered by drugs and hormones. This non-dermatological aspect is not covered here. Patients diagnosed by a dermatologist with a porphyria that has the potential to cause acute attacks (e.g. VP) should be referred to a specialist in the management of acute porphyria who will counsel the patient regarding avoidance of acute attack-precipitating factors, treat any acute attacks that occur and genetically test the family for the disease. The diagnosis of an acute porphyria cannot be excluded by porphyrin testing (outside the acute attack situation).

Laboratory Testing in Porphyria

Although clinical features may raise the possibility of a porphyria, the cutaneous presentations of several porphyrias are very similar. Precise diagnosis is essential because of the great differences in clinical management between porphyrias which can be clinically identical. An accurate diagnosis can only be made on the basis of porphyrin analyses carried out in an experienced laboratory. The clinician's role is to suspect the diagnosis of cutaneous porphyria, and to use laboratory testing to confirm whether this is the diagnosis, and if so to precisely identify the porphyria (Table 79.1) (Deacon 1999; Deacon and Elder 2001).

What Samples to Send

In an adult with suspected bullous porphyria, it is generally sufficient to analyse urine and either plasma (where fluorimetry is available) or faeces (where it is not). Urine, plasma and faeces need to be analysed in children, because of the increased complexity of the differential diagnosis. Faecal analysis is necessary when urine and plasma results do not differentiate HC from CEP and, in renal failure, where urine may be unavailable and

Table 79.1 The major biochemical findings in the cutaneous porphyrias

	Urine	Faeces	Red cell	Plasma fluorimetry
Congenital erythropoietic porphyria	Uroporphyrin I; coproporphyrin I	Coproporphyrin I	Zinc- and free protoporphyrin; uroporphyrin I; coproporphyrin I	Peak 615–620 nm
Porphyria cutanea tarda	Uroporphyrin III; heptacarboxyporphyrin	Isocoproporphyrin; heptacarboxyporphyrin (also hex- and pentacarboxy)	Normal	Peak 615–620 nm
Hereditary coproporphyria	Coproporphyrin III	Coproporphyrin III	Normal	Peak 615–620 nm
Variegate porphyria	Coproporphyrin III	Protoporphyrin, coproporphyrin III, X-porphyrin	Normal	Peak 624–627 nm
Erythropoietic protoporphyria	Normal	Protoporphyrin (not diagnostically helpful)	Free protoporphyrin	Peak at 626–634 nm

Adapted from Deacon and Elder (2001)

plasma analysis unhelpful because renal failure increases plasma porphyrins. In suspected EPP, red cells and either plasma or faeces should be analysed.

Handling of Samples

Laboratory testing of body fluids measures porphyrins, since porphyrinogens are spontaneously oxidized to their respective porphyrins outside the body. Porphobilinogen has a tendency to polymerize to other molecules, but porphyrins are reasonably stable when protected from light. All specimens should be kept at room temperature (or 4 °C) in the dark and, ideally, should be analysed within 48 h of collection.

For urine and faecal analysis, fresh random specimens (10–20 mL urine or 5–10 g dry weight faeces) are preferable to 24 h collections. Very dilute urine (creatinine <4 mmol/L) is unsuitable.

Laboratory Analysis of Porphyrins

Old-fashioned qualitative screening methods for detecting porphyrins in specimens (often involving a Wood's light) are insensitive, and negative results are not of value. For all samples, quantitative assessment (spectrophotometric or fluorimetric) is needed and provides results as the total porphyrin concentration. Whole blood or red cell porphyrin testing measures both the total and free protoporphyrin concentrations. Plasma is analysed by fluorimetric scanning, a diagnostically powerful and simple qualitative technique. In urine and faeces, the finding of an increased porphyrin concentration should lead on to high-performance liquid chromatography (HPLC) to rapidly identify the accumulated porphyrins.

Interpretation of Results

In cutaneous porphyrias, the accumulated porphyrin can usually be detected in plasma as an emission peak on spectrofluorimetry. Uro- and coproporphyrin are excreted into the urine and copro- and protoporphyrin into the faeces. Protoporphyrin accumulates in red cells in EPP.

1. *Plasma spectrofluorimetry.* The sample is excited by 410 nm light and fluorescent emissions detected. An emission peak at 615–620 nm indicates the presence of uro- or coproporphyrin and suggests a diagnosis of PCT, HC and CEP, or HEP. A peak at 624–626 nm indicates the presence of a porphyrin–peptide conjugate diagnostic of VP. This 624–626 nm peak is a sensitive indicator of VP. A peak around 633 nm (it can lie between 626 and 634 nm) is caused by protoporphyrin and suggests EPP: EPP is an unlikely diagnosis in the absence of this peak. Plasma porphyrin concentrations, particularly uroporphyrin, increase in renal failure and can be as high as those found in patients with PCT.
2. *Whole blood/red cell.* An increased free protoporphyrin concentration is the diagnostic finding in EPP. The total protoporphyrin concentration includes both free and zinc protoporphyrin. Zinc protoporphyrin is also increased in iron deficiency, lead poisoning and certain anaemias.
3. *Urinary and faecal analysis.* Increased total porphyrin concentration suggests a diagnosis of cutaneous porphyria. The total urine porphyrin concentration is used to monitor disease activity in PCT. HPLC analysis is used to identify the porphyrins once an increased concentration has been found.
   (a) *In urine.* An increase in uroporphyrin (and other highly carboxylated porphyrins especially heptacarboxyporphyrin) is typical of PCT though this does not exclude VP. Coproporphyrinuria, in the presence of normal faecal porphyrin levels, does not indicate porphyria and can be caused by certain drugs, lead toxicity and hepatobiliary disease.
   (b) *In urine and faeces.* Increased coproporphyrin suggests VP but does not exclude HC. Isomer III to isomer I ratios are increased in every porphyria except CEP (where they are decreased). In CEP, excess type I isomers of uro- and coproporphyrin are present in urine and type I coproporphyrin in faeces.
   (c) *In faeces.* In the presence of a plasma spectrofluorimetry peak at 615–620 nm, if urine HPLC does not show the PCT pattern, faecal analysis is required to differentiate HC (increased coproporphyrin

III concentration) from CEP (increased coproporphyrin I concentration). Increased faecal isocoproporphyrin is characteristic of PCT. In renal failure, faecal analysis is vital, since urine may be unavailable and plasma porphyrins are increased in renal failure. Increased faecal protoporphyrin is suggestive but not diagnostic of EPP, since it can also derive from bacterial degradation of haem in the gut.

Porphyrias that Cause Cutaneous Disease But Do Not Cause Acute Attacks

Congenital Erythropoietic Porphyria (Günther's Disease) (ICD-10 E80.0; ICD-9 277.1; OMIM 263700)

CEP is severe and rare and causes lifelong mutilating photosensitivity and haematological disease. It is caused by an autosomal recessive inherited deficiency of the uroporphyrinogen III cosynthase enzyme. This results in massive accumulation of type I isomer porphyrins in erythroid cells which leak into the plasma. It is rare: the incidence in Europe is 0.007/year/10 million population (Elder et al. 2013), and around 200 cases have ever been reported worldwide. Rare adult-onset cases of acquired CEP are reported secondary to myelodysplasia (Sarkany et al. 2011).

Clinical Presentation

CEP has a wide spectrum of presentation, from hydrops fetalis through severe disease starting in infancy and mild forms presenting later in life. The first sign of CEP is often the child's mother noting brown discoloration of amniotic fluid at the onset of labour, or observing pink or brown porphyrin staining of nappies (which fluoresce red under Wood's light).

The Skin in CEP (Katugampola et al. 2012a)

Severe photosensitivity begins in infancy with blisters developing in exposed skin on minimal light exposure. Phototherapy for neonatal jaundice may trigger lesions. Most children are so sensitive to the light that they have problems throughout the year. Exposed (and sometimes non-exposed) skin is fragile. The repeated bouts of inflammation with vesicles and bullae, often complicated by secondary infection, cause mutilating scarring, particularly of the face and hands. This photomutilation may cause erosion of terminal phalanges, onycholysis and destructive changes of the pinnae and nose. Diffuse pseudosclerodermatous thickening may cause microstomia and sclerodactyly-like changes. Hypertrichosis is common, particularly on the upper arms, temples and malar region. Patchy hypo- and hyperpigmentation occur even in minimally exposed areas. A milder late onset form, presenting at any age from the third decade onward, has been described; this presents like PCT and occurs either as a result of mild gene mutations or as an acquired disease secondary to myelodysplasia (Sarkany et al. 2011).

Involvement of eyes and internal organs (Katugampola et al. 2012a):

- Eyes. Keratoconjunctivitis, blepharitis, cataracts, corneal ulcers, scars, cicatricial ectropion and scarring alopecia of eyelashes and eyebrows may all occur. Scleromalacia, pterygium formation, optic atrophy, retinal haemorrhage and scleral necrosis are less common.
- Bones and teeth. Teeth are stained brown and fluoresce under Wood's light. Decreased bone density, osteopenia and osteolytic lesions secondary to erosion by hyperplastic bone marrow can cause pathological fractures. In the hands, there is resorption of terminal phalanges with acroosteolysis and cortical bone rarefaction. Strict avoidance of the sun reduces levels of vitamin D.
- Haematology. Porphyrins in red cells cause haemolytic anaemia. The haemolysis may cause a severe transfusion-dependent anaemia.

Prognosis (Katugampola et al. 2012b)

Most patients used to die by the age of 40, but improvements in supportive care (particularly use of antibiotics) have improved the prognosis. Haematological complications may be fatal. Long-term hypertransfusion may cause iron overload as patients reach adulthood, even when iron chelation

has been used. Bone marrow transplantation now holds out the promise of cure for these patients (see below). The key markers of poor prognosis in CEP are onset of disease in the first year of life and significant haematological involvement.

Diagnosis

- *Biochemical findings*. Massive accumulation in all tissues of type I isomers of porphyrins, mainly uroporphyrin. Red cells and urine contain large amounts of uro- and coproporphyrin (mainly type I) and faeces contain increased concentrations of coproporphyrin (mainly type I). A plasma spectrofluorimetry peak is seen at 615–620 nm. The absence of isocoproporphyrin and the normal level of 5-carboxylic porphyrin excretion in faeces distinguish CEP from hepatoerythropoietic porphyria.

General Principles of Treatment

The photosensitivity is so severe that photoprotection is crucial. Sun avoidance and use of sun protective clothing and hats are essential. Visible light sunscreens (Moseley et al. 2001), and amber window films on windows can reduce exposure to Soret wavelength light, though more opaque films may be necessary (which are obviously not allowed on car windows). Prompt treatment of secondary infection is important. Hypertransfusion with regular blood transfusions to maintain a polycythaemia inhibits endogenous haemoglobin production and decreases porphyrin formation, and may reduce haemolysis and cutaneous symptoms in moderately affected patients. Splenomegaly may increase transfusion requirements and the value of hypertransfusion can decrease at puberty. Hypertransfusion is frequently complicated by iron overload, even when desferrioxamine has been used. Intravenous haematin has been tried in late-onset disease (Rank et al. 1990). Haemolysis worsens the porphyria by causing anaemia. Splenectomy may be necessary where there is hypersplenism. Lights during surgical procedures cause phototoxic reactions, and filters should be used over theatre lights (e.g. Madico TA81XSR). The allogeneic bone marrow transplantation (bone marrow or umbilical cord blood stem cells) is the treatment of choice in severe CEP. It provides long-term cure (Shaw et al. 2001) though the hazards mean that it should be reserved for the worst affected patients and for children with markers of poor prognosis (Katugampola et al. 2012a, b).

Genetic Counselling

Since CEP is autosomal recessive, the chance of each future sibling of an affected child suffering from the disease is 25 %. The diagnosis may be made before birth by measuring the uroporphyrin I concentration in amniotic fluid, which is increased as early as 16 weeks in utero. If the mutations in the index case have been identified, or the foetus is homozygous for the common C73R mutation, prenatal diagnosis from chorionic villous biopsy is possible.

Porphyria Cutanea Tarda (Sarkany 2001) (ICD-10 E80.1 ICD-9 277.1 OMIM 176100)

Porphyria cutanea tarda (PCT) is the commonest porphyria. It is characterized by fragility and blistering of exposed skin. It is usually acquired and is often associated with liver disease. It does not cause acute attacks. In PCT, deficiency of uroporphyrinogen decarboxylase (UROD) causes accumulation of uroporphyrin and other highly carboxylated porphyrins. Seventy-five percent of patients have *type I* (*sporadic*) (enzyme deficiency is acquired and restricted to hepatocytes), due to inhibition of normal UROD enzyme (Elder et al. 1985). Twenty-five percent have *type II* (*familial*) disease where the enzyme deficiency is hereditary, present in all tissues and associated with a UROD gene mutation. The penetrance of the form is lowland; some acquired enzyme inhibition in the liver occurs even in familial PCT. UROD mutation is a risk factor for the development of PCT, rather than representing a separate form of the disease. *Type III* disease is rare and characterized by hereditary enzyme deficiency localized to the liver. *Toxic porphyria*, in which halogenated aromatic hydrocarbons inhibit the enzyme, is rare and mainly affects workers making herbicides. A major epidemic of toxic porphyria in the 1950s in Turkey was caused by hexachlorobenzene added as a fungicide to seed wheat (Dean 1971).

In PCT, UROD enzyme is inactivated by uroporphomethene, a competitive inhibitor (Phillips et al. 2007) generated in the liver by reactive oxygen species in the presence of iron (Elder 1999b). The uroporphyrin diffuses from the plasma into tissues, causing a phototoxic reaction in the upper dermis in exposed skin. This leads to lysis of cells in the superficial dermis with the formation of membrane-limited vacuoles which merge to produce a blister cavity under the basal lamina (Caputo et al. 1983).

The prevalence in most countries is around 1 in 10,000 (Elder 1998).

Clinical Presentation

Sporadic PCT usually presents in middle age although the familial form can occur earlier. Patients describe increased fragility in exposed skin, particularly the backs of the hands, forearms and face, with minor trauma shearing the skin away to cause erosions (Fig. 79.2). Most patients have bullae, which can be over 1 cm in diameter and may be painful. They crust and resolve over a few weeks, leaving atrophic scars, milia and often mottled hyper- or hypopigmentation. Patients rarely associate development of new lesions with sun exposure, but symptoms are generally worse in the summer. Other common features are scarring alopecia following resolution of bullae on the scalp; hypertrichosis, usually on upper face and forehead, sometimes on the ears or arms and occasionally on the whole body; and hyperpigmentation in a melasma-like pattern on the cheeks and around the eyes, or in a diffuse pattern on light-exposed skin, or occasionally in a reticulate distribution (Grossman et al. 1979; Mascaro et al. 1986). Photo-induced onycholysis and accelerated solar elastosis (Mascaro et al. 1986) may occur. Morphoea-like plaques may develop on the head or upper trunk. These plaques may calcify and may require excision and grafting if they ulcerate (Inglese and Bergamo 2005). On the scalp, morphoea-like changes may cause a slowly expanding scarring alopecia (Grossman et al. 1979; Mascaro et al. 1986). Sclerodactyly or facial appearances mimicking systemic sclerosis are reported. Rare presentations of PCT include cicatricial conjunctivitis

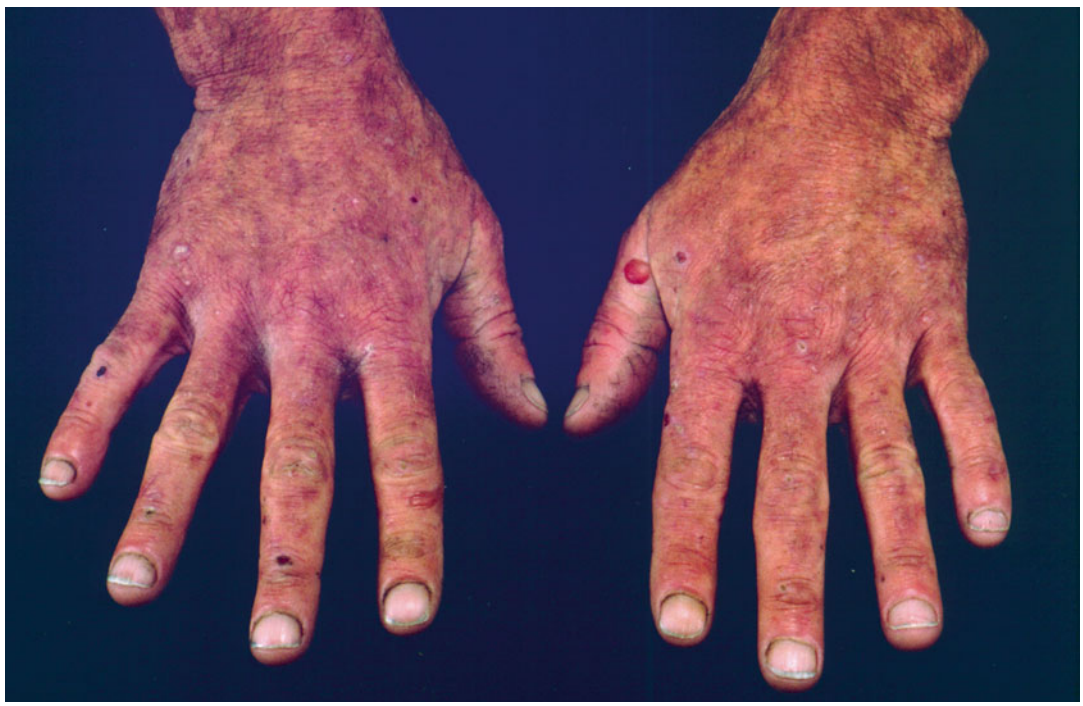

Fig. 79.2 Porphyria cutanea tarda: erosions, blisters, pigmentary changes and scarring (Reproduced with permission from: Sarkany (2008)

(Park et al. 2002) and hair darkening (Shaffrali et al. 2002).

Differential Diagnosis

PCT can be clinically indistinguishable from VP, drug-induced pseudoporphyria, renal pseudoporphyria, HC, late-onset Günther's disease or mild hepatoerythropoietic porphyria. Biochemical analysis is necessary to diagnose PCT, and it is particularly important to exclude VP and HC among the differential diagnoses, since they can cause acute attacks.

Diagnosis

- *Biochemical findings* (Elder 1998). In PCT, the urinary porphyrin concentration is increased, consisting mainly of uroporphyrin, some heptacarboxylic acid porphyrin and, sometimes, also hexa- and pentacarboxylic acid porphyrins. A plasma spectrofluorimetry peak is seen at 615–620 nm. Isocoproporphyrin accumulates in faeces. Urine analysis alone is insufficient to diagnose PCT, since a few patients with VP have the PCT urine pattern ('dual porphyria') (Sturrock et al. 1989). In patients with renal failure, faecal analysis is essential, since plasma porphyrins are increased by haemodialysis, and urine collection may not be possible. The biochemical marker of disease activity is quantitative urinary porphyrin excretion measured in a random urine sample.
- *Histopathology* (Wolff et al. 1982). The bullae in PCT are subepidermal with a sparse inflammatory infiltrate and 'festooning' of dermal papillae into the bullae. There is deposition of PAS-positive diastase-resistant fibrillar glycoprotein material in and around upper dermal blood vessel walls and reduplication of the basement membrane. Immunofluorescence reveals IgG, a little IgM, fibrinogen and complement at the epidermal–dermal junction. Morphoea-like lesions in PCT are histologically indistinguishable from other forms of morphoea.
- *The investigation of the patient with PCT.* PCT is a liver disorder with secondary effects in the skin. It is crucial to investigate patients thoroughly both regarding other systemic diseases predisposing to the development of PCT and to assess the severity of any liver disease.

Risk factors for the development of PCT (Bulaj et al. 2000a)

- The major risk factors are genetic haemochromatosis, hepatitis C infection, alcohol and oestrogens. Since some inhibitions of the hepatic enzyme are also required for clinical expression of familial PCT, the same risk factors apply to sporadic and familial PCT. It is essential to investigate for risk factors in all patients diagnosed with PCT.
  - Haemochromatosis. In the USA and Northern Europe, 20 % of PCT patients have hereditary haemochromatosis (Bulaj et al. 2000a; Roberts et al. 1997), usually homozygous for the Cys282Tyr mutation. Homozygosity for this mutation increases the risk of developing PCT 60-fold (Bulaj et al. 2000a). In Southern Europe, haemochromatosis is a less important risk factor.
  - Hepatitis C infection. In Southern Europe, 70–90 % of all PCT patients are infected with the hepatitis C virus (Quecedo et al. 1996; Fargion et al. 1992), compared with around 60 % of patients in the USA (Bulaj et al. 2000a) and 7–36 % in Northern Europe (Linde et al. 2005; Murphy et al. 1993).
  - Alcohol. Between 30 and 90 % of PCT patients consume over 40 g of alcohol daily, and 2 % of all alcoholics with cirrhosis develop PCT (Elder 1999b).
  - Oestrogens. Ingested oestrogens, in the oral contraceptive pill or in hormone replacement therapy, are the sole risk factor in over a quarter of female patients (Bulaj et al. 2000a). Stopping the hormone may be sufficient to induce remission if the duration of therapy has been short (Haberman et al. 1975). If it is not possible to stop the hormone therapy, transdermal drug delivery is a safer alternative than the oral route (Bulaj et al. 2000b).

  Other less common but significant risk factors for developing PCT are haemodialysis and HIV infection (Blauvelt et al. 1992).

Non-insulin-dependent diabetes mellitus, systemic lupus erythematosus, dermatomyositis, hepatitis A and B infection, haematological malignancy, sideroblastic anaemia, thalassaemia and the drug tamoxifen are reported as much rarer associations with PCT.

Most patients possess more than one risk factor for developing PCT, with hepatitis C infection and alcohol being strongly linked in men.

Liver Disease in PCT (Bruguera 1986)

Liver disease is a major concern. In almost all patients, liver biopsy shows increased stainable iron, fatty change and intracellular porphyrin crystals. Fifty percent of patients have more severe changes (lobular necrosis or inflamed fibrotic portal tracts), and cirrhosis occurs in 15 %. As expected, the most severe liver disease is in patients with alcoholism, hepatitis C infection or iron overload (Bulaj et al. 2000a). PCT increases the risk of hepatocellular carcinoma: in Southern Europe, 3 % of PCT patients develop hepatocellular carcinoma during the decade after presentation (Gisbert et al. 2004). Risk factors for developing hepatocellular carcinoma are a symptomatic period longer than 10 years prior to treatment, severe changes on hepatic histology at presentation, hepatitis C infection, male sex and age over 50 years at presentation. Hepatic function must be assessed at presentation in all PCT patients, and patients at high risk of hepatic malignancy require regular ultrasounds and serum α-fetoprotein measurement to detect carcinoma at a treatable stage (Siersema et al. 1992). PCT should be managed as a liver disorder, and the threshold for referral to a hepatologist should be low.

General Principles of Treatment

- *Photoprotection*. Visible light sunscreens (Moseley et al. 2001), filter films for car and home windows, gloves, hats and clothes help control symptoms during the period of several months before specific therapies take effect.
- *Elimination of risk factors.* Stopping oestrogen therapy (Haberman et al. 1975), if it has not been used for more than 2 years, can induce remission. However, elimination of the underlying cause by abstaining from alcohol, or by treating hepatitis C with interferon-α (Sheikh et al. 1998), does not always induce remission. All patients should be advised to abstain from alcohol or oestrogen therapy to prevent exacerbation of the disease.
- *Specific treatments.* Treatment with venesection or low-dose antimalarials is required in most cases. Venesection eliminates hepatic iron overload, thus restoring normal enzyme activity. Around 500 mL of blood is removed every fortnight or so, aiming to induce mild iron deficiency (plasma ferritin below 25 μg/L (Rocchi et al. 1986a; Ratnaike et al. 1988). Blistering usually resolves within 2–3 months, skin fragility within 6–9 months and urine porphyrin concentrations generally normalize within 13 months or so (Mascaro et al. 1986), at which point treatment should be stopped. Hypertrichosis (Mascaro et al. 1986) and sclerodermoid lesions respond more slowly during the years after treatment has stopped. Excision and grafting may be needed for ulcerated sclerodermoid lesions (Mascaro et al. 1986). Desferrioxamine leads to earlier remission than venesection because it rapidly chelates hepatic iron and may be of value in PCT with renal failure but is expensive and inconvenient (Pitche et al. 2003; Rocchi et al. 1986b). Erythropoietin mobilizes hepatic iron into haemoglobin and is the treatment of choice for PCT in renal failure (Sarkell and Patterson 1993). Low-dose antimalarials are very effective. They complex with uroporphyrin and promote its excretion into the bile (Scholnick et al. 1973). Daily doses of chloroquine can cause a dangerous acute hepatitis, but chloroquine at the low dose of 125 mg (Malina and Chlumsky 1981; Ashton et al. 1984) or 250 mg (Valls et al. 1994; Kordac et al. 1989) twice weekly is safe and effective. It leads to clinical remission within 6 months or so and biochemical remission after 6–15 months, at which point treatment is stopped (Malina and Chlumsky 1981; Ashton et al. 1984; Valls et al. 1994; Kordac et al. 1989). Retinopathy does not occur with such low doses of chloroquine (Valls et al. 1994). Low-dose hydroxychloroquine (100 mg twice

weekly) is also effective (Singal et al. 2012). Low-dose chloroquine is the usual treatment of choice. Venesection should be used for patients who do not respond to chloroquine and patients with haemochromatosis. Remission with low-dose chloroquine generally lasts 17–24 months (Malina and Chlumsky 1981; Ashton et al. 1984). With venesection, relapse generally occurs around 2.5 years after the end of treatment (Grossman et al. 1979). Long-term follow-up is necessary for all patients to monitor for relapse (by measuring urinary porphyrin excretion) and for the management of coexisting liver disease.

Genetic Counselling (Elder 1999a)
In view of the identical management of sporadic and familial PCT, the lack of evidence that identifying latent PCT in relatives alters outcomes and the very low penetrance of familial PCT, family screening is not generally done in familial PCT.

Erythropoietic Protoporphyria (ICD-10 E80.0; ICD-9 277.1; OMIM 177000)

EPP is a hereditary porphyria characterized by painful, lifelong photosensitivity and occasionally liver disease. The incidence of EPP in Europe varies between countries (from 0.03 new cases/million/year in Spain to 0.36 in the UK) (Elder et al. 2013). EPP usually results from deficient activity of ferrochelatase, the final enzyme of haem biosynthesis. In a minority of cases, it is caused by gain-of-function mutations in ALAS-2 (the first enzyme in the pathway) (Whatley et al. 2008). The protoporphyrin accumulates in erythroid cells. Photoactivation of protoporphyrin from red cells and plasma causes an acute injury to the endothelium mediated by singlet oxygen and the hydroxyl radical (Brun and Sandberg 1991; Takeshita et al. 2004). Many ferrochelatase gene mutations have been identified in EPP patients, and none are particularly common (Minder et al. 2002). A few adult-onset cases have been reported which are associated with haematological malignancy and may be associated with chromosomal deletions involving the ferrochelatase gene (Sarkany et al. 2006).

Clinical Presentation (Holme et al. 2006; Deleo et al. 1976)
EPP causes immediate pain on exposure to bright sunlight. It presents most commonly in the first year, quite often in babies who may present with crying in their prams in sunny weather. Onset later in childhood does occur, but onset in adulthood is rare. In spring and summer, after anything from a few minutes to an hour or two of sun exposure, patients describe discomfort, tingling or itching in exposed skin, particularly the dorsum of the hands and the face. The severe burning pain can last anything between an hour and several days. Children often find partial relief with cold water and wet cloths, and this feature may be diagnostically useful. Usually, the only physical sign during an attack is oedema, which may be subtle. Many patients experience 'priming' in which sunlight tolerance is reduced on the day after significant sun exposure (Poh-Fitzpatrick 1989). In severe attacks, purpura and crusted erosions or vesicles occasionally occur. Rare cases of EPP with prominent purpura and histological changes resembling a leukocytoclastic vasculitis, acute photo-onycholysis (Marsden and Dawber 1977) or erythematous plaques (Murphy et al. 1985) are described. Physical signs include slight thickening of skin over the metacarpophalangeal and interphalangeal joints; superficial vermicular waxy scarring on the nose; shallow linear, punctate or small circular scars on cheeks and forehead and radial scars around the lips. The skin over the nose, cheeks and forehead can become roughened. Fifteen percent of patients have no physical signs (Holme et al. 2006). Mild variants of EPP may cause diagnostic confusion because of delayed onset of symptoms, shortened duration of attacks and, occasionally, absence of pain. Oedema and predilection of the reaction to the face and dorsal hands and feet are diagnostic clues. There is an occasional association between EPP and a seasonal palmar keratoderma, more commonly seen in autosomal recessive EPP (Holme et al. 2009). Children with

EPP suffer from social isolation due to difficulty joining friends to play outside, and sensitivity to psychosocial issues is important for clinicians. The disease has a profound impact on quality of life (Holme et al. 2006). Symptoms often improve during pregnancy (Holme et al. 2006; Poh-Fitzpatrick 1997). Patients may develop a mild hypochromic microcytic or normocytic anaemia, which can be associated with decreased serum iron levels and increased serum iron-binding capacity (Deleo et al. 1976). With the exception of patients with EPP liver failure, operating theatre lights do not cause any problems during or after surgery in EPP patients (Wahlin et al. 2008). However, operating theatre lights can cause a potentially fatal phototoxic reaction in patients undergoing liver transplantation for protoporphyric liver failure. Vitamin D deficiency associated with osteoporosis is common in EPP, and vitamin D levels need to be monitored and supplemented as required (Holme et al. 2008; Allo et al. 2013).

Diagnosis

Biochemical Investigation (Deacon 1999)

The diagnostic finding is the increased red cell free protoporphyrin concentration. A peak at 633 nm is seen on plasma fluorimetric scanning. Umbilical cord protoporphyrin concentration is not a useful test to identify EPP in newborns (Hanneken et al. 2010).

Histopathology (Ryan and Madill 1968; Epstein et al. 1973)

In the acute phase, there is visible endothelial damage in superficial dermal vessels (Gschnait et al. 1975). In the chronic phase, in exposed areas of skin, PAS-positive diastase-resistant hyaline material is seen in the walls of blood vessels of the upper dermal and papillary vascular plexuses. Immunofluorescence shows immunoglobulins (mainly IgG) in a similar distribution. On electron microscopy, the hyaline material is seen as a greatly replicated, layered and fragmented basement membrane, with fine fibrillar material permeating the capillary connective tissue sheath and extending beyond the vessel walls (Ryan and Madill 1968; Wick et al. 1979).

General Principles of Treatment

(Holme et al. 2006)

No therapy has ever been proven to be effective in EPP mainly because of the lack of an objective test for disease activity in EPP, and high placebo rates make clinical trials difficult. Attention to sunlight protection is the key to management.

- *Photoprotection.* Basic measures include sun avoidance behaviour, sun-protective clothing and hats. It is important to use visible light sunscreens (Moseley et al. 2001). Dihydroxyacetone paint has been used in some patients with EPP (Johnson 1992), and window films, which absorb violet light, can be useful for car or home windows, particularly in severely affected patients.
- *The acute reaction.* For the acute reaction, complete sun avoidance (even through windows) leads to earlier resolution, and fans and cold water provide some pain relief. Antihistamines and most analgesics are of little value. For severe attacks, hospital admission may be necessary for light avoidance and analgesia (usually opiate).
- *Specific therapies.* Oral β-carotene is the most widely used treatment, usually at a dose around 180 mg daily in adults (90 mg daily in children) taken throughout the spring and summer. Proof of efficacy from controlled trials is lacking. Controlled trials of *N*-acetyl cysteine and cholestyramine have shown them not to be of benefit (Norris et al. 1995; Tewari et al. 2012). Short courses of PUVA (Roelandts 1995) and narrow-band UVB (Collins and Ferguson 1995) in the early spring may help, particularly in milder cases. Narrow-band UVB does not overlap with the EPP action spectrum and cannot trigger attacks of pain. Many other systemic treatments with antioxidant or free radical scavenging properties have been used in EPP in an uncontrolled way on small numbers of patients, with conflicting and generally unconvincing results. Afamelanotide, the alpha-MSH analogue, has shown promising results in initial trials (Harms et al. 2009).

Genetic Counselling

Although cases of autosomal recessive inheritance do occur (Sarkany and Cox 1995; Whatley et al. 2004), EPP is generally an autosomal dominant disorder with incomplete penetrance, the disease resulting from co-inheritance of a gene mutation on one ferrochelatase allele with a low expression variant on the other allele. This low expression variant (IVS3-48C) is present in around 10 % of the Caucasian population and is associated with reduced ferrochelatase mRNA levels (Gouya et al. 2002). Overall, the probability of each offspring of an EPP patient suffering from the disease is under 10 %, but testing for the IVS3-48C polymorphism in a patient's partner can indicate more precisely whether there is a significant probability of offspring being affected. The disease is rarely life threatening, so antenatal diagnosis is not required.

Liver Disease in EPP (Sarkany and Cox 1995; Wahlin et al. 2011)

Protoporphyrin is excreted exclusively into the bile. It forms gallstones in around 12 % of patients. It is hepatotoxic, particularly to bile canaliculi, and severe liver damage occurs in 1 % of patients. EPP liver failure requiring transplantation may occur at any age. Patients develop jaundice, worsening photosensitivity and often upper abdominal pain over weeks to months and have severe cholestasis, with a dramatically high red cell protoporphyrin concentration. Liver histology shows deposition of protoporphyrin in vacuoles within bile canaliculi and hepatocytes, which may be accompanied by cirrhosis. Although such acute episodes may resolve spontaneously, the porphyrin-induced cholestasis may become increasingly severe and itself further increase the protoporphyrin concentration in a vicious cycle, in which case the patient will die unless a liver transplant can be performed. Unless filter films are used over operating theatre lights, the very high protoporphyrin concentration may cause a severe phototoxic reaction with postoperative burns. A severe neuropathy may occur after liver transplant (Wahlin et al. 2011). Protoporphyric liver disease recurs in the graft in 69 % of patients over several years, severe enough to require retransplantation in a minority. Patients with severe liver disease have been treated by bone marrow transplantation. Although the marrow transplantation does cure the EPP, the dangers of the procedure mean that it is reserved for these rare, life-threatening situations (Wahlin et al. 2007; Rand et al. 2006). It is vital to recognize impending protoporphyric liver failure early enough that arrangements can be made for a liver transplant if it should become necessary. Thus, all EPP patients should have liver function tests and red cell protoporphyrin concentration checked at least once a year. The appearance of coproporphyrin in the urine has been proposed as an indicator of significant liver disease in EPP (Doss and Frank 1989). Worsening photosensitivity may be the only clinical indication of the development of severe liver disease. Although protoporphyric liver failure is rare, mild abnormalities of liver function tests are common in EPP (Doss and Frank 1989). Since the significance of these abnormalities is unclear, it is advisable to monitor these patients closely and to refer the patient to a hepatologist if the abnormality is persistent or deteriorating. In such patients, an ion exchange resin such as cholestyramine may protect the liver against further porphyrin toxicity. There is no means of identifying those EPP patients at risk of liver failure. Since several cases have been described in siblings, patients with a relative who has suffered protoporphyric liver failure should be treated as being at risk of developing it themselves. Recessive inheritance of EPP may increase the risk of severe hepatic disease (Sarkany and Cox 1995).

Porphyrias That Cause Cutaneous Disease and Acute Attacks

Hereditary Coproporphyria (ICD-10 E80.2; ICD-9 277.1; OMIM 121300)

Like VP, this porphyria presents from puberty onwards. The skin is not affected in most patients suffering from this rare acute porphyria, but around 10–20 % (Kuhnel et al. 2000) of patients have cutaneous involvement with fragility and

blistering in sun-exposed areas, indistinguishable from that seen in PCT or VP. The skin disease may be triggered or exacerbated by intercurrent liver disease (Hawk et al. 1978). Rare variants include a homozygous form characterized by short stature, acute attacks and skin changes with prominent hypertrichosis and pigmentation (Grandchamp et al. 1977) and, harderoporphyria which causes haemolysis in the neonate or bullae. HC is caused by an autosomal dominant inherited deficiency of coproporphyrinogen oxidase. Patients need to be referred to an expert centre for the management of the acute attacks side.

The biochemical findings are of a 615–620 nm peak on plasma spectrofluorimetry, increased uro- and coproporphyrin concentrations in urine and increased coproporphyrin in faeces. Predominance of the type III isomer in faeces is a sensitive indicator of HC (Kuhnel et al. 2000).

Variegate Porphyria (ICD-10 E80.2 ICD-9 277.1 OMIM 176200)

This rare inherited disease causes a bullous porphyria and can cause acute attacks: VP is caused by an autosomal dominant inherited deficiency of protoporphyrinogen oxidase. In addition to causing photosensitization, accumulated coproporphyrinogen and protoporphyrinogen also inhibit PBG deaminase, the probable mechanism for acute attacks in VP. In South Africa, VP is common (due to a founder effect (Van Tuyll van Serooskerken et al. 2012)) with a prevalence in whites and Afrikaner-descended non-whites of 1/200. The incidence of VP in Europe varies between countries in the range 0.01–0.26 new cases/million/year (Elder et al. 2013). At least 80 % of South African carriers of a pathogenic VP mutation are completely asymptomatic (Day 1986).

Clinical Presentation (Day 1986; Mustajoki 1980; Timonen et al. 1990)

- *Skin.* Of those patients with symptomatic VP, around 70 % have cutaneous involvement, and only around 17 % will ever suffer an acute attack (Elder et al. 1997). Usually, the skin disease begins in adolescence or young adulthood. Patients describe skin fragility, usually fairly mild, affecting sun-exposed skin particularly on the backs of the hands. The skin disease is generally indistinguishable from PCT, with painful tense bullae occurring in sun-exposed skin, as well as scarring, pigmentary abnormalities, sometimes pseudosclerodermatous changes of the hands and fingers and occasionally photo-onycholysis. Many patients do not describe worsening in the summer, and the worst problems are often in late summer and autumn. In addition, around half of patients with VP describe mild, transient, light-related eruptions in the early summer. The examination findings of scarring, patches of hypo- and hyperpigmentation at sites of blisters, milia and mild hypertrichosis particularly around the eyes are indistinguishable from PCT. Intercurrent biliary obstruction exacerbates the cutaneous disease since the accumulated porphyrins are excreted into the bile. Acute photosensitivity can occur in patients with disturbed liver function. Hormonally induced hepatic dysfunction may explain the exacerbations of skin disease seen in females taking oral contraceptives and during pregnancy. VP sometimes goes into clinical and biochemical remission in old age. Patients with VP have recently been shown to be at increased lifetime risk of hepatocellular carcinoma (Schneider-Yin et al. 2010).
- *Acute attacks* (Day 1986; Mustajoki 1980; Elder et al. 1997; Von und zu Fraunberg et al. 2002). As in other acute porphyrias, women are three times as frequently affected as men, and 70 % of acute attacks occur between the ages of 20 and 40 years. Around 17 % of patients with cutaneous VP ever suffer an acute attack; the number has declined recently due to improved use of prophylactic measures. The severity of acute attacks varies from mild abdominal pain, sometimes accompanied by vomiting and constipation, through very severe attacks with bulbar palsy and respiratory paralysis. Patients need to be referred to an expert centre for the management of the acute attacks side of the disease.

In *homozygous VP* (Hift et al. 1993), a mutation on both protoporphyrinogen oxidase alleles results in an enzyme activity less than 20 % of normal, compared to the 50 % in other VP patients. In homozygous VP, fragility, bullae and often hypertrichosis develop in exposed (and sometimes nonexposed) skin in neonates or infants, and the skin disease may be severe. Delayed development, epilepsy, sensory neuropathy, nystagmus, various hand deformities and growth retardation also commonly occur. Acute attacks do not occur in these patients. The biochemical findings are the same as in VP, except for the lower enzyme activity.

Differential Diagnosis

VP cutaneous disease is easily distinguished from non-photosensitive blistering disorders. It can be clinically very similar to PCT, late-onset CEP, HC and pseudoporphyria. Biochemical analysis is required to diagnose VP.

Diagnosis

Biochemical Findings

A plasma spectrofluorimetry peak around 626 nm (caused by a porphyrin–protein complex) is diagnostic of VP in the absence of a raised free red cell protoporphyrin level and is present in virtually all symptomatic cases of VP. It may persist during periods of clinical remission when faecal excretion becomes normal and is a more sensitive test than measurement of faecal porphyrins (Hift et al. 2004). A persistently normal faecal protoporphyrin concentration in adulthood in patients with the VP genetic defect has been proposed as a prognostic marker indicating a greater likelihood of the VP never causing any clinical problems and staying clinically latent (Von und zu Fraunberg et al. 2002). The urine contains increased levels of coproporphyrin, and increased concentrations of copro- and protoporphyrin are found in faeces. In a few patients, the urine shows the typical PCT pattern of uroporphyrin accompanied by hepta- and sometimes hexa- and pentacarboxylic acid porphyrins, a situation known as 'dual porphyria' (Sturrock et al. 1989), hence the importance of sending off plasma as well as urine in bullous porphyria, to avoid the misdiagnosis of VP as PCT, with disastrous consequences. During acute attacks, urinary PBG (and ALA) are raised. The urinary PBG usually falls to normal within weeks of the attack resolving but may stay a little increased outside the context of an acute attack (Deacon 1999).

General Principles of Treatment

The key to successful management of the skin disease is photoprotection with sun avoidance using clothes, hats, gloves and visible light sunscreens. The skin disease is rarely severe enough to require filter films for windows. Since the relationship between sun exposure and skin lesions is not obvious, the role of light in producing the skin lesions should be explained to the patient. β-carotene and canthaxanthin have also been claimed to provide limited protection in some patients, and UVB phototherapy may be of value. If liver function tests indicate biliary obstruction, relief of this may reduce cutaneous symptoms. The risk of acute attacks is the key issue for safe management of patients and their families. Patients should be directed to a list of drugs to avoid (The European Porphyria Network), be advised to wear an emergency identification bracelet, to avoid low calorie diets and to become teetotal. The key thing is that expert assistance should be sought to manage the acute porphyria side. Liver transplantation has been used to cure variegate porphyria (and acute intermittent porphyria) in cases where acute attacks are uncontrollable by medical means (Stojeba et al. 2004).

Genetic Counselling

It is important to identify relatives who have latent VP because of the risk of acute attacks. The plasma 624–626 nm peak is found in the majority of cases of latent VP but only from teenage onwards. A positive plasma fluorimetry result is diagnostic of latent VP, but a negative result is uninformative (Long et al. 1993; Da Silva et al. 1995). The only reliable way to identify those carrying the VP gene defect if the plasma scan is

negative is to identify the protoporphyrinogen oxidase gene mutation in the index case and then assess its presence or absence in relatives. This is labour intensive because, outside South Africa, most families have their own private mutation. Relatives found to have the gene defect are at low risk (roughly 5–10 %) of acute attacks and should take all the precautions taken by any patient diagnosed with an acute porphyria. The risk of a patient passing the mutated gene on to each offspring is 50 %, and around 20 % of those carrying the mutation will eventually develop symptoms of some sort.

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Pruritus

80

Jacek C. Szepietowski and Adam Reich

Key Points

- Pruritus is defined as an unpleasant sensation which provokes a desire to scratch.
- Itch exerts a negative impact on the patient's well-being, markedly decreasing quality of life and substantially affecting sleep quality.
- Valid assessment of pruritus still remains a challenge and no method of pruritus assessment can be considered as a standard, which would be widely accepted. However, unidimensional scales (e.g., verbal rating scale or visual analogue scale) as well as pruritus questionnaires are the most widely used and valuable methods of pruritus measurement in daily clinical setting to date.
- Successful antipruritic therapy may be introduced, if underlying disease for itch is identified.
- Pruritic patients with normal skin or with secondary scratch lesions require basic sets of laboratory examinations to determine the underlying disease.

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Definition and Epidemiology

Pruritus is defined as an unpleasant sensation that produces a desire to scratch. By most researchers and physicians, pruritus and itch are considered as synonymous terms. Itching lasting less than 6 weeks is termed as an acute pruritus, while presenting longer than 6 weeks is defined as a chronic one. Pruritus may be limited to a certain area (localized pruritus) or involve the entire body (generalized pruritus). According to the consensus of the International Forum for the Study of Itch (IFSI), three clinical presentations may be distinguished: (1) pruritus on diseased, inflamed skin; (2) pruritus on normal, non-inflamed skin; and, finally, (3) pruritus with chronic secondary scratch lesions (Ständer et al. 2007).

Pruritus is a very common sensation. It is one of the most frequent and important symptoms in dermatology which may occur with or without visible skin lesions. Based on large epidemiological studies, it is estimated that chronic pruritus may be present even in 8–20 % of the general population. In a self-reported morbidity study, itching was the most frequently mentioned skin symptom. It is a major diagnostic symptom of atopic eczema and urticaria but often may also be observed in patient with psoriasis, eczema, primary cutaneous T-cell lymphomas, dermatitis herpetiformis, and many other skin conditions (Table 80.1). Pruritus may also complicate a number of systemic diseases, like chronic renal disease, cholestatic liver disorders, hematological

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_80, © Springer-Verlag Berlin Heidelberg 2015

Table 80.1 Most relevant skin diseases accompanied by pruritus

Xerosis (skin dryness)
Atopic dermatitis (atopic eczema)
Eczema (all forms)
Seborrheic dermatitis
Urticaria (all forms)
Psoriasis
Palmoplantar pustulosis
Lichen planus
Gianotti-Crosti syndrome
Pityriasis rubra pilaris
Autoimmune blistering diseases: bullous pemphigoid, acquired epidermolysis bullosa, linear IgA bullous dermatosis
Dermatitis herpetiformis (Dühring disease)
Pregnancy dermatoses: atopic eruption of pregnancy, pemphigoid gestationis, polymorphic eruption of pregnancy
Darier's disease
Hailey-Hailey's disease
Ofuji's disease
Fox-Fordyce disease
Grover's disease (transient acantholytic dermatosis)
Dermatomyositis
Systemic sclerosis
Polymorphic light eruptions
Drug-induced skin eruptions
Viral diseases: herpes simplex, herpes zoster, varicella, measles
Tineas
Candidal intertrigo
Malassezia folliculitis
Skin infestations: scabies, lice (pediculosis), cutaneous larva migrans
Insect bites and arthropod reactions
Miliaria
Keloids
Mastocytosis
Mycosis fungoides and its variants
Sezary syndrome

Table 80.2 Non-dermatologic causes of chronic pruritus

Kidney diseases	Chronic kidney insufficiency
Liver diseases	Primary sclerosing cholangitis
	Hepatitis B
	Hepatitis C
	Primary biliary cirrhosis
	Extrahepatic cholestasis
Hematological malignancies	Hodgkin's disease
	Non-Hodgkin's lymphomas
	Leukemias
	Myeloma multiplex
Other hematological diseases	Polycythemia vera
	Myelodysplastic syndromes
	Hypereosinophilic syndrome
	Iron deficiency anemia
Endocrine disorders	Hypothyroidism
	Hyperthyroidism
	Hyperparathyroidism
	Diabetes mellitus
Neurologic diseases (frequently localized pruritus)	Sclerosis multiplex
	Brain injury/brain stroke (frequently unilateral pruritus)
	Brain tumors (frequently unilateral pruritus)
	Postherpetic itch
	Notalgia/cheiralgia/meralgia paresthetica
	Trigeminal trophic syndrome
Tumors	Carcinoid syndrome
	Other solid tumors (rare)
Psychiatric disorders	Depression
	Schizophrenia
Infectious diseases	HIV infection and AIDS
	Parasitic infestation
Drugs	For example, chloroquine, opioids, hydroxyethyl starch, glimepiride

malignancies, or endocrinological disturbances (Table 80.2).

Basic Concepts of Pathogenesis

According to the IFSI clinical classification, pruritus, based on pathogenesis, is divided into dermatological (i.e., due to skin diseases), systemic (i.e., due to internal diseases), neurological (i.e., due to neurological diseases), psychogenic/psychosomatic (i.e., due to psychiatric disorders), mixed (i.e., due to overlapping and coexistence of multiple caused), and other category (i.e., with undetermined origin). However, the exact pathomechanism of these subtypes of chronic pruritus has still not been fully elucidated. In the past, pruritus was considered as a variant of subclinical pain, but recent discoveries clearly indicated that it represents a distinct sensation possessing separate neurons dedicated

solely for itch transmission, albeit showing some similarities and cross-linking with feeling of pain. Pruritus may be evoked in the skin by a number of neuromediators, including, but not limited to histamine, proteases, neuropeptides, serotonin, endogenous opioids, prostaglandins, leukotrienes, and some interleukins. Some of them induce itch by direct activation of pruritoceptors on dermal nerve endings, while others act indirectly causing, e.g., mast cell degranulation. However, the exact mechanism, how they induce or modulate itch, frequently remains poorly understood. Pruritus is transmitted to the spinal cord via mechano-insensitive unmyelinated afferent C-fibers that have a particularly low conduction velocity, large innervation territories, and high transcutaneous electrical threshold. To a lesser degree, pruritus may also be transmitted via myelinated delta-A-fibers. At least two different pruritus pathways have been identified, namely, histaminergic (processing histamine-induced itch) and non-histaminergic ones (processing cowhage-induced itch), the latter being mediated via proteinase-activated receptors (PARs). Both pathways overlap, but also show distinct neuronal networks in the central nervous system. In addition, studies on chloroquine-induced itch led to identification of new pruritus receptors on C-fibers, namely, Mrgprs (Mas-related G protein-coupled receptors) belonging to a family of G protein-coupled receptors that are expressed exclusively on peripheral sensory neurons (Wilson et al. 2011). These receptors may be activated by endogenous peptides and by exogenous substances (e.g., chloroquine). Mice lacking a cluster of Mrgpr genes displayed significant deficits in chloroquine-induced itch but not in histamine-evoked itch. It was suggested that Mrgprs may be even more important for non-histaminergic itch transmission, than PARs, which are thought be the most relevant receptors linked with chronic itch sensations (Liu et al. 2011). Another important molecule that has also recently been identified as an important pruritogen, especially in inflamed skin, is interleukin 31 (IL-31). Expression of IL-31 significantly correlated with scratching counts in a mouse model of atopic dermatitis and anti-IL-31 antibodies effectively reduced scratching behavior in these animals (Grimstad et al. 2009). It was also demonstrated that IL-31 is an important cytokine in the pathogenesis of atopic dermatitis in human beings, and its level was related to disease severity, sleeplessness, total serum IgE level, and subjective itch intensity (Raap et al. 2012).

Central transmission of itch may be modulated by endogenous opioid system. Activation of μ-opioid receptors (MOR) in the central nervous system causes pruritus, while activation of κ-opioid receptors (KOR) seems to alleviate itch. Blocking central opioid receptors was supposed to be a potential antipruritic therapeutic modality; however, central-acting drugs may also produce a number of side effects, like nausea and vomiting, sleeping difficulty, fatigue, and reversal of analgesia, which limit their wider use as antipruritic medications. Interestingly, recent data documented that opioid receptors are also present on peripheral sensory neurons and might partake in itch perception, acting on pruritus in a similar way comparing to central nervous system (MOR activation augmenting pruritus, while KOR activation diminishing itch) (Reich et al. 2010; Yamamoto and Sugimoto 2010). Nelson et al. (2006) reported that endogenous opioid-mediated antinociception in cholestatic mice was mediated peripherally supporting the idea of the importance of peripheral opioid system in itch perception. In addition, it was demonstrated that photochemotherapy (PUVA) diminished MOR immunoreactivity in the skin of patients with atopic dermatitis and the decrease of MOR immunoreactivity corresponded with pruritus improvement. It was also suggested that pruritus in psoriasis might be related to the imbalance of peripheral opioid system activation, as subjects with pruritus showed a decreased expression of KOR and dynorphin A (the endogenous KOR agonist) within the epidermis, while the expression of MOR and β-endorphin (the endogenous MOR agonist) was similar in both groups (Tominaga et al. 2007). Based on these observations it could be suggested that lower cutaneous KOR tone might be responsible for chronic pruritus in selected dermatological diseases, like atopic dermatitis and psoriasis. Furthermore,

potentiating peripheral KOR activity via KOR selective ligands or inhibiting peripheral MOR would offer a new possibility of itch controlling (Reich et al. 2012a, 2012b).

Spinal pathway of pruritus has still not been exactly identified. Pruritic stimuli are transmitted in the spinal cord by specific neurons of dorsal horns to the posterior part of the ventromedial thalamic nucleus, which projects to the dorsal insular cortex. Recently identified gastrin-releasing peptide (GRP)-positive dorsal root ganglion neurons seem to be itch-specific. These GRP-positive neurons are located in lamina I of the dorsal spinal cord. A direct injection of a GRP receptor antagonist into spinal cerebrospinal fluid significantly diminished scratching behavior in three independent itch models, while various pain sensations remained unchanged. Similar effect was produced by selective ablation of GRP-positive spinal neurons. It was also shown that these neurons transmit both histamine-dependent and histamine-independent itch sensations, but they seem to mediate more non-histaminergic itch stimuli. Interestingly, transmission of itch stimuli by GRP-positive neurons was modulated by Toll-like receptors 3 (TLR-3). Furthermore, activated by imiquimod TLR-7 were also shown to mediate pruritus transmission in primary sensory neurons (Liu et al. 2012).

Following itch induction multiple sites are co-activated in the brain including anterior cingulate cortex, supplementary motor area, insular cortex, precuneus, cuneus, and inferior parietal lobe predominantly in the left hemisphere. Such multifocal brain activation argues against the existence of a single itch center and reflects the multidimensionality of pruritus. Importantly, it has been demonstrated that the central processing of itch stimuli differs between patients suffering from chronic pruritus and healthy subjects suggesting the existence of central itch sensitization in chronic itch patients.

Assessment of Pruritus

Due to its subjective character, an objective measurement of pruritus remains a challenge. Pruritus can also be assessed according to various dimensions including its intensity, duration, localization or its influence on patient's well-being and quality of life, and thus, different measurement techniques might be best suited for different physician and patient needs. In our opinion, a reliable assessment of pruritus would be of great help in making decisions regarding particular antipruritic therapy and evaluating its efficacy. However, to date, none of available assessment methods have been approved as a gold standard for itch measurements.

Methods of pruritus evaluation can be divided into subjective assessments of itch and measurements of scratching. In addition, brain imaging techniques like positron emission tomography or functional magnetic resonance imaging enable visualization of brain activation during itch episodes and also may help in pruritus characterization, but, for now, in itch studies they are used for scientific purposes only (Table 80.3).

Unidimensional Scales

Among subjective methods of itch assessment, unidimensional intensity scales are most commonly used in daily clinical settings. They include verbal rating scale (VRS: expressions of, e.g., none, mild, moderate, severe, very severe pruritus), visual analogue scale (VAS), or numeric rating scale (NRS). With VRS patients verbally express the degree of pruritus they feel. This is probably the easiest method of pruritus assessment, but to date there is no consensus how many degrees should be included in the scale. In addition, a limited number of possible answers to choose might significantly reduce its power to detect changes of pruritus intensity during antipruritic therapy.

VAS is another method of subjective assessment of itching. It constitutes a 10-cm long line, on which patients mark the severity of itching they feel, knowing that the start point of the line means "no itch" (0 points) and the finish means "worst imaginable itch" (10 points). Based on available data it could be stated that VAS is a valid, reliable, and repetitive method of itch measurement. It shows good correlation with other pruritus assessments like NRS, VRS, or pruritus questionnaires confirming its good convergent

Table 80.3 Methods of pruritus measurements

Type of assessments	Examples of instruments/measurements	Short description
Unidimensional instruments (intensity scale)	Verbal rating scale Visual analogue scale Numeric rating scale	These instruments usually focus on the intensity of pruritus. They are commonly used in daily clinical settings as they constitute an easy and rapid assessment of pruritus. Major limitation is rather simple evaluation of pruritus, which omits many other important aspect of itch beside intensity
Questionnaires	Eppendorf Itch Questionnaire 5D-itch scale Itch Severity Scale 4-item itch questionnaire	Questionnaires enable assessment of different characteristics of pruritus, including, e.g., localization, duration, frequency, intensity, sensory qualities, scratch response, affective dimensions, disability, and many others. Good questionnaire should be balanced in respect of its simplicity, which is important for patients, and complicity to provide as much information as possible for researchers and physicians. They also require some psychometric expertise and time for proper interpretation
Measurement of scratching	Muscle potentials from forearms Motion sensitive limb meters Pressure sensors Infrared video camera taping	These methods were developed to measure pruritus in more objective way, but usually this methodology is expensive and time consuming, and results are difficult for interpretation. Most available devices only enable evaluation of nocturnal scratching
Other methods of pruritus assessment	Quality of life assessment (ItchyQoL) Assessment of psychic status (depression scale, anxiety scales) Assessment of sleeping problems (e.g., Athens Insomnia Scale) Brain imaging (PET, fMRI)	These assessment focus on a very specific aspect of pruritus providing additional valuable information on the comprehensive influence of itch on human beings

validity. VAS changes of 2.3 points seem to be clinically relevant. According to IFSI consensus following grading scoring has been proposed: 0, no pruritus; 0.1–2.9 points, mild pruritus; 3.0–6.9 points, moderate pruritus; 7.0–8.9 severe pruritus; and 9.0–10.0 very severe pruritus (Ständer et al. 2013). The major limitations of VAS include the fact that it does not characterize the clinics of itch (localization, frequency, etc.), does not assess the influence of itch on patient's well-being, relies on patient's memory, and may be inappropriate for patients with motor or cognitive dysfunctions. Furthermore, several problems have to be solved in the future regarding VAS, e.g., how frequent itch should be assessed with VAS and which timespan should the scale refer to. NRS is similar to VAS, as patients indicate a number from 0 to 10 that corresponds to perceived itch intensity. However, results achieved with NRS were revealed to be slightly higher compared to results of VAS. As it is still unclear, whether this difference is of clinical relevance, it is recommended that both scales should not be used interchangeably (Reich et al. 2010, 2012a).

Pruritus Questionnaires

Pruritus questionnaires should be considered as a good alternative or even better as an amendment of unidimensional scales. A number of questionnaires have been developed to date. The major advantage of questionnaires is the fact that they enable assessment of different characteristics of pruritus. Questionnaires may contain questions about localization, duration, frequency, and intensity of itch, sensory qualities, scratch response, opinion of origin, affective dimensions, aggravating or relieving factors, disability, response to current and previous treatments, itch

cognition, coping, and quality of life. According to recent recommendations, the "ideal" questionnaire should consider the patients' perspective, the medical doctors' perspective, as well as needs of various measurements in clinical trials. Regarding patients, it should be easy to understand and to complete, for physicians should provide important information about relevant characteristics of itch and discriminate between different types of pruritus and regarding clinical trials; it must be useful as an outcome measure and should be able to detect changes in itch over time. However, these objectives are frequently conflicting. The more detailed questionnaire is the longer one. However, too lengthy instruments are time consuming and are difficult for repeated assessments, especially in clinical settings. They also require some psychometric expertise and time for proper interpretation, which limit more frequent use of them. Therefore, despite a number of existing itch questionnaires, none has been more widely accepted. Currently, efforts are made to develop a new questionnaire, which will overcome shortcomings of previous questionnaires and will be more frequently used in clinical trials and in daily practice (Weisshaar et al. 2012a).

Measurements of Scratching

Itching provokes a desire to scratch; thus, measurement of scratching might provide valuable data about itch intensity. Measurement of scratching might simply be based on the counting skin lesions induced by scratching, like excoriations or lichenification. However, not all patients scratch their skin with nails; sometimes they only rub itchy skin areas. Therefore, there is not a simple relationship between itch intensity and the type and number of scratch lesions. In some itchy conditions, like in urticaria, excoriations or other scratch marks are observed quite rare, even despite the fact that itching might be very severe.

Several other methods have been developed to assess scratching. They include measurement of hands, feet, or bed motions by scratching (e.g., muscle potentials from forearms, motion sensitive limb meters, electromagnetic movement detector, pressure sensor, fingernail vibration transducer) or images of scratching (e.g., scratch radar or infrared video camera taping). However, this methodology is expensive and time consuming, and results are difficult for interpretation, as many movement episodes do not have to be necessarily connected with itching. In addition, most of available devices only enable evaluation of nocturnal scratching and, thus, are not well suited for the assessment of itch experienced during a day.

Other Methods of Pruritus Assessment

As mentioned above, patients with chronic pruritus seem to demonstrate different processing of itchy stimuli within the brain suggesting an existence of a phenomenon of central sensitization for pruritus in this group of patients. It was also supposed that subjects with chronic pruritus might also be more sensitive to itchy stimuli because of lowering of itch threshold at the periphery. Following this idea, evaluation of tactile thresholds in chronic itch patients might be a valuable adjunct to other pruritus measurements.

Itch also greatly impacts the patient's well-being. Wide range of questionnaires assessing quality of life (QoL) of patients with health problems might also be used in chronic itch subjects. Importantly, a new, itch-specific QoL questionnaire – ItchyQoL – has been developed by Desai et al. (2008). This questionnaire is solely dedicated for the assessment of QoL impairment in itchy patients evaluating three QoL dimensions, namely, symptoms, emotions, and functioning. Pruritus may also cause other psychic problems, including symptoms of depression and anxiety. Again, a number of available questionnaires (e.g., Hospital Anxiety and Depression Scale – HADS, Beck's Depression Inventory – BDI) may help to properly evaluate the impact of pruritus on patient's psyche providing additional valuable information on the comprehensive influence of itch on examined individuals.

Many patients suffering from pruritus also complain of problems with sleeping, which often result in the need to use sleeping medications. Measurement of sleeping problems may provide further data on pruritus severity. The Stanford Sleepiness Scale (http://www.stanford.edu/~dement/sss.html) or the Athens Insomnia Scale may be applied to assess sleep quality and diurnal sleepiness in patients with chronic itch.

Diagnosis

Pruritus is a subjective sensation and its diagnosis is based solely on the patients' complaints. However, in the vast majority of patients, pruritus is a symptom, not a disease, and generally antipruritic therapy may only be successful, if underlying cause is identified. Due to a very complex and heterogeneous pathogenesis, establishing of pruritus origin may be challenging and every patient with itch has to be considered individually. We do believe that the thorough diagnostic procedure enables identification of the underlying cause for itching in most patients.

Every patient with pruritus should undergo careful history and full physical examination. A detailed history of itching episodes should begin with the inquiries onto onset, location, intensity, diurnal rhythm, sleeping problems, and alleviating or aggravating factors surrounding an itching period. In addition, medical history regarding ongoing or past systemic diseases which might evoke itching has to be collected. The physician should also take a thorough medication history to establish the likelihood of drug-induced pruritus as a cause for the itch. Abrupt onset of itch is uncommon for systemic causes of pruritus and is more frequently observed in drug reactions, infestations, and contact dermatitis. Worsening of pruritus after showering is typical for asteatotic eczema, but may also be seen in aquagenic pruritus accompanying polycythemia vera. Increasing of pruritus during night is observed in nearly all types of itch, but is especially characteristic for scabies. The patient history should also include detailed data about symptoms of pruritus in the close relatives, history of travelling, presence of skin lesions, and potential allergens at home or at places where the patient is living.

Physical examination must include a detailed skin assessment. Special attention should be paid to identify any signs of secondary scratch lesions, such as excoriations, erosions, or nodular prurigo-like lesions. Dermatologic pruritus is diagnosed in patients with primary skin lesions that can be linked with itch sensation; however, primary skin eruption must be differentiated from secondary scratch lesions. If primary skin lesions are present, the diagnosis of underlying cause of pruritus is made based on clinical presentation, skin biopsy, and additional examinations, if necessary.

Pruritic patients with normal skin or with secondary scratch lesions require basic sets of laboratory examinations (Table 80.4). If any abnormalities are found, further diagnostic procedures or consultations should be performed to precisely establish the underlying disease (1). In contrast, if all screening laboratory examination are negative, skin biopsy should be considered to exclude subclinical dermatoses or skin conditions camouflaged by secondary scratch lesions. Alternatively, psychogenic/psychosomatic pruritus may be considered as potential explanation for reported itching – psychiatric consultation is then recommended.

Table 80.4 Basic diagnostic procedures recommended in pruritic patients without primary skin lesions

Blood smear with differential blood count
Erythrocyte sedimentation rate
Serum iron level (only in patients with anemia)
Serum urea and creatinine level
Liver function tests including liver enzyme activity and serum bilirubin level
Serum glucose level
Thyroid gland function tests (TSH)
Stool examination for parasite detections
Screening for HBV, HCV, HIV infection (only in at-risk patients)
Neurological consultation
Skin biopsy (only, if all above tests are negative)
Psychiatric consultation (only, if all above tests are negative and psychogenic/psychosomatic pruritus is suspected)

General Principles of Treatment

General Measures

General measures, beside a specific antipruritic treatment, should be used in all patients with itch as a treatment adjunct. This includes wearing of loose, airy clothes made from natural fabrics (e.g., cotton, silk); avoiding contact with wool and animal furs; avoiding hot or frequent baths, spirits, and spicy foods; and keeping proper humidity and tepid temperature of living rooms. In addition, all patients suffering from pruritus should regularly moisturize their skin, as dry skin may exaggerate or in some subjects even cause itching itself. A twice daily application of an emollient is usually sufficient, but in patients with a very dry skin, more frequent skin moisturizing might be recommended (every 2–3 h). A number of emollients are currently available and every patient should try a couple of them to choose the most suitable and convenient formulation. Oil baths with natural or mineral oils may also help to decrease xerosis. Emollients may act as moisturizing agents only or, in addition, may contain some active compounds, like cooling agents (e.g., calamine, menthol) or mild anesthetics (e.g., polidocanol) which further improve their antipruritic activity. In some patients with localized pruritus, itching may be also diminished by using cold wet dressings.

All patients with chronic pruritus must also keep their nails short to decrease the risk of inducing excoriations and other secondary scratch lesions. In those subjects, who severely scratch their skin while sleeping, wearing of cotton gloves should be suggested (Weisshaar et al. 2012b).

Specific Antipruritic Therapy

Topical Treatments

Cooling Agents

It was observed that cooling the skin may decrease itch sensation. As mentioned above, the so-called cooling agents may be added to topical moisturizers. These substances, like menthol, directly activate low temperature receptors in the skin causing the feeling of cold and thus diminishing pruritus. The major limitation of currently available cooling agents is its relatively short-term efficacy, usually lasting not longer than about 30–60 min. Some patients may also develop contact irritant dermatitis upon prolonged use of menthol (Reich et al. 2011).

Local Anesthetics

Localized pruritus, like notalgia paresthetica or postherpetic itch, may be effectively treated with topical anesthetics, e.g., benzocaine or lidocaine. However, their wider and more frequent use is linked with the risk of evoking allergic contact dermatitis. Their clinical efficacy may be also limited by short-term effect and insufficient penetration through the intact, non-diseased skin. They should not also be applied too frequently or on the larger skin areas due to possibility of circulatory system side effects.

If larger areas should be treated, 3 % polidocanol formulations may be used, as this compound possesses weak anesthetic properties. It has been successfully used for itching accompanying psoriasis, for atopic and other forms of dermatitis, and in uremic pruritus (Weisshaar et al. 2012b; Wąsik et al. 1996).

Capsaicin

Capsaicin, an active component of chili pepper, showed antipruritic properties when used regularly on itchy skin areas. Topical capsaicin has been shown effective in the treatment of notalgia paresthetica, brachioradial pruritus, postherpetic itch, or prurigo nodularis. Regular use of capsaicin (at least three to five times a day) causes desensitization and degeneration of sensory nerve fibers that leads to inhibition of transmission of pruritus and/or burning pain stimuli to the central nervous system. However, antipruritic activity of capsaicin is limited by the fact that during the first days of its application, this substance activates sensory C-fibers causing dose-dependent erythema and burning, which sometimes may be very severe. To overcome this shortcoming of capsaicin therapy, formulation containing low concentration of capsaicin might be applied initially, which should be gradually increased to 0.1 % or even greater, as higher concentrations act more rapidly and the treatment effect is more durable.

Alternatively, within the first days, capsaicin treatment may be combined with prior application of local anesthetic, which will decrease the burning sensations.

Recently, a new formulation of capsaicin becomes available, namely, a patch containing 8 % capsaicin. It was shown that single application of this 8 % capsaicin patch for 60 min on itchy area may provide a long-lasting pruritus relief (Ständer et al. 2001; Wallace and Pappagallo 2011).

Antihistamines

Topical antihistamines are rather uncommon antipruritics. Significant risk of allergic contact dermatitis largely limits their suitability for the treatment of chronic pruritus. Topical formulations include 5 % doxepin cream available only in some countries and 0.1 % dimethindene maleate gel. Topical doxepin should be applied to a maximum of 10 % of body surface and the total daily dose must not exceed 3 g, due to potential systemic side effects. It may be tried in atopic and contact dermatitis and in microbic eczema, but usually the treatment should not exceed 1 week. Dimetinden maleate may be used for acute pruritus, e.g., after insect bites (Weisshaar et al. 2012b).

Calcineurin Inhibitors

Calcineurin inhibitors (pimecrolimus, tacrolimus) have been shown to be effective in atopic dermatitis with greater efficacy of tacrolimus compared to pimecrolimus. At the beginning the treatment with both agents may be complicated by burning or itching sensations, which are related to the release of neuropeptides from dermal nerve endings and usually subside within couple of days. Calcineurin inhibitors have been shown to decrease pruritus intensity in a number of other skin conditions, like seborrheic dermatitis, inverse psoriasis, genital lichen sclerosus, or cutaneous lupus erythematosus. They were also suggested to be effective in other pruritus types, but controlled studies did not confirm these observations.

Corticosteroids

Topical corticosteroids should not be considered as antipruritic drugs. However, they can diminish pruritus accompanying cutaneous diseases by decreasing the inflammatory process in the skin. Their longer use is limited by the risk of skin atrophy and related skin problems (e.g., telangiectasis, purpura, impaired wound healing).

Cannabinoid Receptor Agonists

Topical cannabinoid receptor agonists seem to have antipruritic and anti-inflammatory properties, but to date, only uncontrolled studies documented their efficacy in atopic dermatitis, uremic pruritus, prurigo nodularis, and anal pruritus (Szepietowski et al. 2005). Currently they are only available as one of the ingredients of some cosmetics (Table 80.5).

Systemic Treatments

Antihistamines

Antihistamines are the oldest and most widely used antipruritic drugs to date. They are the treatment of choice in the histamine-dependent pruritus, such as urticaria or mastocytosis, and to avoid sedation new, non-lipophilic drugs (e.g., bilastine, levocetirizine, desloratadine) are recommended for these indications. Their efficacy in other pruritus types is a matter of debate. It is suggested that histamine blockade in such situations is usually not sufficient to achieve pruritus improvement and sedative antihistamines are usually prescribed in patients with itching suffering from atopic dermatitis or psoriasis as sedation may result in decreasing of pruritus feeling. However, recent study by our group indicates that even nonsedating antihistamines may be effective in pruritus in psoriasis [unpublished observation]. Importantly, new antihistamines should be usually used in higher doses than approved (up to four times) to achieve significant pruritus decrease.

Opioid Receptor Antagonists and Agonists

As mentioned in the pathogenesis section, current concepts of chronic pruritus consider the imbalance of opioid system as a key player for itch perception. Several studies documented that blockade of μ-receptor with its antagonists (naltrexone, naloxone, nalmefene) significantly

Table 80.5 Overview of topical antipruritic treatment options

Treatment option		Indication	Limitations
Cooling agents (e.g., menthol)		Adjunct therapy for patients with localized or generalized pruritus	Short-term efficacy (usually lasting less than 30–60 min.)
			Some patients may develop contact irritant dermatitis after menthol application
Local anesthetics	Benzocaine, lidocaine	Localized pruritus, like notalgia paresthetica or postherpetic itch	Possible risk of allergic contact dermatitis
			Short-term efficacy
			Not suitable for larger skin areas due to absorption and potential cardiovascular side effects
	Polidocanol	Adjunct therapy for patients with localized or generalized pruritus	Improvement is usually modest
Capsaicin		Treatment of localized itch (notalgia paresthetica, brochioradial pruritus, postherpetic itch, prurigo nodularis)	Feeling of severe burning during first days of use significantly affects the compliance with the treatment recommendations
Antihistamines		Short-term treatment for pruritus in atopic and contact dermatitis, microbic eczema, insect bites	Significant risk of allergic contact dermatitis after prolonged use
Calcineurin inhibitors		Atopic dermatitis, optionally other forms of dermatological pruritus	Licensed only for atopic dermatitis
			Initial therapy may be complicated with transient itching or burning sensations
Corticosteroids		Dermatological pruritus (pruritic dermatoses with inflammation)	Prolonged use connected with the risk of skin atrophy
			Ineffective in other pruritus types
Cannabinoid receptor agonists		Atopic dermatitis, uremic pruritus, prurigo nodularis, anal pruritus	Lack of controlled studies confirming their efficacy
			Only used as compounds in cosmeceuticals (no licensed drugs available)

diminished pruritus severity. These agents were successfully used in uremic pruritus, cholestatic pruritus, prurigo nodularis, and opioid-induced pruritus. The treatment can be started with oral naltrexone monotherapy (25–100 mg/day) or with intravenous naloxone (0.4–2 mg *i.v. or infusion with* 0.2 μg/kg/min) followed by oral naltrexone (50 mg/day). Alternatively, nalmefene in the dose of 20 mg twice daily may be tried (Metze et al. 1999).

Due to potential side effects of μ-receptor antagonists (sleep problems, anxiety, agitation, signs of withdrawal syndrome), recent attempts were directed on the development of κ-receptor agonists that should possibly possess the same antipruritic effect as μ-receptor antagonists, but should be better tolerated by patients. Recently, nalfurafine, a selective κ-opioid receptor agonist, has been approved in Japan for the treatment of uremic pruritus (Kumagai et al. 2010).

Gabapentin and Pregabalin

Gabapentin and pregabalin are antiepileptic drugs that decrease the neuronal transmission acting as GABA (γ-aminobutyric acid) receptor agonists. Both drugs were successfully used in neurological pruritus (e.g., postherpetic itch, brachioradial pruritus) and in severe pruritus of chronic renal failure, cholestasis, and post-burns. Especially patients with uremic pruritus seem to benefit from such treatment most. The initial dose of gabapentin is 300 mg/day and can be gradually (of about 300 mg every third day) increased to the most effective dose (the maximum is 2,400 mg/day, but usually much lower doses are sufficient to control pruritus). Pregabalin is administered in the initial dose of 50–75 mg and can be increased to 300 mg/day. It must be remembered that it may take several weeks to observe the clinical effect of the treatment (Goutos et al. 2010; Solak et al. 2012).

Antidepressants

Many patients with chronic pruritus demonstrate symptoms of depression. On the other hand, depression may also cause pruritus. Consequently, antidepressants, mainly serotonin reuptake inhibitors (e.g., paroxetine or sertraline), were observed to be potent antipruritic compounds. Pruritus relief was noted in polycythemia vera, paraneoplastic pruritus, and prurigo nodularis and, most importantly, in cholestatic pruritus. Mirtazapine is another antidepressant with both noradrenergic activity and serotonergic activity which show some antipruritic efficacy. Because of potential side effects, antidepressants are recommended as a second- or third-line antipruritic therapy (Weisshaar et al. 2012b; Shaw et al. 2007).

Aprepitant

Aprepitant is a new drug that acts via blocking neurokinin 1 receptor, which is activated by a neuropeptide – substance P. Aprepitant is currently used for the treatment of recalcitrant nausea and vomiting during anticancer chemotherapy. However, a number of reports indicated that this compound may also be effective in the treatment of chronic pruritus. The major limitation of such treatment is the very high cost of the drug (Santini et al. 2012).

Cholestyramine

Resins, such as cholestyramine, may be helpful in cholestatic pruritus. The maximal dose is 12–16 g/day. It must be remembered that prolonged use of cholestyramine may cause deficiency of lipid soluble vitamins. Treatment may also be complicated by nausea, flatulence, and constipation, which frequently impair the adherence to therapy.

Cyclosporin A

Cyclosporin A was shown to effectively alleviate pruritus in atopic dermatitis patients. Some authors also suggested its activity in prurigo nodularis. Cyclosporin A is a potent immunosuppressive drug, but improvement of pruritus severity was noted before significant decrease of inflammation was observed, which suggests an additional antipruritic mechanism. The usually applied dose lies in the range of 3–5 mg/kg/day.

Other Treatment Options

Phototherapy

Ultraviolet B phototherapy may be helpful in the treatment of uremic pruritus, cholestatic pruritus, and HIV-associated pruritus. Due to its favorable safety profile, it is worth to try this treatment before other, more toxic therapies are introduced. The exact antipruritic activity of ultraviolet B phototherapy is unknown; it was observed that it decreases the number of mast cells and free nerve endings in the skin (Szepietowski et al. 2002). UVA1 phototherapy showed similar antipruritic efficacy to ultraviolet B treatment in patients with atopic dermatitis. Photochemotherapy (PUVA treatment) may also be of help, mainly in inflammatory skin diseases accompanied by pruritus like psoriasis, atopic dermatitis, lichen planus and in primary cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome). In addition, PUVA was observed to be effective in some patients with pruritus accompanying polycythemia vera and in aquagenic itch (Weisshaar et al. 2012b).

Psychotherapy

Some chronic itch patients, especially those suffering from somatoform pruritus, may benefit from psychotherapy. Psychotherapy can also be of great importance in patients with atopic dermatitis to combat stress-related itching episodes. Regarding various psychotherapeutic modalities, habit reversal with awareness training techniques seems to be of greatest relevance in patients with chronic pruritus.

Acupuncture

Both classical acupuncture and electroacupuncture can be considered as an alternative, adjunct therapy for patients with chronic pruritus and may bring them some relief; however, it has not been widely used as antipruritic treatment so far and definitely cannot be considered as first-line therapy.

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Psoriasis

81

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Abbreviations

5-MOP	Bergapten
8-MOP	8-Methoxsalen
BMI	Body mass index
BSA	Body surface area
CsA	Cyclosporine A
DCs	Dendritic cell
DMARDs	Disease-modifying antirheumatic drugs
EMA	European Medicines Agency
FAEs	Fumaric acid esters
FDA	Food and Drug Administration
GLB	Golimumab
LS-PGA	Lattice System Physician's Global Assessment
MED	Minimal erythema dose (MED)
MHC	Major histocompatibility complex (MHC)
MTX	Methotrexate
NAFLD	Non-alcoholic fatty liver disease (NAFLD)
NAPSI	Nail Psoriasis Severity Index
NASH	Nonalcoholic steatohepatitis
PASI	Psoriasis Area and Severity Index
PEGylated	Polyethylene glycolylated
PGA	Physician Global Assessment
PsA	Psoriatic arthritis
PUVA	Photochemotherapy with psoralens (PUVA)
SAPASI	Self-administered PASI
SPI	Salford Psoriasis Index
Th	T helper

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Key Points

- Psoriasis is a common, chronic, inflammatory, and debilitating skin disease associated with several comorbidities. Histologically, it shows peculiar features resulting from a complex pathogenic mechanism not fully understood.
- Based on the severity of disease, the therapeutic approach is either topical or systemic.
- A wide array of validated treatments, showing antiproliferative and/or anti-inflammatory, are current available.

Definition and Epidemiology

Psoriasis vulgaris is a chronic inflammatory disease characterized by great variation in prevalence within and between countries because of geographical, environmental, and genetic factors. Psoriasis seems to be most prevalent in Caucasian population and less frequent in yellow-brown individuals and in black populations.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_81, © Springer-Verlag Berlin Heidelberg 2015

Prevalence has been shown to vary between 1.5 and 3 % in Europe and the United States. Psoriasis shows a strong genetic susceptibility with non-Mendelian mode of inheritance that plays a key role in its pathogenesis. It has been nearly 30 years since researchers first recognized that certain variations in the HLA system (MHC classes I and II) on chromosome 6p conferred an increased risk of developing psoriasis.

More in detail, people with an allele called HLA-Cw6 are 20 times more likely to have psoriasis than expected by chance. This locus, known as PSORS1, identifies a chromosomal region including a cluster of genes: HCR (alpha-helix coiled-coil rod homolog), CDSN (corneodesmosin), and HLA-C. The PSORS1 locus, although considered the major susceptibility locus for psoriasis, accounts for less than 50 % of familial aggregation in psoriasis.

Based on these findings, multiple susceptibility loci, localized in different chromosomes, have been identified, confirming the genetic heterogeneity of psoriasis.

The analysis by genome-wide association studies linked psoriasis to a larger number of genetic risk factors, identifying more than 30 susceptibility genes.

Together with the genetic predisposition, a wide range of trigger factors have been involved in the pathogenesis psoriasis and include stressful events, depression, anxiety, mechanic damages (Koebner's phenomenon), ultraviolet rays, bacterial and viral infections, alcohol, smoke, and drugs.

Among bacterial infections, it is well documented that the acute onset of guttate psoriasis as well as the exacerbation of the chronic form are induced by streptococcal throat infection in a significant proportion of patients (56–98 %). In these individuals, an acute sore throat precedes by 1–2 weeks the cutaneous sudden eruption and the serological evidence of a recent bacterial infection. Many drugs can precipitate or exacerbate psoriasis and other cutaneous disorders via chemical interaction with genetically susceptible epidermal cells. Beta-blockers; lithium; synthetic antimalarial drugs; nonsteroidal anti-inflammatory drugs; tetracyclines; interferons (IFNs)-α, IFN-β, and IFN-γ; interleukin-2 (IL-2); granulocyte colony-stimulating factor (G-CSF); and angiotensin-converting enzyme (ACE) inhibitors are few examples.

Basic Concepts of Pathogenesis

Psoriasis is characterized by marked epidermal hyperplasia, neo-angiogenesis, and dense dermal and epidermal immune cell infiltrate. Various immune cell types are involved in psoriasis pathogenesis, particularly CD4+ T helper (Th) 17 and Th1 cells that are demonstrated to be central to the pathogenic mechanisms leading to the psoriatic plaque formation. Together with CD4+ T cells, CD8+ T cells infiltrating the epidermis represent the major source of IFN-γ, IL-17, IL-22, and TNF-α, though other T-cell subsets participate to psoriasis pathogenesis such as Th22, Th21, and IL-17-producing γ/δ T cells. Psoriatic lesional skin shows a large amount of these cytokines in addition to increased levels of dendritic cell (DCs)-derived cytokines (IL-23, IL-20, TNF-α) and keratinocyte-derived cytokines and chemokines (i.e. CXCL8, CXCL1, CCL20). Though T cells are the key drivers of most relevant inflammatory circuits, DCs, as well as keratinocytes, offer a relevant contribution to the psoriatic lesional skin formation.

An important role is played by keratinocytes, which amplify skin inflammation and regulate immune cell trafficking through the production of a variety of cytokines, chemokines, and antimicrobial peptides (AMPs). Keratinocytes also synthesize many cytokines that can induce epidermal hyperplasia (autocrine growth factors) or neo-angiogenesis (paracrine growth factors).

Histology

Psoriasis pathognomonic histologic changes are the following: parakeratosis of cornified layer, hypogranulosis, acanthosis with elongation of epidermal crests (papillomatosis), and increased number of mitotic figures in the basal layer and above (Fig. 81.1). In the dermal papillae, typical

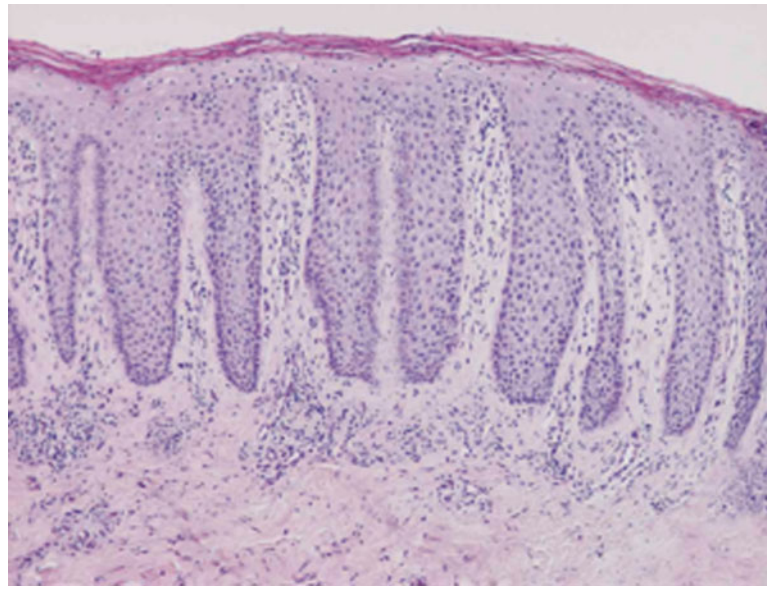

Fig. 81.1 Parakeratosis of cornified layer, hypogranulosis, acanthosis with pale cytoplasm of keratinocytes, and elongation of epidermal crests (papillomatosis) (HE, 10×)

findings are ectatic capillaries perpendicular to the epidermis with stacked erythrocytes (liable of the diagnostic semiologic Auspitz sign) and a lymphocytic infiltrate of variable density. Papillary dermis presents slight oedema, dilated tortuous perpendicularly oriented capillaries of the superficial plexus with extravasated erythrocytes packed within lumina. Within the epidermis of a fully developed lesion (scaly plaque), confluent parakeratosis containing neutrophils, focally compact orthokeratosis, and, sometimes, plasma in parakeratotic areas might be observed. Granular layer is usually reduced, except in those foci beneath areas of compact orthokeratosis, and spongiform pustules can be observed within the spinous, granular, and cornified layers.

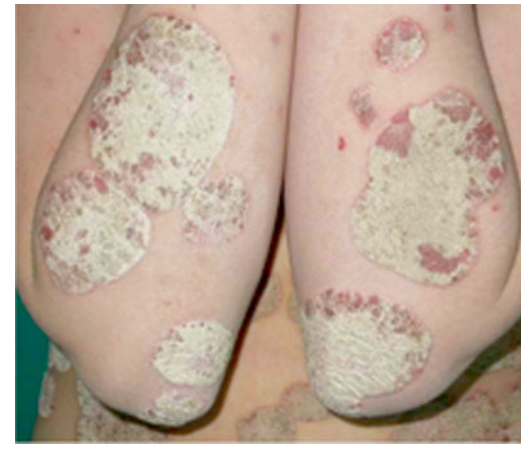

Fig. 81.2 Psoriatic lesions on the elbows characterized by prominent hyperkeratosis plaques

Clinical Presentation

Typical psoriatic lesion is characterized by an erythemato-squamous patch or papule usually evolving into a plaque with a sharply demarcated border (Fig. 81.2).

The erythematous patch may vary in colour from light red to "salmon pink" or intense red, typically more evident at the margin, with congested aspect that disappears with vitropression. The squamous component is extremely variable and whitish to silvery colour, and different degrees of coherence to the plaque may be observed. Scales can be small and thin producing a fine pityriasic desquamation or large and thick with an "ostraceous" or "rupioid" appearance. Different combinations of both erythematous and

squamous components determine the various features reflecting the typical polymorphism of psoriatic lesions.

Itching in psoriasis is an important symptom, and it is a common observation that its intensity is dependent on the extent of psoriatic lesions. However, the molecular basis of itching remains largely unexplained.

Morphologic features of psoriasis are extremely proteiform. The most common clinical variant is psoriasis vulgaris (also named plaque-type psoriasis) that occurs in more than 80 % of patients. Erythemato-squamous plaques, round or oval, variable in size, typically affect the elbows and knees, often in a symmetrical pattern, scalp, lower back, intergluteal cleft, and umbilical area.

The number of the lesions can vary from few (minimal psoriasis) to several elements, also confluent that can cover the whole body surface area (generalized and/or universal psoriasis).

Psoriasis can develop at any age and last for just a limited period or for a lifetime, with alternating periods of relapses and remissions. It is difficult to predict the course of the disease, and spontaneous remissions occur with varying frequencies.

The psoriatic lesion may present as punctiform, follicular, guttate, lenticular, nummular, annular, circinate, gyrate, geographic, serpiginous, and linear psoriasis. Moreover, psoriasis can be further classified according to topographic localization in palmo-plantar psoriasis, genital psoriasis, face and ear psoriasis, scalp psoriasis, nail psoriasis, inverse psoriasis, sebopsoriasis, ocular psoriasis, and mucosal psoriasis.

Palmo-plantar psoriasis is characterized mostly by typical scaly patches or less well-defined hyperkeratotic elements often surrounded by an area of erythema.

Guttate psoriasis presents as small (0.5–1 cm in diameter) round or oval lesions scattered more or less evenly over the body, particularly on the upper trunk and proximal extremities, not infrequently on the face and scalp. These drop-like eruptive papules show a salmon-pink hue. A fine scale, which is usually absent in early-stage lesions, may be appreciated on the more established ones.

The onset is often acute, and the eruption is accompanied by slight itching. This form is characteristic of psoriasis in childhood and young adults. Streptococcal throat infection (by group A beta-haemolytic streptococcus) frequently precedes the onset or flare of eruptive guttate psoriasis in children. Guttate psoriasis may be self-resolving, leaving patient free of further relapses, or it may clear temporally to reappear later as patches of plaque psoriasis.

Severe forms of psoriasis include erythrodermic, generalized pustular psoriasis, and psoriatic arthritis. The rate of erythroderma among patients with psoriasis ranges from 3 to 31 %. Erythrodermic psoriasis can evolve from pre-existing chronic plaque psoriasis or rarely can occur de novo as a generalized erythema.

The commonest causes implicated in the development of erythrodermic psoriasis are the following: reaction to some drugs (lithium, beta-blocker, interferon-alpha, antimalarials, anti-inflammatory, tetracyclines, and inhibitors of angiotensin-converting enzyme), withdrawal of systemic and topical corticosteroids, overtreatment with tar or dithranol, PUVA phototoxic reaction, insolation, acute infection, and emotional stress.

Erythrodermic psoriasis is clinically characterized by generalized red-violet erythema and superficial, fine, white scaling. Additional features include oedema, fissures, exudation, and severe nail dystrophy such as subungual hyperkeratosis and onycholysis. The main subjective symptoms associated are varying itching, chills, feeling of cold, movement limitation, fatigue, and malaise. General condition is impaired with fever, lymphadenopathy, weight loss, dehydration, and oliguresis. *Pustular psoriasis* is subdivided in two major clinical variants, localized and generalized, which are characterized by the same elementary lesion, a sterile pustule, and are differentiated by the body surface area involved and, consequently, by the clinical severity. As mentioned above, the elementary lesion is a flat, sterile, non-follicular pustule of variable diameter, ranging from 1 to 5 mm, milk coloured, and generally evolving in yellowish crusts. In some variants, the lesions show the tendency to

confluence with polycyclic margins. Histologically, the pustules are situated in the upper part of spinosus layer and are filled with neutrophils configuring a peculiar aspect named "spongiform pustule of Kogoj". About 2–6 % of patients suffer from inverse form with the involvement of major skin folds (such as groins, axillae, sub-mammary, intergluteal, and periumbilical region).

Erythrodermic generalized pustular psoriasis of *von Zumbusch* is the most severe variant characterized by the following symptoms: acute onset, fever lasting for several days, worsening of general conditions, generalized erythema and oedema, and eruption of sterile pustules of 2–3 mm in diameter. The pustules are disseminated over the trunk and extremities, including the nail beds, palms, and soles. The pustules usually appear as single and then confluent lesions with an exacerbation of the disease. The fingertips may become atrophic in patients with prolonged disease. The oral mucosa is often involved. Characteristically, the disease occurs in waves of fever and pustules. Simultaneously with the pustules, a polyarthritis is likely to occur in many cases. Blood tests show neutrophilic leucocytosis and elevation of ESR.

Psoriatic arthritis (PsA) is an inflammatory arthritis that is commonly associated with cutaneous psoriasis. The percentage of patients with psoriasis which have psoriatic arthritis varies between 5 and 42 %. Many patients are affected by psoriasis several years before developing arthritis. The severity of joint involvement is not related to the pattern of the skin disease. The major extra-articular feature in PsA is psoriasis. In 70 % of the patients, arthritis symptoms develop years after skin changes present, and in 10–15 % arthritis precedes psoriasis, yet a significant family history of psoriasis is useful for the diagnosis. In 15 % of the patients, the initial presentation includes arthritis and psoriasis together. Psoriasis vulgaris is the most frequent form of psoriasis associated with PsA, but pustular and guttate psoriasis have been also reported. Only 35 % of patients with PsA had a relationship between the extent and severity of psoriasis and joint manifestations. Extra-articular manifestations of PsA include conjunctivitis or iritis (in 7–33 % of patients) and aortic incompetence (in less than 4 % of patients) that may occur late during the course of PsA.

Nail psoriasis is reported in 10–55 % of adult psoriatic patients, it is uncommon in children (7–13 %), and it frequently reaches the percentage of 80 % in psoriatic arthritis. Clinical presentation of nail psoriasis is directly related to the specific affected nail apparatus (matrix, nail bed, nail plate, periungual skin) with the following findings: pitting (irregular and not geometrical depressions on the nail plate), oil spots (yellowish or pinkish nail bed discoloration surrounded by an erythematous halo), ridging (Beau's lines, trachonychia), thickening and brittle, onycholysis (detachment of the nail plate from the nail bed), subungual hyperkeratosis (hyperparakeratosis of the nail bed), paronychia, and splinter haemorrhages.

Psoriatic lesions may also involve the oral and genital mucosae. On the tongue, psoriasis shows features of benign migratory tongue or geographic tongue, consisting in one or more erythematous patches with a raised whitish or yellow serpiginous border.

Comorbidities

There is increasing evidence that psoriasis has many immunological and metabolic associations that may play a role in disease in other organ systems. Epidemiological studies have evidenced an association between psoriasis and noncutaneous diseases such as tonsillitis, Crohn's disease, obesity, heart diseases, and chronic alcoholism.

Patients with psoriasis have an increased risk of developing cardiovascular disease and metabolic syndrome compared with controls without psoriasis.

Metabolic and Cardiovascular Diseases

Metabolic syndrome and its components have been largely associated with psoriasis. This syndrome is characterized by several factors including central obesity, atherogenic dyslipidaemia, hypertension, and glucose intolerance. Patients with psoriasis tend to have significantly higher

concentrations of triglycerides and total cholesterol, as well as higher concentrations of low-density lipoprotein and very low-density lipoprotein cholesterol, all of which are established risk factors for cardiovascular disease. An association between psoriasis and type 2 diabetes is supported by several epidemiologic studies. Type 2 diabetes is usually preceded by impaired glucose tolerance, and accordingly psoriatic patients are more likely than healthy individuals to demonstrate insulin resistance when challenged with oral glucose. Obesity is a common comorbidity of psoriasis, and multiple studies have demonstrated that patients with psoriasis are more frequently overweight (BMI $\geq$25 kg/m^2 and <30 kg/m^2) or obese (BMI $\geq$30 kg/m^2) compared with patients without psoriasis.

The cardiovascular system is one of the most commonly affected. This association has been found in several studies: increased rates of concurrent cardiovascular disease including hypertension, diastolic dysfunction, and heart failure have been noted.

Gastrointestinal Diseases

Crohn's disease and ulcerative colitis are chronic inflammatory diseases of the digestive system. The underlying aetiology and exact pathogenesis of the inflammatory bowel diseases are still unknown, but the current hypothesis of their pathogenesis relates to dysregulation of the gastrointestinal immune system in genetically predisposed individuals. Epidemiological, pathologic, and therapeutic connections exist between psoriasis and Crohn's disease. The prevalence of psoriasis in patients with Crohn's disease is 9 %, while in the general population is 2–3 %. Also, a family history of psoriasis has been frequently observed in Crohn's disease patients.

The genetic links between the two diseases were investigated, with findings demonstrating that the susceptibility loci of psoriasis, Crohn's disease, and ulcerative colitis all appear in the *6p21* locus, an area which encompasses the major histocompatibility complex (MHC). This area includes the *IBD3* locus involved in Crohn's disease and ulcerative colitis and the *PSORS1* locus involved in psoriasis. Several non-MHC-related genes, such as the IL-23 receptor (*IL-23R*) and *IL-12B* genes, have been associated with psoriasis, Crohn's disease, and ulcerative colitis. Other genes have been identified that are common to both conditions, residing on chromosomes 16, 4, and 3. NOD2, located on chromosome 16, encodes a cytoplasmic protein that regulates nuclear factor-kappa B (NF-kB) signalling. Polymorphisms of NOD2 associated with Crohn's disease appear to be associated with NF-kB dysregulation.

Liver Disease

Severe abnormalities of liver function may occur in psoriasis and are likely to be related to drugs and alcohol intake. Liver cirrhosis and other associated disorder are much more frequent cause of death and morbidity than in the general population. Non-alcoholic fatty liver disease (NAFLD), comprising a spectrum of conditions ranging from simple steatosis to steatohepatitis (NASH) and cirrhosis, is now regarded as the hepatic manifestation of metabolic syndrome and represents the most common cause of abnormal serum liver enzymes in Western countries, affecting up to one-third of the general population. NASH is characterized by morphological evidence of fatty change with lobular hepatitis, but in the absence of alcoholism. Histological studies of the liver in patients with psoriasis have shown that fatty degeneration within the liver lobules, inflammatory cell infiltration in the portal area, and focal necrosis are more common than in controls. The frequency of NAFLD diagnosed by patient history, blood sampling, and characteristic sonographic features in patients with chronic plaque psoriasis is remarkably greater than that in non-psoriasis control subjects, who were matched for age, gender, and BMI, affecting up to nearly half of these patients and that NAFLD was strongly associated with psoriasis severity independently of potential confounders such as age, gender, BMI, psoriasis duration, and alcohol.

Psychiatric Morbidity and Alcoholism

The most commonly diagnosed conditions are depressive and anxiety disorders. Other less common general psychiatric illnesses encountered included social phobia, alcohol dependence, obsessive–compulsive disorder, post-traumatic stress disorder, and anorexia nervosa. Stress, such as from anxiety, depression, marital problem, or "near-death" experiences, has been identified as a triggering and exacerbating factor in the appearance of psoriasis in most of psoriatic patients. Moreover, depression and suicidal ideation affect many patients with psoriasis.

Alcoholism is a multifactorial disorder and affects virtually every organ system, including the skin. Alcohol may exacerbate pre-existing psoriasis but does not appear to induce it; 13 % of patients with psoriasis are alcoholics, while 18 % of psoriatic patients had a problem with alcohol abuse. Heavy drinking was found significantly more commonly in male patients with severe psoriasis than other group with the disease and could be a symptom of stress caused by severe skin disease.

General Principles of Treatment

Topical Therapies

Corticosteroids

Corticosteroids still represent the milestone in the topical treatment of psoriasis in all age groups. Owing to their anti-inflammatory and antiproliferative properties, they reduce erythema, scaling, and pruritus in psoriasis.

Corticosteroids, ranging from low to high potency, are available in a variety of formulations including creams, emollient cream, ointment, gel, spray, lotion, solution, nail lacquer, tape, and foam.

According to their therapeutic potential, they may be classified into four classes: mild, medium, potent, and very potent. The efficacy rates of ultrapotent corticosteroids range from moderate or better improvement of Physician Global Assessment (PGA) in 58 % of patients to overall improvement of PGA in 92 % of patients, while with mild corticosteroids, PGA improvement has been reported as excellent or good in 41 % of patients and as good or better in 83 % of treated patients.

Usually, lower-potency corticosteroids are used in childhood and on sensitive skin sites including the face, axillae, diaper area, and gluteal cleft, whereas hyperkeratotic areas, such as the palms and soles, or chronic lesions require high-potency corticosteroids.

High-potency agents can be used for a limited period of 2–4 weeks, no more than twice daily and at a dose of no more than 50 g/week. For long-term strategies based on potent corticosteroids, intermittent therapy, weekend therapy, and combined therapeutic schemes with other topical medications could be considered.

Local side effects including skin atrophy, striae, telangiectasia, purpura, rosacea, acneiform dermatoses, and rebound erythema may occur because of long-term therapies at the site of application, particularly at steroid-sensitive areas. Another relevant side effect of chronic application of corticosteroids is tachyphylaxis. Applications should be gradually tapered down in order to avoid rebound effects. To minimize the side effects, it could be useful to consider a switch to lower-potency corticosteroids after successful treatment with potent agents. Moreover, "weekend therapy" or "pulse therapy" should be considered for reducing the amount of corticosteroids, as well as combination therapy or rotation therapy using alternative nonsteroidal drugs such as coal tar, anthralin, calcipotriene, and topical calcineurin inhibitors.

Vitamin D Derivates

Vitamin D3 analogs were introduced in the early 1990s since oral vitamin D was demonstrated to be effective in improving psoriasis. Three vitamin D3 analogs are commonly used for the treatment of psoriasis: calcitriol, calcipotriol, and tacalcitol. They bind to the vitamin D receptor, normalizing keratinocyte proliferation and differentiation and modulating the immune response.

Calcipotriol is available in the form of a cream, solution, or ointment for the treatment of plaque-type psoriasis, scalp psoriasis, and nail

psoriasis, respectively. It has been found to be effective and safe, even when it is associated with sun exposure. Tacalcitol is a synthetic vitamin D3 analog, which is administered once daily. Several studies assessed efficacy and safety of tacalcitol reporting successful clinical outcomes. Treatment with calcitriol shows better tolerability in sensitive and irritated areas of the skin, and thus it may be used in psoriatic children.

Usually local side effects are not severe, and they may include erythema, burning, pruritus, and oedema.

Combined Therapy with Vitamin D3 Derivatives and Corticosteroids

Compound products consisting of calcipotriol and betamethasone dipropionate are currently available. This formulation, combining the action of calcipotriol (regulation of keratinocyte differentiation and antiproliferative effects) with the anti-inflammatory effects of steroids, enhances the effectiveness of this compound, and, presumably, it could offer the possibility of reduction in the dose of either or both single agents, with a potential decrease in the occurrence of their side effects, as assumed by some authors.

Long-term efficacy of this formulation applied once daily resulted in an improvement in PGA ranging from 69 to 74 % of patients continuously treated with the combination compound, achieving "clear" or "almost clear" status with no serious adverse events.

An increasing number of medications, particularly for the scalp, have been developed into innovative, easy-to-use formulations. A lipophilic, non-alcoholic gel containing the same active ingredients (calcipotriol and betamethasone dipropionate) has been developed and used with the same therapeutic scheme (once daily).

Retinoids

Tazarotene represents the only topical retinoid that can be used for plaque psoriasis as gel or cream in 0.05 and 0.1 % formulations. In keratinocytes, tazarotene regulates transcription signalling through the retinoic acid receptors (RAR)-γ, RAR-β, and RAR-α, thus inhibiting proliferation and normalizing differentiation. It also acts as inflammation-suppressing agent.

The use of tazarotene is limited by quite common side effects such as erythema, irritation, and burning that may occur with protracted use, and they might be minimized by using the cream instead of the gel formulation, lowering the concentration, and performing a short-contact therapy or alternate-day applications.

Tars and Anthralin

Coal tar has been used for more than 100 years for the treatment of psoriasis. Coal tar and wood tars (birch, pine, and beech) are available as topical antipsoriatic agents in different formulations, including ointment, cream, gel, lotion, shampoo, and soap.

Tar-based formulations are indicated for the treatment of chronic stable forms of plaque-type psoriasis, scalp psoriasis, and palmo-plantar psoriasis, whereas their use might be limited in sensitive areas, including the genital area and flexural areas, because of their irritant potential.

Coal tar may be used as a monotherapy or in association with UVB (Goëckerman regimen). Its use is limited because of poor patient acceptance due to cosmetic inelegance, including staining of clothes and a potent tar odour that is present in almost all products. Additional potential adverse effects include irritant contact dermatitis, folliculitis, and photosensitivity to UVA light.

Keratolytics

Keratolytics represent a class of therapeutic compounds characterized by the capability of decreasing cell-to-cell cohesion in the stratum corneum and, therefore, promoting the physiologic shedding process. Salicylic acid is a keratolytic agent that is used to reduce hyperkeratosis and increase the absorption of other medications. It is the oldest keratolytic agent used in dermatology at low concentrations, usually ranging from 2 to 6 %. Extensive use may be correlated with important side effects such as salicylate toxicity (salicylism) characterized by dizziness, headache, confusion, and ringing or buzzing in the ears.

Other keratolytic agents include α-hydroxy acids (mainly lactic acid and propylene glycol), urea, and glycerin.

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors could be taken into consideration as a maintenance therapy after a satisfactory steroid therapy, possibly by reducing corticosteroids gradually and introducing calcineurin inhibitors as substitute therapeutic agents. They could constitute a valid alternative to corticosteroids because of their ability to suppress T-cell activation and proliferation. The off-label use of pimecrolimus (1.0 %) and tacrolimus (0.03 and 0.1 %) seems to be effective in treating facial and flexural psoriasis. Their use is limited because of their poor penetration into hyperkeratotic psoriatic plaques, and thus they might be considered as optimal therapeutic option in treating intertriginous areas and more sensitive body sites such as the face where the absorption is naturally increased. However, in order to increase the limited penetration of these agents, they could be applied under occlusion or in combination with keratolytics such as salicylic acid and urea. Regarding the safety profile, only mild side effects including itching, stinging, and the feeling of warmth have been reported.

Phototherapy

It has been well known that natural sunlight improves psoriasis in the majority of patients.

UVB

Mild-to-moderate eruptive plaque-type psoriasis responds rapidly to broadband UVB. Narrowband (311–313 nm) phototherapy is superior to conventional broadband UVB with respect to both clearing and remission times. The initial therapeutic UV dose lies at 75–100 % of the minimal erythema dose (MED). Treatments are given two to four times per week. As peak UVB erythema appears within 24 h of exposure, increments can be performed at each successive treatment. The rate of increase depends on treatment frequency and the effect of the preceding therapeutic exposure. The objective of the dose increments is led to maintain a minimally perceptible erythema as a clinical indicator of optimal dosimetry. Upon clearing, treatment is either discontinued or a maintenance therapy for 1 or 2 months may be prescribed.

Concerning short-term side effects, erythema, dry skin with pruritus, occasional blistering, and all increased recurrence herpes simplex eruptions have been reported. Painful erythema resulting from overexposure is treated with topical corticosteroids. Systemic nonsteroidal anti-inflammatory agents and corticosteroids have also proven useful for severe cases. Excimer laser and monochromatic excimer light utilize specific wavelength (308 nm) belonging to the UVB spectrum, and they appear to offer relapse-free periods and a prolonged stabilization of localized psoriasis comparable or better than that offered by standard topical therapy regimes and by 311 nm UVB treatment.

UVA1

Long-wavelength ultraviolet A light (UVA1, 340–400 nm) has been used to treat skin disease for more than 30 years. UVA1 penetrates deeper than other ultraviolet phototherapies and has different biologic effects than UVB and shorter-wavelength UVA (UVA2, 315–340 nm). UVA1 works via oxygen-dependent mechanisms after photosensitization of endogenous lipids and proteins. UVA1 spectrum has been used in the treatment of psoriasis. The monochromatic coherent and coordinate UVA1 light, based on a 1,064 wavelength neodymium-doped yttrium orthovanadate laser, optically pumped using a 808 nm infrared beam able to achieve a third harmonic 355 nm wave delivery, has shown high success rate in the treatment of mild-to-severe psoriasis reaching both the epidermis and the dermis indicating. From a therapeutic perspective, exposition to the UVA1 radiation therapy can be divided into low (10–30 J/cm^2), medium (40–80 J/cm^2), and high (80–120 J/cm^2) doses. The effects of UVA1 in psoriasis could be associated with the modulation of the local immune response, T-cell depletion, and alterations in apoptosis-related molecules.

Photochemotherapy with Psoralens (PUVA)

Psoralen photochemotherapy (PUVA) is the combined use of psoralens (P) and long-wave UV radiation (UVA). The combination of drug and radiation results in a therapeutic effect, which is not achieved by the single component alone. PUVA is performed by the administration of a fixed dose of a psoralen preparation at a constant interval before UVA exposure. Psoralens are linear furocoumarins, which were originally derived from plants. Currently, 8-MOP (methoxsalen) is most commonly prescribed, but 5-MOP (bergapten) is also used where available. The synthetic furocoumarin 4,5,8-trimethylpsoralen (TMP) is used for bathwater-delivered PUVA. 8-MOP and 5-MOP are available as oral preparations, which either contain crystals, micronized crystals, or solubilized psoralens. Oral psoralens are metabolized in the liver and excreted with the urine within 12–24 h. Topical application of a psoralen molecule *(bath PUVA)* instead of ingestion of the drug has been shown to be very effective, thereby removing the common side effect of nausea occurred after ingestion of the psoralen.

Systemic Treatments

Systemic treatments are generally reserved for moderate-to-severe extensive psoriasis, psoriatic arthritis, erythrodermic psoriasis, pustular psoriasis, moderate psoriasis when topical agents or phototherapy are ineffective or contraindicated, or mild psoriasis in case of severe psychosocial disability (facial/genital psoriasis) or when patients' quality of life is greatly compromised (as in palmo-plantar pustulosis) (Fig. 81.3).

Among those, cyclosporine and methotrexate are considered first-line agents, while acitretin is a second-line therapeutic option, except in the case of pustular erythrodermic psoriasis. Fumaric acid esters are an effective treatment, as demonstrated by several trials performed in Germany, Austria, and the United Kingdom, but they are not available in all European countries (Tables 81.2 and 81.3).

There are several physical measures to define psoriasis severity and the impact of a given therapy: body surface area (BSA), Psoriasis Area and Severity Index (PASI), Psoriasis Global Assessment (PGA), Lattice System Physician's Global Assessment (LS-PGA), Salford Psoriasis Index (SPI), Nail Psoriasis Severity Index (NAPSI), and self-administered PASI (SAPASI). One of the most used psoriasis scoring systems is the PASI that is commonly reported in clinical trials. Fredriksson and Petterson created the PASI in 1978 as a method to evaluate the clinical efficacy of a new treatment for psoriasis. Typically, PASI would be calculated before, during, and after a treatment period in order to determine how well psoriasis responds to the treatment.

Severity is measured by four different parameters: erythema, infiltration and desquamation of the plaques, and the percentage of involved body surface area.

Cyclosporine

Cyclosporine A (CsA) is a decapeptide derived from the fungus *Tolypocladium inflatum* W. Gams. Since the 1970s, its immunosuppressive properties were described, and CsA was introduced in the treatment and prevention of transplant rejection. The beneficial effect of CsA may, at least in part, be attributed to the modulation of T-cell responses: the molecule passively enters into the cell and forms a complex with the cytosolic immunophilin, cyclophilin, causing inactivation of calcineurin-mediated dephosphorylation of the nuclear factor of activated T cells (NFAT). CsA is effective at concentrations ranging from 2.5 to 5 mg\kg\day. The efficacy of intermittent short courses of CsA has generally been expressed as a rapidly produced improvement in all efficacy parameters or as complete clearance of disease and found approximately in 80–90 % of patients. The average duration of treatment has been reported to be between 8 and 16 weeks, and median time to relapse was 72 days. The side effect profile of CsA is well known and predictable. The major safety concerns of CsA therapy are nephrotoxicity, hypertension, and the potential risk of malignancies.

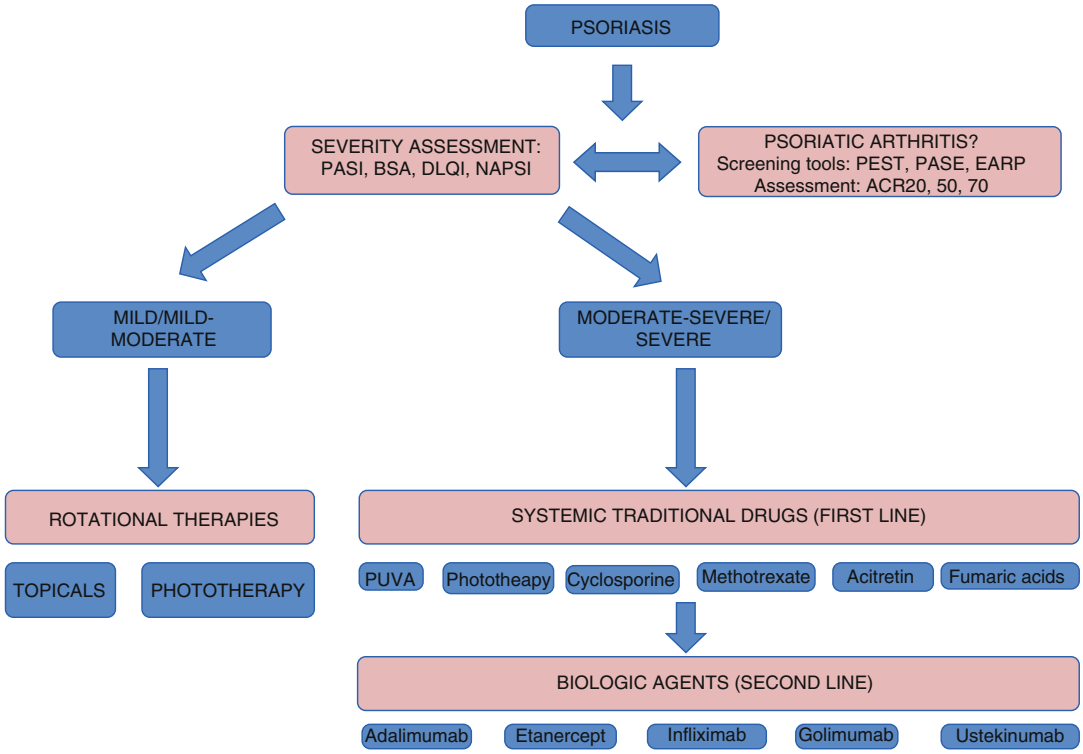

Fig. 81.3 Diagnostic and therapeutic adalimum for plaque-type psoriasis and psoriatic arthritis

Other adverse events observed include gastrointestinal symptoms (diarrhoea, nausea), metabolic abnormalities (hypertriglyceridaemia, hypercholesterolaemia, hyperbilirubinaemia, hypercalcaemia, and hypomagnesaemia), nervous system symptoms (headache, paresthesia), fatigue, gingival hyperplasia, and other general symptoms (influenza-like). Except for some rare cases, these side effects are dose dependent and reversible with treatment interruption or dose adjustments (Tables 81.1, 81.2, and 81.3).

Retinoids

Retinoids are a class of compounds all formally derived from vitamin A (retinol) and successfully used in the treatment of a large spectrum of dermatological and non-dermatological diseases. Acitretin represents the systemic retinoid approved for the treatment of severe psoriasis that, in monotherapy, it is generally more effective for pustular psoriasis than plaque-type, guttate, or erythrodermic psoriasis. When acitretin is used as monotherapy for generalized pustular psoriasis, the initial dose required is 25–50 mg/day. Optimal dosing for individual patients may be achieved through a dose-escalation strategy involving initiation of therapy at low doses (10–25 mg/day) and, if necessary, gradually increasing the dose as tolerated until optimal response is achieved. A rapid resolution of generalized pustular psoriasis is achieved usually within 10 days after initiating acitretin. Mucocutaneous adverse events including cheilitis, skin peeling, alopecia, xerosis, rhinitis, nail dystrophy, epistaxis, sticky skin, retinoid dermatitis, and xerophthalmia may occur (Tables 81.1, 81.2, and 81.3).

Methotrexate

Methotrexate (MTX) is an effective immunosuppressive compound, applied in the prophylaxis and treatment of several diseases. High-dosage MTX is currently used in the treatment of malignancies and in graft-versus-host disease. When used at low or moderate doses, MTX has

Table 81.1 Therapies for psoriasis

	Recommended dose	Remarks
Topical therapies		
Corticosteroids	Once daily	Limited period of 2–4 weeks
	No more than 50 g/week	
Vitamin D3 derivatives	Tacalcitol once daily, calcipotriol twice daily	Their use can be longer than corticosteroids (alone or in combination)
Combined therapy with vitamin D3 derivatives and corticosteroids	Once daily	Limited period of 2–4 weeks
Retinoids	Once daily	Possibility of short-contact therapy
Topical calcineurin inhibitors	Once daily	As maintenance therapy for intertriginous areas
Phototherapy and laser therapy	UVA1: medium (40–80 J/cm^2) and high (80–120 J/cm^2) doses	UVB broad- and narrowband phototherapy
	NB-UVB initial dose (75–100 % minimal erythema dose) to be increased	UVB 308–311 laser therapy
		UVA1 phototherapy
		UVA1 355 nm laser therapy
PUVA	8-methoxypsoralen (8-MOP) 0.3–0.6 mg/kg 1–2 h prior UVA exposure (1 J/cm^2), then increasing UVA doses	
Systemic therapies		
Cyclosporine	2.5–5 mg/kg/die (optimal 4 mg/kg/die)	The average duration of treatment between 8 and 16 weeks and median time to relapse is about 72 days
Methotrexate	5–10 mg weekly as initial dose, escalation dose up to 30 mg weekly	Two dosage schedules (single weekly or intermittent oral schedule (Weinstein regimen))
Acitretin	0.3–0.8 mg/kg/die (optimal 0.5 mg/kg/die)	Useful in pustular and acral psoriasis
Fumaric acid esters	Up to 1.2 g daily	
Adalimumab	80 mg at week 0, 40 mg at week 1, then 40 mg every 2 weeks	
Etanercept	50 mg biweekly for plaque psoriasis for 12 weeks, then 50 mg weekly	
	50 mg weekly for psoriatic arthritis	
Infliximab	5 mg/kg at weeks 0, 2, and 6 and every 8 weeks	
Golimumab	50 mg if body weight <100 kg, 100 mg if body weight >100 kg every 4 weeks	
Ustekinumab	45 mg if body weight <100 kg, 90 mg if body weight >100 kg at week 0, at week 4, and every 12 weeks	

Recommended doses for both topical and systemic therapies

antiproliferative and anti-inflammatory effects and is a useful drug in rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, sarcoidosis, immunobullous disorders, and psoriasis. MTX has an antiproliferative effect as a folic acid antagonist on the basis of its competitive binding to dihydrofolate reductase. Despite these well-known pharmacological effects, the mechanism of action of MTX at low dose in the treatment of psoriasis remains unclear, having both *immunomodulatory* and profound *anti-inflammatory* properties.

Table 81.2 Common potential adverse events related to the use of systemic conventional therapies and biologics

Agents	Potential occurrence of important side effects				
	Very frequent	Frequent	Occasional	Rare	Very rare
Infliximab	Infusion reactions	Infections, headache, flush, pruritus, urticaria, fever, transaminase elevation	Serum-sickness-like disease, (cutaneous) lupus erythematodes syndrome, severe infections, tuberculosis, anaphylactoid reaction	Opportunistic infections, pancytopenia, vasculitis, demyelinating diseases	
Etanercept	Injection-site reactions, infections (upper respiratory tract, bronchitis, skin infections)	Pruritus	Thrombocytopenia, urticaria, angio-oedema, severe infections (pneumonia, cellulitis, sepsis), weight gain	Anaemia, leucopenia, neutropenia, pancytopenia, vasculitis, subacute and discoid lupus erythematodes, demyelinating disease, tuberculosis	Aplastic anaemia
Adalimumab	Injection-site reaction	Upper respiratory tract infections, sinusitis, injection-site reactions, headache, and rash	Tuberculosis		Drug-induced lupus, lymphoma
Golimumab	Upper respiratory tract infection, viral infections, bronchitis, superficial fungal infections, sinusitis, injection-site reaction	Hypertension, dizziness, paresthesia, constipation, liver enzyme elevations		Vasculitis, other infections and infestations	
Ustekinumab	Upper respiratory infections, headache, tiredness, injection-site reaction, back pain, fatigue	Itching, joint pain, muscle pain or tenderness, injection-site reaction, skin rash or rashes, sore throat, urticaria, depression, diarrhoea, hypersensitivity reaction, dizziness	Other infections	Facial palsy	

(continued)

Table 81.2 (continued)

Agents	Potential occurrence of important side effects				
	Very frequent	Frequent	Occasional	Rare	Very rare
Cyclosporine	None	Renal failure (dose dependent); danger of irreversible renal damage (long-term therapy); hypertension; gingival hyperplasia; reversible hepatogastric complaints (dose dependent); tremor; weariness; headache; burning sensation in hands and feet; reversible elevated blood lipids (especially in combination with corticosteroids); hypertrichosis	Seizures, gastrointestinal ulcerations, weight gain, hyperglycaemia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, acne, anaemia	Ischemic heart disease, pancreatitis, motor polyneuropathy, impaired vision, defective hearing, central ataxia, myopathy, erythema, itching, leucopenia, thrombocytopenia	Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome, colitis (isolated cases), papillary oedema (isolated cases), idiopathic intracranial hypertension (isolated cases)
Methotrexate	Nausea, malaise, hair loss	Elevated transaminases, bone marrow suppression, gastrointestinal ulcers	Fever, chills, depression, infections	Nephrotoxicity, liver fibrosis, and cirrhosis	Interstitial pneumonia, alveolitis
Retinoids	Vitamin A toxicity (xerosis, cheilitis)	Conjunctival inflammation (cave: contact lenses), hair loss, photosensitivity, hyperlipidaemia	Muscle, joint, and bone pain, retinoid dermatitis	Gastrointestinal complaints, hepatitis, jaundice. Bone changes with long-term therapy	Idiopathic intracranial hypertension, decreased colour vision, and impaired night vision
Fumaric acid esters	Diarrhoea, flush	Abdominal cramps, flatulence, lymphocytopenia, eosinophilia	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes	Isolated increases in ALT or bilirubin	

Table 81.3 Screening tests required for systemic drug prescription

Agent	Full blood count	Liver enzymes	Serum creatinine	Urine sediment	Pregnancy test (urine)	HBV/ HCV	Serum albumin	PIIINP where available	Electrolytes	Uric acid	Cholesterol, triglycerides	Magnesium	Fasting blood sugar	ESR, CRP	HIV	TB gold quanti-feron
MTX	X	X	X	X	X	X	X	X			X					
Cya	X	X	X	X	X				X	X	X	X				
Retinoids	X	X	X		X						X		X			
FAEs	X	X	X	X	X						X					
Adalimumab	X	X	X	X	X	X					X			X	X	X
Etanercept	x	X	X	X	X	X					X			X	X	X
Infliximab	X	X	X	X	X	X					X			X	X	X
Ustekinumab	X	X	X	X	X	X					X			X	X	X
Golimumab	X	X	X	X	X	X					X			X	X	X

MTX is indicated in moderate-to-severe psoriasis, in symptomatic control of recalcitrant psoriasis not responsive to topical therapy or other systemic therapies such as PUVA or retinoids, in psoriatic erythroderma, in psoriatic arthritis, in acute pustular psoriasis (von Zumbusch type), in localized pustular psoriasis, and in psoriasis that affects certain areas of body so that normal function and employment are prevented. Two dosage schedules for MTX are commonly used: single weekly oral, intravenous, intramuscular, or subcutaneous administration or intermittent oral schedule (Weinstein regimen) of three divided doses over a 24-h period each week (every 12 h three times in 1 week).

An *initial test dose* of 2.5–5.0 mg should be used first to detect any unusual predisposition to toxic effects (Table 81.1).

Several studies have been published concerning the efficacy of MTX in psoriasis. Heydendael et al. (2003) compared MTX to cyclosporine without a placebo arm. At 12 weeks PASI 75 was 60 % for MTX and 71 % for cyclosporine. Similarly, Flytstrom et al. (2008) also compared MTX to cyclosporine without a placebo arm. The mean PASI change from baseline was 72 % in the cyclosporine group and 58 % in the MTX arm.

All forms of therapy (phototherapy, photochemotherapy, MTX, oral retinoids, cyclosporine) for moderate-to-severe psoriasis have varying degrees of long-term toxicity. Although the risk of side effects could increase when MTX is combined with other systemic drugs, in selective cases combination or rotational therapy should be considered in the management of psoriasis. The rotational therapy concept recommends switching from one modality to another before reaching a cumulative toxic range. The first concern on MTX long-term treatment is that hepatotoxicity may occur at approximately 1.0–1.5 g of cumulative dose. Thus, if MTX is discontinued at about 1.0–1.5 g and patients are rotated to another modality, the risk of long-term liver changes can be minimized by providing a "rest period" for several years.

The most commonly reported adverse reactions to the doses of MTX used in the treatment of psoriasis include malaise, bone marrow toxicity, stomatitis, gastrointestinal intolerance, hepatotoxicity, fevers, and alopecia. The severity of side effects is, in general, dose dependent and related to renal and hematologic function. Leucovorin calcium (citrovorum factor or folinic acid) is the only antidote for the hematologic toxic effects of MTX. When an overdose of MTX is suspected for any reason, including minimal renal impairment, the patient should be given leucovorin immediately (Tables 81.2 and 81.3).

Fumaric Acid Esters

Fumaric acid ester (FAE) therapy has proved to be safe and effective in patients with severe psoriasis vulgaris. Fumaric acid and its esters are a group of simple structured compounds. Because fumaric acid itself is poorly absorbed after oral intake, esters are used for treatment. FAEs are almost completely absorbed in the small intestine. Dimethylfumarate is rapidly hydrolyzed by esterases to monomethylfumarate, which is regarded as the active metabolite. The composition of this mixture includes dimethylfumarate, calcium, magnesium, and zinc salts of monoethyl hydrogen fumarate. FAEs, mainly dimethylfumarate, have been successfully utilized with evidence of high clinical efficacy in several double-blind placebo-controlled studies, on patients who had previous failed systemic therapies, such as methotrexate, cyclosporine A, etretinate, and others. Although the mode of action of FAEs in the treatment of psoriasis is not fully understood, recent experimental data reported that FAEs are able to improve psoriasis by modulating leucocyte, keratinocyte, and/or endothelial functions. The first randomized, double-blind trial of FAE therapy for psoriasis was published by Nugteren-Huying et al. in 1990. Three groups consisting of a total of 39 patients with psoriasis were treated for 4 months with FAEs. The first group of patients received a mixture of dimethylfumarate and monoethylfumarate (calcium, magnesium, and zinc salts), while the second group was treated with a mixture of octylhydrogenfumarate and monoethylfumarate as zinc and magnesium salts. Placebo tablets were given to the third group. The results showed a reduction in the lesional skin area of 68 % in the group treated with a combination of dimethylfumarate and monoethylfumarate, while the groups treated

with octylhydrogenfumarate and monoethylfumarate or with placebo showed only a marginal clinical response. There is a characteristic spectrum of adverse events in FAE treatment; therefore, it is important to monitor the patients during the course of therapy. The most frequently noted adverse events associated with FAE treatment are gastrointestinal complaints, which occur in more than two-thirds of patients. The symptoms vary from mild stomach upsets, increased frequency of stools, and tenesmus to stomach cramps, tympanites, and diarrhoea; these become most frequent between weeks 4 and 12. Flushing is seen in about one-third of patients treated with FAE. Symptoms include a sudden redness of the skin and a sensation of heat lasting between a few minutes and a few hours. Headaches may be associated. Frequency of flushing is greatest at the onset of therapy and decreases with prolonged treatment time (Tables 81.1, 81.2, and 81.3).

Biologic Agents

Biologic treatments for psoriasis include anti-TNF-alpha, anti-p40 agents, and anti-IL-17.

Patients suffering from moderate-to-severe psoriasis/PsA that do not tolerate or do not achieve sufficient results with at least two systemic treatments can benefit from a treatment with biological agents (Fig. 81.3). These agents, with their individual clinical profile, demonstrated to be effective in different aspects of the disease, including skin lesions, joint pain and swelling, enthesitis, and dactylitis resulting in a significant improvement either in mobility or in radiographic progression and quality of life parameters. Treatment with biologic agents increases the risk of latent tubercular infection reactivation (Tables 81.2 and 81.3).

Anti-TNF-Alpha

Etanercept

Etanercept is a fully human dimeric fusion protein comprising the extracellular domain of the TNF-α p75 receptor fused to the inert FC portion of IgG1 molecule. Differently from monoclonal antibodies, etanercept is not associated with the development of neutralizing antibodies. This ensures a sustained and prolonged efficacy without loss of response. The FC portion of IgG1 serves to stabilize etanercept and prolongs the median half-life which is 4.8 days. For the treatment of psoriasis, etanercept is prescribed at 50 mg dose twice weekly, for 12 weeks followed by 50 mg weekly, while for psoriatic arthritis is administered at fixed dose of 50 mg weekly (Table 81.1).

Infliximab

This agent is a chimeric anti-tumour necrosis factor-α (TNF-α) monoclonal IgG1 antibody, with high affinity and avidity for soluble and cell surface transmembrane forms of TNF-α. Infliximab is prescribed at the dose of 5 mg/kg of body weight, showing rapid improvement from baseline. The regimen consists of an induction dosing with intravenous drip treatments over 2 h at weeks 0, 2, and 6 and a maintenance dosing with booster infusions at the same dosage every 8 weeks.

Adalimumab

Adalimumab is a fully human monoclonal antibody that binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab is prescribed as a subcutaneous injection at the standard dosing regimen: initial dose of 80 mg at week 0 that is followed by 40 mg at week 1, then 40 mg every 2 weeks.

Golimumab

Golimumab (GLB) is the last anti-TNF-α agent approved by the EMA (European Medicines Agency) and FDA (Food and Drug Administration) for the treatment of PsA. GLB is a fully human monoclonal antibody IgG1k neutralizing TNF-α. Randomized clinical trials demonstrated satisfactory efficacy of GLB in comparison to other anti-TNF-α agents in improving signs and symptoms of PsA and also in treating the structural damage caused by the disease. Actually, there are no data showing superiority of TNF-α inhibitors in combination with synthetic DMARDs (disease-modifying

antirheumatic drug) versus TNF-α inhibitor monotherapy, and no comparative studies between anti-TNF-α therapies are available.

Certolizumab

Certolizumab is a polyethylene glycolylated (PEGylated) Fab fragment of a humanized monoclonal antibody that binds and neutralizes human TNF-α. The PEG moiety of the Fab fragment markedly increases the half-life of certolizumab and confers to the drug a unique structure that differs from the other anti-TNF-α agents. Additionally to the PEGylated portion, the smaller molecular weight is responsible of a higher penetration into inflamed tissues. In premarketing studies, certolizumab has been tested at an initial dose of 400 mg followed by 200 or 400 mg every 2 weeks.

Anti-p40 Agents

Briakinumab and Ustekinumab

In the recent years, two antibodies targeting the p40 subunit have been developed: ustekinumab and briakinumab. Briakinumab (abt-874) is a fully humanized antibody that reached a preregistration status, but its development has been discontinued. Conversely, ustekinumab is approved for the treatment of plaque-type psoriasis at the dosage of 45 mg or 90 mg according to patient's weight lower or higher than 100 kg, at week 0, at week 4, and every 12 weeks. Large phase II and phase III trials proved ustekinumab effective and safe in the treatment of psoriasis.

The major phase III trials comparing ustekinumab with either placebo in PHOENIX I/II or etanercept in ACCEPT have confirmed superior safety and efficacy.

PHOENIX I, a 76-week, randomized, double-blind, placebo-controlled, multicenter study enrolling 766 patients, showed 67.1 and 66.4 % of subjects receiving 45 and 90 mg dosages, respectively, who achieved 75 % of improvement by the Psoriasis Area and Severity Index (PASI-75). There results were subsequently confirmed by PHOENIX II study and ACCEPT.

IL-17-Targeting Agents

Three agents targeting the IL-17 signalling have been tested in premarketing phase for the treatment of psoriasis. These biologics, ixekizumab, secukinumab, and brodalumab successfully passed phase II clinical trials and are presently investigated in phase III trials. Ixekizumab and secukinumab are fully humanized antibodies neutralizing IL-17, while brodalumab is a fully humanized antibody binding to IL-17R.

Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody (mAb) neutralizing IL-17A. The safety and efficacy of ixekizumab was evaluated in a phase II, double-blind, placebo-controlled trial with 142 patients affected by moderate-to-severe plaque-type psoriasis. Patients were randomized into five groups receiving 150, 75, 25 mg, 10 mg ixekizumab or placebo, subcutaneously at 0, 2, 4, 8, 12, and 16 weeks. The achievement of 75 % reduction of PASI after 12 weeks of treatment constituted the primary endpoint of the study occurring in 82.1, 82.8, 76.7, 29, and 7.7 % of patients treated with 150, 75, 25, 10 mg ixekizumab or placebo, respectively.

Brodalumab

Brodalumab is a human mAb blocking IL-17RA, the receptor subunit shared by IL-17A, IL-17F, and IL-17A/F heterodimer ligands. The antagonism of IL-17 signalling by brodalumab was initially proven effective in inducing clinical, histologic, and genomic resolution of psoriasis after only 1 week of treatment in a phase I, proof-of-concept study enrolling 10 patients with psoriasis. Further substantiating the efficacy is a more recent phase II, randomized, double-blind, placebo-controlled, dose-ranging study involving 198 patients randomly assigned to receive subcutaneous brodalumab at the dosage of 280 mg monthly or 70, 140, 210 mg brodalumab or placebo at weeks 0, 1, 2, 4, 6, 8, and 10. This 12-week study assessed the efficacy of brodalumab in treating psoriasis with a mean percentage improvement of 45, 85.9, 86.3, 76, and 16 % of PASI score using

280, 210, 140, 70 mg, or placebo, respectively ($p<0.001$ for all comparison versus placebo). Common adverse events occurred with greater frequency in the high-dose brodalumab group; among the serious adverse events, two cases of mild neutropenia (grade III) were reported.

Secukinumab

Secukinumab (AIN 457) is human IgG1κ that neutralizes IL-17A. A phase II, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of different subcutaneous doses of secukinumab (single dose of 25 mg or monthly administration of 25, 75, or 150 mg) compared to placebo.

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Purpuras

82

Torello M. Lotti, Lara Tripo, Alice Garzitto, Aldona Pietrzak, and Ilaria Ghersetich

Key Points

- Purpura is a group of diseases entity characterised by macules and plaques that manifest as skin discoloration caused by extravasation of red blood cells.
- Clinically, purpuras are subdivided into three main types: palpable purpura, non-palpable purpura and capillaritis of unknown cause.
- Different treatments are reserved for palpable purpura, non-palpable purpuras and capillaritis of unknown cause.

Definition and Epidemiology

Purpura is a disease entity characterised by macules. By definition, macules are flat skin lesions not raised above the surrounding skin. Purpura manifests as skin discoloration caused by extravasation of red blood cells.

Pressure by fingers or diascopy fails to blanch the purpuric lesion (Fig. 82.1), thus distinguishing it from erythema and telangiectasia. Purpuric lesions vary in colour from purple to bluish-red or brown with evolution through a greenish-yellow or a brownish-yellow hue due to intradermal chemical degradation of haemoglobin into haemosiderin deposits. Haemosiderin deposits with coexisting chronic inflammation might stimulate melanogenesis. Clinically, purpuras are subdivided into three main types: palpable purpura, non-palpable purpura and capillaritis of unknown cause.

Palpable Purpura: Basic Concepts of Pathogenesis

This clinical condition is mainly related to cutaneous necrotising vasculitis (CNV) characterised by angiocentric segmental inflammation, endothelial cell swelling and fibrinoid necrosis of blood vessel walls. The skin is often the only organ apparently involved; nevertheless, clinically relevant systemic involvement occurs in many cases and skin lesions may just represent the initial signs of a systemic

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_82, © Springer-Verlag Berlin Heidelberg 2015

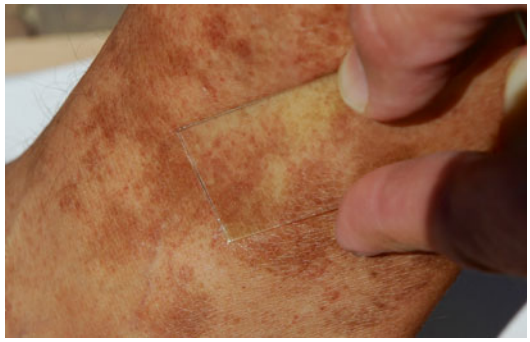

Fig. 82.1 Purpuric lesions not blanching during diascopy

disease. CNV may also represent the cutaneous manifestation of any systemic vasculitis.

The disorder equally affects patients of both sexes and at all ages; approximately 10 % of cases occur in children. No genetic factors have been recognised.

Many incidental factors, especially drugs (insulin, penicillin, sulphonamides, etc.), chemicals (insecticides, petroleum products), foods (e.g., milk proteins) and infections (viral, bacterial, fungal, protozoan, helminthic), should be considered as the causes of CNV.

CNV has been reported in association with coexisting diseases (e.g., collagen vascular diseases, hyperglobulinaemic purpura, cryoglobulinaemia, inflammatory bowel disease, malignant neoplasm, cystic fibrosis, etc.). In many cases the cause of CNV remains unknown (i.e., in Henoch–Schönlein purpura, urticarial vasculitis, erythema elevatum diutinum, nodular vasculitis, atrophie blanche, cutaneous polyarteritis nodosa).

Although blood vessels of any size may be affected in systemic vasculitis, CNV usually occurs in small venules (post-capillary venules), being characterised by two main histological patterns: a leukocytoclastic form with a presumed pathogenesis mediated by immune complexes and a lymphomonocytic form, in which a cell-mediated pathogenesis is implicated.

More recent data seem also to suggest the participation of a secondary cell-mediated immune response in the late phase of the leukocytoclastic CNV.

In particular, a role of gamma/delta T cells has been suggested in CNV that may indicate multiple potential functions of this subset of T cells in the immune system of the skin. Microscopic examinations of changes show deposition of fibrinogen in the walls of the post-capillary venules in the upper dermis, along with a perivenular and intramural inflammatory infiltrate consisting predominantly of neutrophils. Most T cells infiltrating tissues and organs undergoing fibrosis have the potential to produce high levels of interleukin 4, which is particularly true for the CD8+ or CD4+ CD8+ double-positive T-cell subsets.

As mentioned above, strong experimental and clinical evidence suggests that the leukocytoclastic form of CNV is an immune complex disease. After antigenic exposure, soluble antigen-antibody complexes are formed. In the presence of antigen excess, these complexes can precipitate in the vessel wall. Following the deposition of antigen-antibody complexes, a complex series of events is initiated, ultimately leading to vessel wall damage, fluid and red blood cell *leakage* and ischaemia. In addition to the immunologic events, several non-immunologic factors may play a role in disease expression. Vasoactive amines, especially endogenous histamine, can precipitate the deposition of complexes. Endothelial cells also appear to be primarily involved. These cells may produce and release cytokines that enhance the inflammatory response. Finally, local factors, such as anatomic location and viscosity, may help explain the clinical manifestations of a given vasculitic syndrome.

The fibrinolytic system is responsible for the degradation of fibrin into fibrin degradation products.

Cutaneous fibrinolytic activity is usually increased in the early form of CNV (characterised clinically by urticarial wheals) and reduced or absent in the late phase (clinically manifested by palpable purpura). This may lead to microvascular thrombosis due to excessive intra-/perivascular deposition of fibrin, with consequent tissue hypoxia and necrosis.

Palpable purpura is the major clinical presentation of CNV, whereas erythematous macules, wheals, papules, blisters, large palpable nodules, ecchymoses, pustules, haemorrhagic vesicles, ulcers and a netlike pattern of the skin (livedo reticularis) are less common manifestations (Fig. 82.2).

The eruption most often appears on the legs, persisting for 1–4 weeks, leaving hyperpigmentation and/or atrophic scars, and may be recurrent for years.

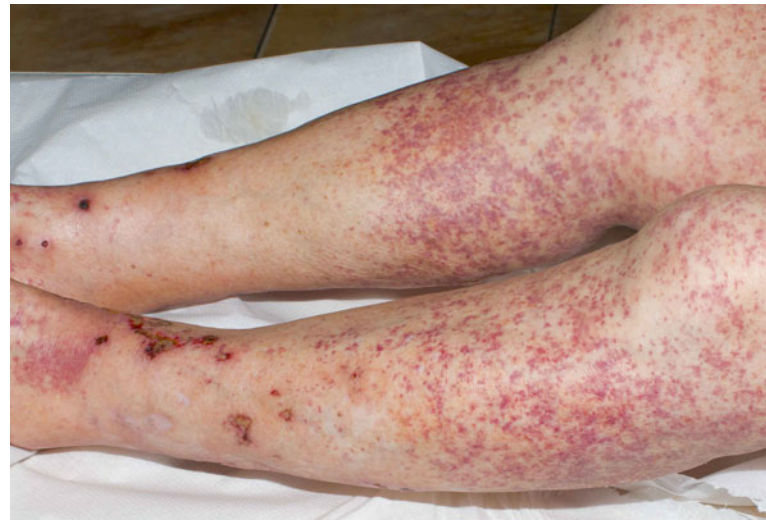

Fig. 82.2 Cutaneous necrotising vasculitis. Multiple erythematous macules and necrotic ulcers are present on the shins

Non-palpable Purpura: Basic Concepts of Pathogenesis

Non-palpable purpura is characterised by the distinctive clinical feature of cutaneous non-infiltrated haemorrhagic spots (Fig. 82.3).

Non-palpable purpura is more frequently observed in relation to platelet and vascular tissue alterations (often coexistent), and in such cases, it is frequently characterised by simultaneous gingival bleeding and microhaematuria. Coagulation disturbances, instead, are manifested more frequently in cases with internal haemorrhage (i.e., visceral, intra-articular) that usually lasts for a long time. In dermatological clinical practice, platelet and vascular tissue disorders are often associated, and the patient commonly presents with petechiae, generally without relationship to previous trauma, often accompanied by gingival bleeding and/or micro- or macro-haematuria of recent onset.

One of the most common platelet alterations is an autoimmune disorder called idiopathic thrombocytopenic purpura (ITP). The condition results in immunologic destruction of normal platelets due to the presence of anti-platelet antibodies in the blood. It often occurs in children, being the most common cause of bleeding diathesis in childhood. The onset is associated with a wide range of infections, and recent genetic studies indicate the relationship between disease susceptibility and some genetic polymorphisms. An acute form is likely to resolve spontaneously.

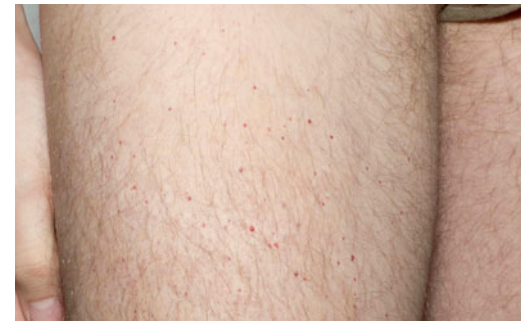

Fig. 82.3 Small (1–2 mm) haemorrhagic macules on the thigh

Coagulation disorders can be inherited (like haemophilias or von Willebrand disease) or acquired and are manifested by deep haematomas and gastrointestinal or intra-articular haemorrhage that generally lasts for several days. In these cases family history and the report of prolonged bleeding after tonsillectomy or dental extraction may be helpful for the diagnosis; however, the family history is usually non-contributory in one-third of haemophiliacs and in all patients with acquired coagulation disorders.

The 'vascular' purpuras, clinically polymorphous, are not usually associated with extracutaneous bleeding, with the exception of the pattern of 'relapsing juvenile epistaxis' (with nasal

bleeding) and the pattern of 'hereditary haemorrhagic telangiectasia' (with possible visceral bleeding).

Careful physical examination may be important for the diagnosis based on the criteria summarised in Table 82.1, together with the information obtained from the diagnostic tests listed in Table 82.2.

Capillaritis of Unknown Cause: Basic Concepts of Pathogenesis

Capillaritis of unknown cause (CUC) is a group of dermatoses whose aetiology is unknown. The fundamental clinical characteristics of CUC consist of red-brownish pigmentation, particularly on the lower extremities. These disorders are much more common in males. Familial incidence has been reported. Histologically CUCs are all similar, the histological examination revealing lymphomonocytic perivascular infiltrate confined to the vessels in the upper dermis with endothelial swelling, extravasation of red blood cells and, in old lesions, haemosiderin deposits in macrophages.

Recent histochemical and ultrastructural studies have suggested that a lymphocyte-mediated immune reaction evoked by unknown circulating antigens might play an important role in the pathogenic mechanism. The group of CUC includes some clinically autonomic varieties, such as Schamberg's disease (Fig. 82.4), eczematide-like purpura of Doucas and Kapetanakis, pigmented

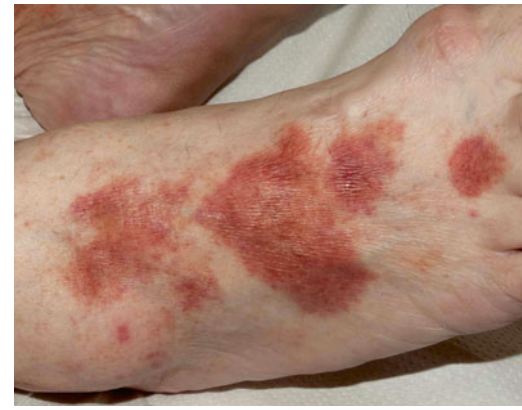

Fig. 82.4 Schamberg purpura. Brownish-red-orange, irregular macules varying in size on the dorsum of the foot and shin. No symptoms of venous insufficiency are present

Table 82.1 Clinical criteria for differential diagnosis among purpuras related to platelet, vascular tissue and coagulative alterations

	Platelet alterations	Vascular tissue alterations	Coagulation disturbances
Sex	Both	Generally women	Generally men
Family history	Generally negative	Often positive	Generally positive
Past history (bleeding)	Generally negative	Often positive	Generally positive
Outbreak	Spontaneous or microtrauma	Spontaneous or microtrauma	Traumatic or spontaneous
Systemic manifestations	Gums, gastrointestinal or genitourinary apparatus	Nasal mucous membrane (males)	Large joints, muscles, visceral organs
Kind of bleeding	Sudden, short duration	Short duration	Long duration (days)

Table 82.2 Principal diagnostic tests in cutaneous and systemic haemorrhagic diseases

Tests	Platelet alterations	Vascular tissue alterations	Coagulation disturbances
Bleeding time	Lengthened	Normal or lengthened	Normal
Platelet count	Sometimes decreased	Normal	Normal
Functional platelet deficiency	Possible	Absent	Absent
Negative pressure test	Positive	Positive	Negative
Hammer test	Positive	Positive	Negative
Hess test	Negative	Often positive	Negative
Partial thromboplastin time	Normal	Normal	Altered
Prothrombin time	Normal	Normal	Altered

purpuric lichenoid dermatosis of Gougerot and Blum, lichen aureus, purpura annularis telangiectodes and purpura telangiectasia arciformis.

Other Purpuras of Dermatological Interest

Senile Purpura

SP is a quite common, benign dermatosis affecting >10 % of individuals over the age of 50. The condition is caused by age-related loss of supportive tissue and damage to the small blood vessels in the skin. It manifests as non-palpable purpura and most complaints are associated with cosmetic issue.

Amyloidosis Purpura

In amyloidosis, purpura may occur because of amyloid deposits within vessel walls, platelet changes or liver disease. The lesions are most commonly located on the eyelids, nose, periorbital region, mouth and neck.

Contact Purpura

A list of substances capable of causing contact purpura includes khaki clothing, azo dyes in clothing, various rubber additives and optical whiteners. In contact purpura, the lesions may involve areas wider than those of actual contact (Fig. 82.5a, b).

Gravitational Purpura

This purpura is often a consequence of chronic venous hypertension of the legs.

It occurs most frequently in adult men. The characteristic clinical feature of the dermatosis is the presence of yellowish-brown, brownish or bluish-violet spots on the lower legs. The lesion may extend to the dorsa of the feet and toes. Oedema, ulceration and sclerosis may be associated.

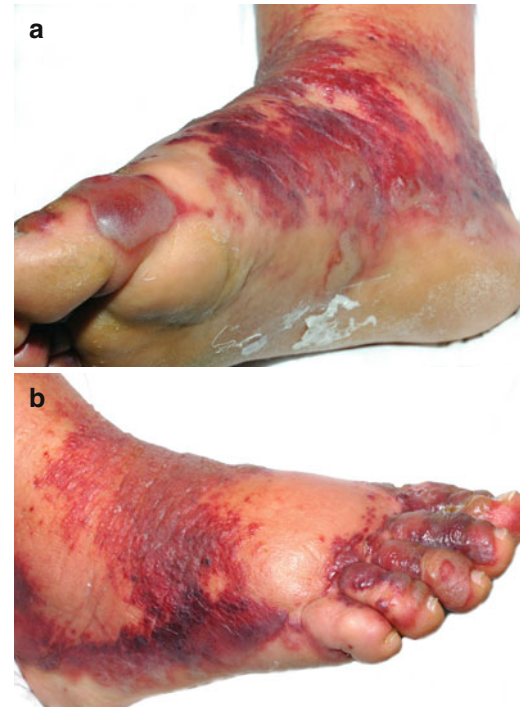

Fig. 82.5 (**a**) and (**b**) Contact purpura caused by direct contact with hygroscopic granules used for protection of the shoes

Neonatal Purpura

Neonatal purpura may be due to an accentuation of the normal fall of prothrombin within the first week of life. Nowadays the widespread use of vitamin K has reduced its incidence.

Purpura also may be associated with the Wiskott-Aldrich syndrome or with the neonatal rubella syndrome. It may also occur in a child whose mother has systemic lupus erythematosus.

Gardner–Diamond Syndrome

In the Gardner–Diamond syndrome (psychogenic purpura, painful bruising syndrome, autoerythrocyte sensitisation syndrome), the onset of painful ecchymotic lesions usually occurs in middle-aged women with hysterical personality after acute psychoemotional stress, often in areas subjected to microtrauma. The patients may experience concomitant recurrent epistaxis and visceral bleeding.

Initially it was thought that extravasated red blood cells might stimulate the formation of skin-sensitising antibodies, but more recent studies gave negative results. Skin tests with autologous blood cells have been reported to reproduce clinical lesions, but only when the patient had been previously informed about the expected reaction, suggesting a psychogenic origin of this disease. Recent research has shown that this purpuric condition may be caused by systemic or, more often, local (cutaneous) abnormal activation of the fibrinolytic system due to excessive release of tissue-type plasminogen activator from endothelial cells, finally leading to cutaneous haemorrhage.

Main Investigations in Palpable Purpura (CNV)

In patients with CNV, a laboratory screening is always required to confirm the diagnosis and pathogenesis and to determine the extent of involvement of systemic vasculitis and/or the existence of underlying associated diseases.

Laboratory evaluation includes histopathological and immunofluorescence studies, blood tests and urinalysis.

In the leukocytoclastic form, direct immunofluorescence of the lesional skin may show immunoglobulins, complement components and fibrin deposits in the walls of blood vessels and around them; immunoglobulin G (IgG) rather than IgM are more likely to be present when there is an underlying collagen vascular disease, and IgA may be indicative of Henoch-Schönlein purpura.

Decreased levels of complement components are often found in leukocytoclastic CNV associated with rheumatoid arthritis (C1, C4, C2), systemic lupus erythematous (C1q, C4, C2, C3, factor B, C9), cryoglobulinaemia and Sjogren's syndrome. Circulating immune complexes, rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies and cryoglobulins can be detected with antistreptolysin antibodies and hepatitis B (C and A) surface antigens. Moreover, in patients in whom systemic syndromes are being considered, tests such as antineutrophil cytoplasmic antibody (ANCA) for Wegener's granulomatosis may be diagnostically helpful. Urine analysis may reveal proteinuria, haematuria and cylindruria caused by a possible renal involvement. In the lymphocytic form of CNV, these laboratory tests are usually normal or negative.

General Principles of Treatment

Different treatments are reserved for palpable and non-palpable purpuras and capillaritis of unknown cause (Table 82.3).

General Principles of Treatment of Palpable Purpura

In patients with CNV, when possible, identification and removal of causative agents (drugs, chemicals, infections, and foods) represents the best aetiological treatment, followed by rapid clearance of skin lesions, so that no other treatment is necessary. In the remaining cases, local and systemic therapies are recommended.

Local Treatments

Topical therapy (corticosteroid creams) may be helpful in some cases. Gradient support stockings may be useful for lesions on the legs with coexistent chronic venous hypertension.

Systemic Treatment

These treatments include corticosteroids, nonsteroidal anti-inflammatory drugs, colchicine, dapsone, potassium iodide, fibrinolytic agents, aminocaproic acid, immunosuppressive agents, drugs reducing platelet aggregation and antihistamines.

Systemic treatment with oral corticosteroids (prednisone 60–80 mg/day) is advised in the majority of patients for 7–15 days in the acute phase (especially in Henoch-Schönlein purpura, urticarial vasculitis, Behçet's disease).

Table 82.3 Different treatments for palpable and non-palpable purpuras and capillaritis of unknown cause

Palpable purpura	Non-palpable purpura	Capillaritis of unknown cause
In the acute phase (especially in Henoch Schönlein purpura, urticarial vasculitis, Behçet's disease)	In drug-induced purpura	Hydrocortisone creams
Oral prednisone (60–80 mg/day) for 7–15 days	A short treatment (3–7 days) of oral prednisone (0.5–1 mg/kg per day)	PUVA treatment
Vasculitis with more persistent or necrotic lesions	When bleeding is observed in cases with severe thrombocytopenia	Narrow-band ultraviolet B therapy
Acetylsalicylic acid (150–1,000 mg/day) and indomethacin (25–150 mg/day)	Platelet transfusion	In selected cases with reduced cutaneous and plasma fibrinolytic activity
In the chronic forms	Haemophilias	Stanozolol (3–6 mg/day) for 1–3 months or pentoxifylline (300 mg day) for 8 weeks
Oral colchicine (0.6 mg twice daily)	Supplementation of deficient clotting factor	
Erythema elevatum diutinum	Idiopathic thrombocytopenic purpura	
Dapsone (50–200 mg day)	Corticosteroids or immunosuppressants, intravenous immunoglobulins, monoclonal antibodies (e.g., rituximab), splenectomy or new drugs like thrombopoietin receptor agonists (romiplostim, eltrombopag)	
Nodular vasculitis	Disseminated intravascular coagulation	
Potassium iodide (0.3–1.5 g four times daily)	High doses of intravenous heparin (20,000–30,000 U/day) plus antithrombin III (500–1,000 U/day)	
In various types of hypofibrinolytic vasculitis	Hyperfibrinolytic conditions	
Stanozolol (5 mg twice daily) or phenformin hydrochloride (50 mg twice daily) plus ethylestrenol (2 mg four times daily) or heparin (5,000 units twice daily), mesoglycans (50–100 mg/day) or defibrotide (700 mg i.m./day)	Aprotinin (500,000 U) or oral ε-aminocaproic acid preparations (4–6 g/day)	
In the vasculitis associated with livedo reticularis and the livedoid vasculitis	Thrombocytosis-dependent purpuras	
Low molecular weight dextran (500 ml i.v./day)	Anti-aggregating agents [acetylsalicylic acid (100–300 mg/day), ticlopidine hydrochloride (250–500 mg/day), dipyridamole (400–800 mg/day)]	
In the hyperfibrinolytic states of vasculitis	Purpuras due to both microangiopathic and angiophilic microvascular defects	
Aminocaproic acid (8–16 g/day for many months)	Systemic and/or local corticosteroids and administration of vitamin PP (100–500 mg/day) or vitamin C (1–2 g/day), etamsylate (1–1.5 g/day), calcium dobesilate (1–2 g/day)	
In patients with CNV with a rapidly progressive course or with systemic involvement which is not controlled with corticosteroids		

(continued)

Table 82.3 (continued)

Palpable purpura	Non-palpable purpura	Capillaritis of unknown cause
Immunosuppressive agents: cyclophosphamide (2 mg/kg/day), methotrexate (5–25 mg/week), azathioprine (50–200 mg/day) and cyclosporin A (3–5 mg/kg/day)		
In the course of vasculitis induced by immune complexes with concomitant arterial disease		
Drugs reducing platelet aggregation – dipyridamole (400–800 mg/day), acetylsalicylic acid (100–300 mg/day, ticlopidine hydrochloride (250–500 mg/day) – and plasmapheresis		

Nonsteroidal anti-inflammatory drugs, such as acetylsalicylic acid (150–1,000 mg/day) and indomethacin (25–150 mg/day), have been used for vasculitis with more persistent or necrotic lesions.

Some cases of urticarial vasculitis have responded to indomethacin.

Phenylbutazone (400–600 mg/day), oxyphenbutazone (300–400 mg/day) and ibuprofen (600–900 mg/day) are indicated for thrombophlebitis in the course of nodular vasculitis.

Oral colchicine, which inhibits neutrophil chemotaxis, in doses of 0.6 mg twice daily may be helpful in the chronic forms of the disease.

Dapsone (50–200 mg/day) has also been used usually in patients with skin involvement alone (especially in patients with erythema elevatum diutinum).

Potassium iodide (0.3–1.5 g four times daily) is useful for nodular vasculitis.

Fibrinolytic agents can be used in patients with reduction of plasma and/or cutaneous fibrinolytic activity.

Stanozolol (5 mg twice daily) or phenformin hydrochloride (50 mg twice daily) plus ethylestrenol (2 mg four times daily) can be administered for about a year.

Other fibrinolytic agents as heparin (5,000 U twice daily), mesoglycans (50–100 mg/day) and defibrotide (700 mg i.m./day) seem beneficial in various types of hypofibrinolytic vasculitis.

Low molecular weight dextran (500 ml i.v./day) is also indicated in the hypofibrinolytic phase of disease because of its fibrinolytic effect. This seems to produce beneficial effects in the vasculitis associated both with livedo reticularis and with the livedoid vasculitis.

Aminocaproic acid (8–16 g/day for many months) can be used in the hyperfibrinolytic states of CNV. Immunosuppressive agents such as cyclophosphamide (2 mg/kg per day or as a monthly intravenous pulse), methotrexate (5–25 mg/week), azathioprine (50–200 mg/day) and cyclosporin A (3.5 mg/kg per day) are effective, especially in patients with CNV with a rapidly/progressive course or with systemic involvement, which is not controlled with corticosteroids.

In the course of vasculitis induced by immune complexes with concomitant arterial disease, drugs reducing platelet aggregation – dipyridamole (400–800 mg/day), acetylsalicylic acid (100–300 mg/ day) and ticlopidine hydrochloride (250–500 mg/day) – and plasmapheresis can be used.

H1-antihistamines alone or in combination with H2-antihistamines are used to alleviate itch and to block histamine-induced venular endothelial gap formation with resultant trapping of immune complexes. The correction of local factors such as trauma, cold stasis and lymphoedema may also be important.

Experimental Treatments

Recently a patient with intractable systemic vasculitis has been treated with two monoclonal antibodies, Campath-1H and rat CD4.

General Principles of Treatment of Non-palpable Purpura

The treatment of various forms of non-palpable purpura is strictly dependent on their aetiopathogenesis.

Idiopathic thrombocytopenic purpura can be treated with corticosteroids or immunosuppressants, intravenous immunoglobulins, splenectomy or new drugs like thrombopoietin receptor agonists (romiplostim, eltrombopag). In spontaneous bleedings or when platelet counts are less than 10^3 per ml, platelet transfusion is a treatment of choice.

Haemophilias should be treated by regular infusions of deficient clotting factors.

In drug-induced purpura, it is necessary to stop the ingestion of the suspected drug(s). A short treatment (3–7 days) of oral prednisone (0.5–1 mg/kg per day) may be useful, above all in forms with immunological pathogenesis. When bleeding is observed in cases with severe thrombocytopenia, platelet transfusion may be indicated. Disseminated intravascular coagulation may be successfully treated with high doses of intravenous heparin (20,000–30,000 U/day) plus antithrombin III (500–1,000 U/day).

Hyperfibrinolytic conditions can be corrected by administration of aprotinin (500,000 U) or oral ε-aminocaproic acid preparations (4–6 g/day). Thrombocytosis-dependent purpuras may be advantageously treated with anti-aggregating agents – acetylsalicylic acid (100–300 mg/day), ticlopidine hydrochloride (250–500 mg/day) or dipyridamole (400–800 mg/day).

Purpuras due to microvascular defects both of microangiopathic and angiophilic origin require discontinuation of systemic and/or local corticosteroids (or, rarely, other presumably responsible drugs) and administration of vitamin PP (100–500 mg/day) or vitamin C (1–2 g/day) (scurvy), etamsylate (1–1.5 g/day) or calcium dobesilate (1–2 g/day).

General Principles of Treatment of Capillaritis of Unknown Cause

Capillaritis of unknown cause may require hydrocortisone creams, psoralen and ultraviolet A (PUVA) treatment or narrow-band ultraviolet B therapy.

In selected cases with reduced cutaneous and plasma fibrinolytic activity, oral stanozolol for 1–3 months or pentoxifylline (300 mg/day) for 8 weeks may result in complete clearance of purpuric lesions.

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Pyoderma Gangrenosum

83

Clio Dessinioti and Andreas D. Katsambas

Key Points

- Pyoderma gangrenosum (PG) is a rare, chronic, neutrophilic skin disease of unknown origin, characterized by painful, sterile, necrotic ulcers with violaceous undermined borders.
- PG is idiopathic in 40–50 % of patients; however, in the remaining cases, it may be associated with underlying diseases including ulcerative colitis, Crohn's disease, leukaemia, monoclonal gammopathy, rheumatoid arthritis and immunodeficiencies.
- PG has been reported as part of PAPA, PASH and PAPASH syndromes.
- Four clinical variants of PG have been described: ulcerative, pustular, bullous and vegetative.
- Extracutaneous pulmonary and splenic neutrophilic infiltrates may rarely occur in patients with PG.
- Despite the paucity of randomized, controlled trials evaluating treatments for PG and the lack of a standardized treatment algorithm, systemic corticosteroids and cyclosporine are often used for severe PG.
- PG may demonstrate a chronic, recalcitrant course posing a therapeutic challenge.

Definition and Epidemiology

Pyoderma gangrenosum (PG) is a rare, chronic, inflammatory dermatosis characterized by painful, sterile, necrotic ulcers with violaceous undermined borders. It was first described by Brocq in 1916 as 'phagédenisme géométrique'.

The incidence of PG is estimated to be 3–10 patients per million per year, affecting mainly patients aged 20–50 years old. It is extremely rare in the paediatric population, with only 4 % of patients being infants and children. Among the childhood cases of PG, 25 % are idiopathic, while familial PG has only rarely been reported.

There is a slight female preponderance. Fifty per cent of cases are associated with an underlying systemic disease, mainly inflammatory bowel disease (IBD), arthritis and lymphoproliferative disorders. PG may cause significant morbidity. Increasing age and male sex are associated with a poorer outcome.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_83, © Springer-Verlag Berlin Heidelberg 2015

Basic Concepts of Pathogenesis

PG is a neutrophilic dermatosis of unknown aetiology. It belongs to the group of neutrophilic dermatoses including Sweet's syndrome, subcorneal pustular dermatosis, erythema elevatum diutinum and Adamantiades-Behçet's disease. PG has been characterized as a cutaneous autoinflammatory disease. Autoinflammatory diseases are clinically characterized by recurrent sterile inflammation in affected organs, in the absence of high titres of circulating autoantibodies and autoreactive T cells.

Two cases of familial PG were described in two siblings with common variable immunodeficiency (CVID) with unaffected parents, suggesting an autosomal recessive mode of inheritance.

PAPA syndrome includes the clinical triad of PG, acne and pyogenic sterile arthritis. It is a rare autosomal dominant autoinflammatory syndrome, caused by mutations in the proline-serine-threonine-phosphatase protein 1 (*PSTPIP1*) gene (chromosome 15q24–25.1). PSTPIP1 has been shown to bind to pyrin, the protein mutated in familial Mediterranean fever linking both diseases to the same pathway. The mutations lead to a hyperphosphorylation of PSTPIP1, thus increasing its binding affinity to pyrin. As a result, pyrin loses its inhibitory effect on the signalling pathway that cleaves pro-interleukin (IL)-1ß into active IL-1ß. The overproduction of IL-1 beta in turn stimulates the release of proinflammatory cytokines and chemokines, leading to the recruitment and activation of neutrophils.

PASH syndrome (PG, acne, hidradenitis suppurativa) is similar to PAPA but lacks arthritis and does not share the same genetic basis (an increased number of CCTG microsatellite repeats in the *PSTPIP1* promoter region were reported in both patients of Braun-Falco et al). PAPASH syndrome with pyogenic arthritis, PG, acne and hidradenitis suppurativa in a 16-year-old patient was reported by Marzano et al.

Drug-induced PG has been reported with granulocyte colony-stimulating factor, interferon, gefitinib and propylthiouracil.

Clinical Presentation and Variants

The clinical manifestations of PG are outlined in Table 83.1. Four clinical variants of PG have been described: classic (ulcerative), pustular, bullous and vegetative (Fig. 83.1).

Ulcerative PG classically presents as a painful pustule or nodule that becomes a progressively enlarging, painful ulcer with erythematous to violaceous, raised, undermined, irregular borders. Lesions may be single or multiple, coalescing to multicentric, irregular ulcerations. PG most commonly affects the legs, but it may also affect any body area. Ulcers heal with atrophic pigmented scars. PG is accompanied by the phenomenon of pathergy in 20 % of patients, i.e. the development of new lesions or aggravation of existing ones following injury with a sharp object. Associated symptoms include fever, especially during the acute onset of PG, malaise, myalgias and arthralgias.

Table 83.1 Clinical manifestations of pyoderma gangrenosum

Cutaneous	
Ulcerative (classic form)	Very painful ulceration with undermined borders and purulent base
Pustular	Discrete painful pustules surrounded by an erythematous halo
Bullous	Painful bullae surrounded by an erythematous halo
Vegetative	Superficial ulceration without undermined borders or purulent base, slowly progressive
Peristomal	Ulcers in the peristomal area in patients with IBD
Mucosal	Oral, vulvar, penile or scrotal ulcers
Extracutaneous	
Pulmonary system	Pleural effusion, pulmonary cavitation and neutrophilic infiltration
Gastrointestinal	Splenic neutrophilic infiltrates
Cardiovascular	
Skeletal	
Neurological	

IBD inflammatory bowel disease

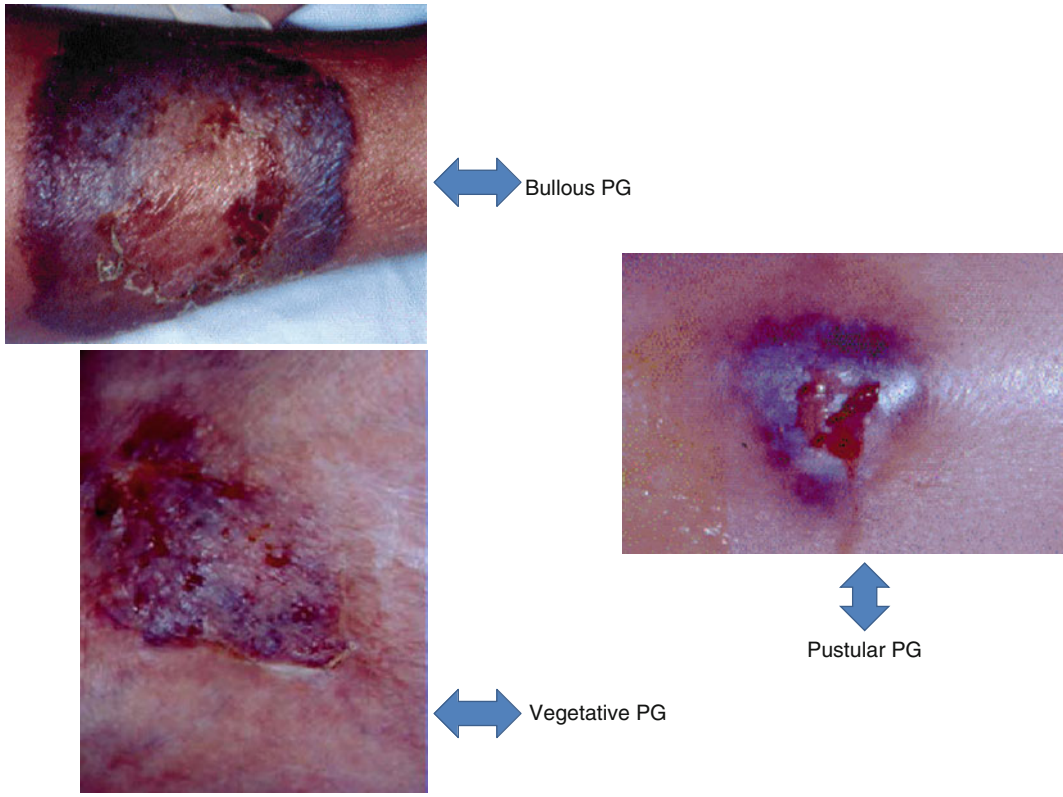

Fig. 83.1 Pustular, bullous and vegetative clinical variants of PG

The pustular variant is characterized by multiple painful pustules with inflammatory halo, fever and arthralgias.

In the bullous form, bullae with perilesional erythema evolve into painful shallow erosions and necrotic ulcers.

Vegetative PG (superficial granulomatous PG) presents with more superficial ulceration, without purulent base, undermined borders or surrounding erythema, which gradually transforms into an exophytic lesion. Unlike classical ulcerative PG, vegetative PG shows an indolent and slowly growing course.

Malignant pyoderma gangrenosum is considered a rare variety of PG with a predilection for the preauricular region, absence of undermined borders, poor responsiveness to treatment and increased risk for relapse.

Mucous membranes are usually spared, but the genital and oral mucosa may rarely be affected. Vulvar, penile or scrotal involvement may occur. Familial PG with oral (pyostomatitis vegetans) and cutaneous body lesions (recurrent, painful ulcers with undermined, violaceous margins and indurated base) has been described by Boussofara et al.

Extracutaneous neutrophilic infiltrates can rarely occur, reported in patients with PG, and any organ system may be affected, including the pulmonary, cardiovascular, skeletal, neurological and gastrointestinal system. The lung is the most frequently involved organ, manifesting by pleural effusion, pulmonary cavitation and infiltration and chronic sterile inflammation on biopsy.

PG is idiopathic in 40–50 % of patients; however, in the remaining cases, PG may be associated with underlying diseases including IBD, rheumatologic and haematological disorders or malignancy (Table 83.2). It represents the second most common cutaneous manifestation of IBD, and it has been reported in 5–20 % of ulcerative colitis (UC) and

Table 83.2 Underlying diseases reported with PG

IBD, gastric and duodenal ulcers
Arthritis: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis
Monoclonal gammopathy, leukaemia, myeloproliferative syndrome
Internal malignancy

1–2 % of Crohn's disease (CD) patients. Marzano et al. report that PG usually appears after the onset of the UC and may correlate with an exacerbation of UC. In only a few cases, PG may appear before the onset of IBD symptoms. Paraneoplastic PG has been reported in association with underlying haematological or solid organ malignancies. In IBD, classic and pustular PGs are most frequently observed, while bullous PG is the most common variant in myeloproliferative diseases.

Diagnosis

The diagnosis of PG is mainly clinical after other conditions have been appropriately ruled out. A detailed medical history for weight loss or altered bowel function may reveal an underlying malignancy or inflammatory bowel disease.

The histopathological features of PG are nonspecific. Histology will rule out other suspected skin diseases. Skin biopsy reveals an ulcerated epidermis with a massive neutrophilic infiltration of the upper and lower dermis.

Laboratory and other investigations should exclude underlying inflammatory bowel disease, haematological malignancy, rheumatological disorder, immunodeficiency or ophthalmological problems (Table 83.3). High C-reactive protein is always present in PG.

Cultures for bacteria and fungi from skin lesions are negative unless there is a superinfection.

Differential Diagnosis

PG should be differentially diagnosed from other diseases presenting with ulcers, including:

- Adamantiades-Behçet's disease: diagnosis based on the new diagnostic International Criteria proposed by Davatchi et al. Apart from genital or oral aphthosis (ulcers), other manifestations should be present.
- Wegener's granulomatosis (WG): c-ANCA positive in 80–90 % of patients with active classic WG.
- Deep fungal infections: special stains for fungi are positive.
- Mycobacterial infections: tissue polymerase chain reaction, tuberculin skin test.
- Protozoal infections (ulcerative amebiasis cutis, acanthamoeba): histology, cultures.
- Syphilis: not painful (usually genital) ulcer, positive serology for syphilis.
- Cutaneous malignancies (squamous cell carcinoma, metastatic skin cancers, lymphomas): usually characterized by slow evolution, not painful, different histology.
- Ulcerative sarcoidosis: histology.
- Self-inflicted lesions (factitia).

Table 83.3 Laboratory investigations for PG

Full blood count, biochemistry
Serum protein electrophoresis
Complement levels
Antinuclear antibody
Antineutrophil cytoplasmic antibodies (ANCA): positive c-ANCA indicate Wegener's granulomatosis
Syphilis serology
HIV serology
Urinalysis
Chest X-ray
Computed tomography: to exclude an underlying malignancy
Bone marrow biopsy: in case of suspicion of a haematologic malignancy (plasma cell dyscrasia, leukaemia)
Colonoscopy: to exclude IBD
Skin biopsy, with Gram and PAS stains
Imaging: for splenic, pulmonary involvement of PG
Cultures from skin ulcers

General Principles of Treatment

As the incidence of PG is low and there are no prospective, randomized, controlled trials evaluating treatments, there are no established guidelines for treatment of PG.

Management of PG should encompass investigations to establish diagnosis, exclusion of an associated underlying disease and appropriate

treatment to reduce pain and promote healing with minimum side effects.

In mild cases and those not associated with systemic disease, topical treatment, prevention of trauma and supportive care may be sufficient for re-epithelialization. In case of a more widespread or rapidly progressive disease, systemic treatment is used. Despite the scarcity of randomized, controlled trials and the lack of a standardized treatment algorithm for PG, systemic corticosteroids and cyclosporine are often used for severe disease. Other treatments may be considered for patients with refractory PG or contraindications to prednisolone or cyclosporine.

When there is an underlying disease, treatment should aim to control this as well. The successful treatment of the associated disease can result in improvement or complete remission of PG.

Relapses are common and may occur in up to 70 % of PG patients.

Topical Therapy: Corticosteroids and Calcineurin Inhibitors

For mild PG, local measures such as dressings, limb elevation, rest, topical corticosteroids or intralesional corticosteroid injections can be sufficient to control the disease process.

An evidence-based review of the literature on treatments for PG in more than 350 patients, by Reichrath et al. in 2005, reported that topical treatment with potent corticosteroids or topical tacrolimus, pimecrolimus or intralesional injections with corticosteroids, as first-line therapy, may be sufficient for selected cases of localized PG, especially for patients with contraindication to oral corticosteroid or cyclosporine therapy, with no underlying systemic disease, or for superficial PG (Fig. 83.2).

General Principles of Treatment

Systemic Therapy

In their evidence-based review, Reichrath et al. suggested that for patients with widespread PG, systemic treatment is in general required. Systemic corticosteroids or cyclosporine, alone or in combination, were recommended as first-line therapy (grade of recommendation B). Response with these agents is usually rapid, while maintenance therapy may be needed. For steroid-refractory PG, immunomodulators and biological response modifiers may be promising. Treatment with mycophenolate mofetil, azathioprine (AZT), methotrexate, infliximab, plasmapheresis, intravenous immunoglobulin therapy, thalidomide, dapsone or interferon alfa received a C grade of recommendation for PG. Systemic antibiotics including tetracyclines (minocycline) have been used in isolated cases (Fig. 83.2).

Glucocorticoids

Corticosteroids, like prednisolone 1–2 mg per kg per day, are widely used for initial therapy, and they are tapered with clinical improvement. However, long-term (more than 4 months) oral glucocorticoid therapy is associated with various side effects, and such patients should be closely monitored and appropriately managed for osteoporosis, arterial hypertension, diabetes, electrolyte imbalance and glaucoma.

Cyclosporine

Cyclosporine A at a daily dose of 2–5 mg/kg may be used for widespread PG after initial steroids or in combination with steroids in resistant cases. Side effects with cyclosporine treatment include arterial hypertension, renal insufficiency, electrolyte imbalance, hirsutism and gingival hyperplasia.

Other Systemic Therapies

Dapsone (1.5–2 mg/kg/day), azathioprine (1.5–2 mg/kg/day), cyclophosphamide (1–1.5 mg/kg/day), methotrexate (15–25 mg/week), intravenous immunoglobulins (400 mg/kg/day for five consecutive days), mycophenolate mofetil and plasmapheresis are considered second-line agents.

Biologic Agents

Biologic agents that have been used off-label for the treatment of PG include anti-tumour necrosis

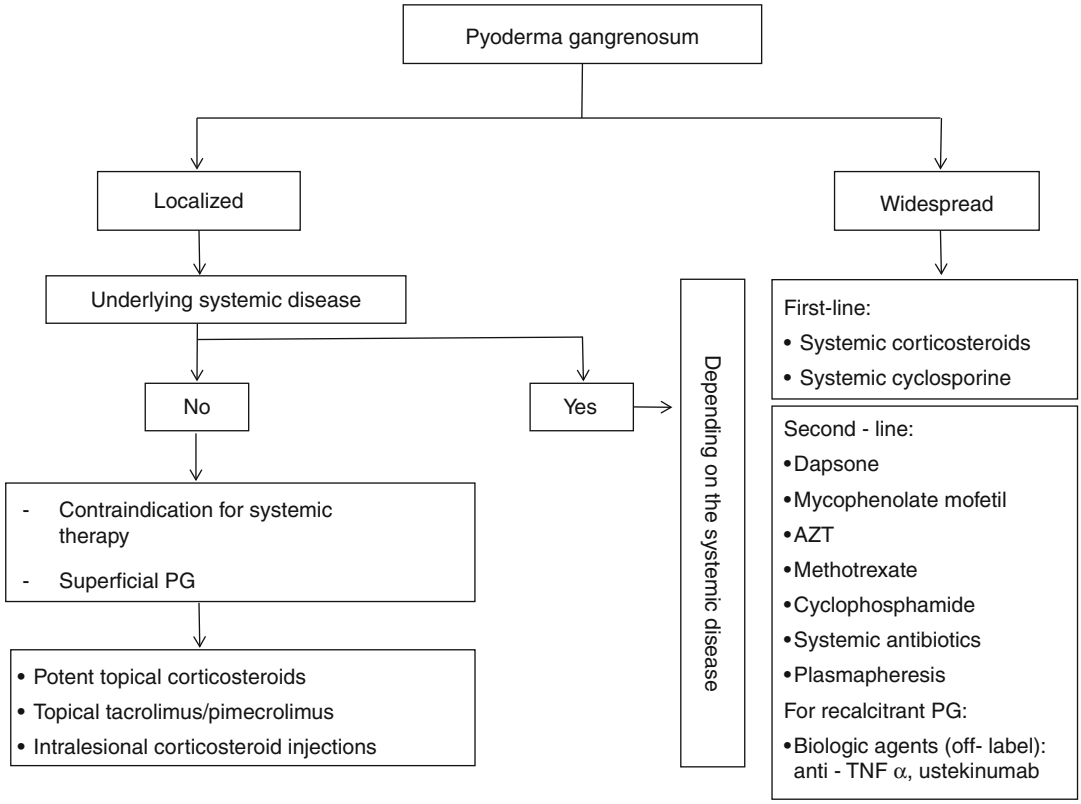

Fig. 83.2 Proposed treatment algorithm for PG (Based on the recommendations by Reichrath et al. 2005)

factor (TNF)-α agents and the interleukin 12/23 inhibitor ustekinumab. Most publications are case reports of anti-TNF therapy of PG in the context of underlying IBD. There is only one randomized, double-blind, placebo-controlled trial investigating the efficacy of anti-TNFα agents in the management of PG. Brooklyn et al. randomized 30 patients with PG (idiopathic or associated with IBD) to receive one infusion of either infliximab 5 mg/kg or placebo at week 0, and nonresponders were offered infliximab at week 2. At week 2, significantly more patients treated with infliximab had improved compared to placebo ($p = 0.025$). Final evaluations at week 6 reported that 29 patients received infliximab with 69 % (20/29) demonstrating a beneficial clinical response.

There have been isolated case reports of the successful use of ustekinumab for severe PG, recalcitrant to previous treatments.

It should be pointed out that, due to the lack of adequate well-designed studies demonstrating their efficacy for PG, biologic agents are not currently approved for the treatment of PG by the FDA or European Medicines Agency (EMA) and thus their high cost is not covered by medical insurances for this condition.

Mycophenolate Mofetil

Li et al. investigated mycophenolate mofetil (MMF) 1–3 g/day as a steroid-sparing agent in a retrospective study in 26 patients with PG. The

average duration of therapy was 12.1 months. All patients received concomitant oral prednisolone (range: 15–80 mg/day), while the majority of patients also received additional immunomodulatory medications. Clinical improvement was reported in 22 patients (84.6 %). Adverse events were reported in 14 patients (53.8 %), including one death after sigmoid colon perforation.

Surgical Intervention

Surgical intervention is not usually carried out in order to avoid pathergy. However, surgical debridement and grafting may be considered in some patients, especially when there is a large amount of necrotic eschar, after the disease is controlled and in conjunction with systemic PG therapy.

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Rosacea

84

Síona Ní Raghallaigh and Frank C. Powell

Key Points

- Rosacea is a common inflammatory facial dermatosis, more prevalent in lighter skin phototypes.
- Its pathophysiology remains incompletely understood, but the process involves an abnormal cutaneous innate immunity, neurovascular dysregulation, altered vasculature and epidermal barrier dysfunction.
- The standard classification into four clinical subtypes provides a useful guide to medical treatment.
- While effective medical therapies have been limited in erythematotelangiectatic rosacea (ETTR) to date, newer treatment options such as the α-adrenoreceptor agonist brimonidine tartrate gel help to reduce the transient and persistent erythema experienced by these patients.
- Antibiotics (topical and systemic) are important in the management of papulopustular rosacea (PPR). In recent times, low-dose doxycycline in particular has been shown to be effective in the treatment of this subtype of rosacea.
- Skin care management, patient education and psychological support are important in optimising control of this disease.

Definition and Epidemiology

Rosacea is a chronic inflammatory dermatosis affecting mainly the centrofacial region. Signs and symptoms range from transient and persistent facial erythema, telangiectasia, inflammatory papules and pustules, sebaceous gland hypertrophy and ocular changes, according to the subtype of rosacea involved. Many patients report increased facial skin sensitivity and dryness and can often identify particular exacerbants which may worsen their disease. The progression of rosacea is variable and at times unpredictable, with sporadic periods of exacerbation and remission. For some patients, the psychosocial impact of this disorder can be marked (Figs. 84.1, 84.2 and 84.3).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_84, © Springer-Verlag Berlin Heidelberg 2015

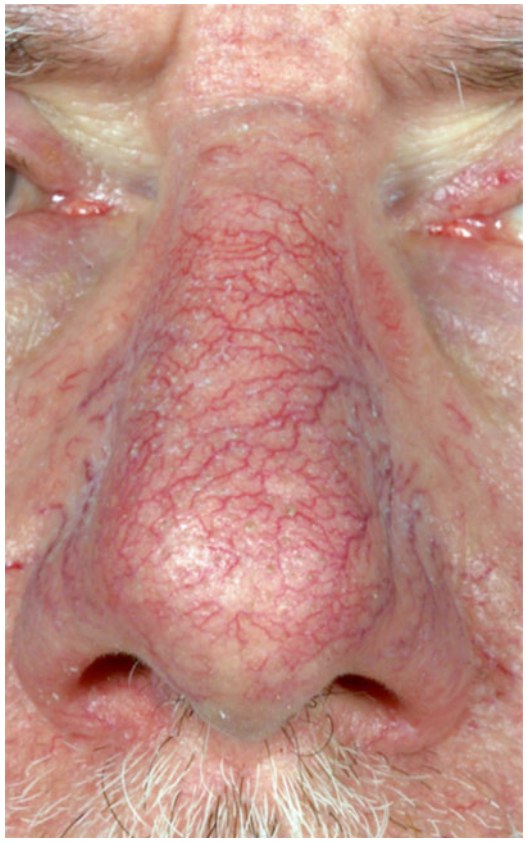

Fig. 84.1 Erythematotelangiectatic rosacea. Telangiectatic vessels on the nose with surrounding erythema

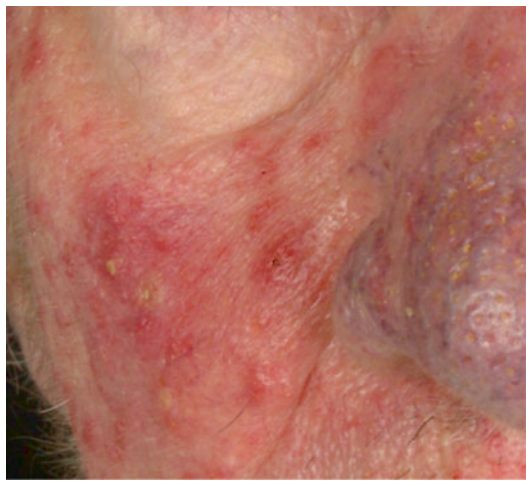

Fig. 84.2 Papulopustular rosacea. Inflammatory papules and pustules affecting the cheek with surrounding erythema. Note the coexistent rhinophyma as evidenced by tortuous, dilated vessels on the nose as well as large, patulous follicular ostia

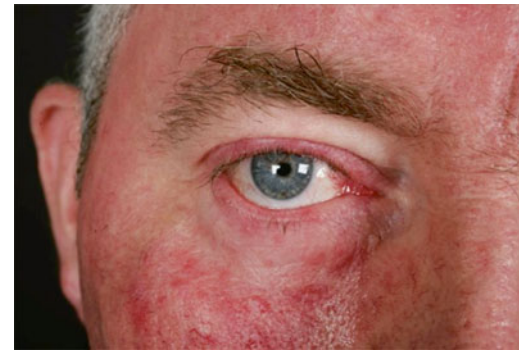

Fig. 84.3 Ocular rosacea. Erythema, telangiectasia and oedema of the upper eyelid, with milder features evident on the lower lid. This patient also has features of papulopustular rosacea affecting the cheek

Epidemiology

Rosacea is a common disorder. Exact prevalence rates vary between studies, probably due to discrepancies in disease definition and study populations. Prevalence rates in Caucasian populations range from 0.09 to 22 %. Although ETTR is often clinically indistinguishable from heliodermatitis, general population studies indicate that subtype 1 is more prevalent than subtype 2. A study of 1,000 Irish indoor and outdoor workers reported a prevalence rate of 2.7 % for subtype 2 (McAleer et al. 2008). The fair-skinned are most susceptible, although the disease can occur in darker phototypes. Gender distribution has been shown as equal or with a female preponderance. Men are more likely to develop phymatous changes. Patients usually present between 30 and 50 years of age, and it is estimated that approximately 57 % of cases are diagnosed before 50 years of age.

Classification and Clinical Presentation

Rosacea has been classified into four main subtypes based on predominant lesion morphology (Wilkin et al. 2004) (Table 84.1).

Variants of rosacea include rosacea fulminans (very sudden onset of inflammatory lesions; may have associated fever), rosacea conglobata (inflammatory cysts and scarring) and granulomatous

Table 84.1 Rosacea subtypes – clinical features

Subtype	Clinical features
Erythematotel-angiectatic (ETTR) (Subtype 1)	Flushing
	Persistent erythema
	Telangiectasia
	Skin sensitivity – burning and stinging
Papulopustular (PPR) (Subtype 2)	Persistent erythema
	Papules and papulopustules (unlike acne, heal without scarring)
	Centrofacial distribution but can occur on the scalp, behind the ears, neck and upper chest
	Flushing and skin sensitivity (may be present but tend not to be as severe as in subtype 1)
Phymatous (Subtype 3)	Thickened, nodular skin
	Patulous follicles (early disease)
	Bulbous, distorted features (advanced disease)
	Most commonly affects nose
	Can also affect chin, forehead, ears, eyelids
	May be associated with other features of rosacea or occur in isolation
Ocular (Subtype 4)	Usually bilateral
	Dry, gritty sensation
	Blepharitis
	Meibomian gland dysfunction
	Eyelid telangiectasia and oedema
	Collarettes around eyelashes
	Chalazia and hordeola
	Conjunctivitis
	Keratitis, episcleritis, scleritis, iritis (rare)

rosacea (persistent red-brown to skin-coloured papules; non-caseating granulomatous histology).

Histology

The histopathological findings of rosacea are not diagnostic and biopsy is not usually recommended. Histology may show perifollicular inflammation, perivascular infiltrates, matrix degeneration, actinic elastosis and dilated hyperaemic vessels. The perifollicular infiltrate has been shown to consist mainly of T-lymphocytes and can occasionally assume a granulomatous pattern. Histological features of rhinophyma include sebaceous hyperplasia, dilated infundibula with occasional cysts, suppuration, granulomatous inflammation and focal fibroplasias.

Basic Concepts of Pathogenesis

The pathogenesis of rosacea is complex, multifactorial and likely subtype specific. Numerous pathogenic pathways have been shown to be involved in rosacea, many of which overlap. These include the following.

Dysregulated Innate Immunity

Innate immunity leads to a controlled release of cytokines and antimicrobial molecules such as the peptide cathelicidin (LL-37). In rosacea, there is upregulation of cathelicidin and its processing serine protease (kallikrein 5). Cathelicidin peptides and their enzymes have proinflammatory and angiogenic activity. Toll-like receptors (TLRs) are pathogen-associated molecular pattern sensors that are involved in the innate immunity of the skin. In the lesional skin of patients with rosacea, keratinocytes express elevated levels of TLR2, leading to increased expression and activity of kallikrein proteases. Dysfunction of the innate immune system may be related to other associated features of rosacea such as the skin's response to ultraviolet radiation.

Epidermal Barrier Dysfunction

Dryness, stinging and burning are common features of rosacea. Abnormal skin barrier homeostasis has been demonstrated in rosacea patients, as evidenced by increased transepidermal water loss (TEWL) and increased sensitivity to a skin irritation test. Patients with PPR have a more alkaline centrofacial region and reduced epidermal hydration levels as compared with controls. In addition, these patients have reduced levels of sebaceous long-chain saturated fatty acids, which are known to contribute to the barrier function of the stratum corneum.

Neurogenic Inflammation

Neuromediators, released by sensory nerve endings and other cells such as keratinocytes, activated endothelial cells and fibroblasts, induce neurogenic inflammation, resulting in vasodilatation, oedema and inflammation. Recent research in rosacea has focused on transient receptor potential channels (TRPs) and in particular TRP vanilloid receptor 1 (TRPV1), also known as the capsaicin receptor, and TRP ankyrin receptor 1 (TRPA1). These can be activated by common exacerbants of rosacea such as heat, ethanol or spicy food (TRPV1) or cold, formalin or other chemicals (TRPA1). Activation of TRPV1 and TRPA1 results in the release of substance P and calcitonin gene-related peptide, important mediators of neurogenic inflammation and pain.

Ultraviolet Radiation

While UVR can often trigger rosacea, a definite causal relationship has not been described. An epidemiological study of 1,000 Irish individuals found no association between sun exposure and PPR prevalence but did find an association with ETTR. UVR exposure has been shown to induce angiogenesis, increase the secretion of the angiogenic factors such as VEGF from keratinocytes and produce proinflammatory reactive oxygen species.

Vascular Alterations

Increased blood flow in skin lesions of rosacea has been demonstrated. Rosacea patients flush more readily in response to heat as compared with controls, and their heat pain thresholds have been demonstrated to be lower. In addition, there is elevated expression of vascular endothelial growth factor (VEGF), CD31 and lymphatic endothelium marker D2–40, suggesting the presence of an increased stimulant for vascular and lymphatic cells in rosacea.

Demodex Mites (*D. folliculorum* and *D. brevis*)

Demodex mites are commensals of normal skin but are found in greater numbers in rosacea patients, and infestation has been shown to be associated with an intense perifollicular infiltrate of predominantly CD4 helper T cells. Antigenic proteins related to a bacterium (*Bacillus oleronius*) isolated from a *Demodex* mite have been shown to stimulate an inflammatory response in patients with PPR. *Demodex* mites and their associated bacteria may induce an upregulation in surrounding cutaneous proteases, thereby potentiating the dysregulation of the local innate immune response. It has been proposed that chitin, released from these mites, could serve as the trigger for TLR2 on keratinocytes and link *Demodex* with increased protease activity and cathelicidin-induced inflammation in rosacea.

Differential Diagnosis

The differential diagnosis of the various subtypes is outlined in Table 84.2.

Table 84.2 Rosacea subtypes – differential diagnosis

Rosacea subtype	Differential diagnosis
Erythematotelangiectatic	Heliodermatitis
	Flushing due to systemic causes such as menopause, carcinoid syndrome and phaeochromocytoma
Papulopustular rosacea	Acne
	Perioral dermatitis
	Pityriasis folliculorum
	Rosaceiform dermatitis due to topical calcineurin inhibitors
	Rosaceiform eruption due to EGFR inhibitors
	Steroid-induced rosacea
Phymatous	Morbihan's disease
	Lupus pernio (sarcoid of the nose)
	Lymphoma/angiosarcoma (rare)
Ocular	Chronic blepharitis
	Chronic dry eye syndrome (numerous causes)

General Principles of Treatment

The management of patients with rosacea should involve the following three aspects of care: (a) skin care management, (b) medical therapies and (c) patient education.

Skin Care Management

General principles of skin care useful in the management of rosacea are outlined in Table 84.3.

Medical Treatment

Medical Treatment of ETTR

The treatment of subtype 1 rosacea is often unsatisfactory for both patient and clinician. Of particular importance in these patients is a skin care regime aimed at reducing skin sensitivity and improving epidermal barrier function. In addition, strict photoprotection is advised, as UV exposure may potentiate dermal matrix and vascular damage.

Topical antibiotics such as metronidazole or other agents such as *azelaic acid* may reduce erythema in some patients with ETTR. Azelaic acid is a naturally occurring, straight-chain dicarboxylic acid with anti-inflammatory properties. However, the use of such topical agents in this subtype is often limited by their irritant effects.

Topical *α-adrenoreceptor agonists*, which produce vasoconstriction, have shown early promising results in the treatment of the transient and non-transient erythema of rosacea. Brimonidine tartrate is a highly selective α_2-adrenoreceptor agonist used in ophthalmic solution for the treatment of open-angle glaucoma. Topical brimonidine tartrate gel has been shown in controlled, prospective, randomised clinical trials to reduce the facial erythema of rosacea after single and repeated once-daily applications, with an optimal concentration of 0.5 % gel formulation. No major adverse events were noted in this trial, and tolerability was good. Case reports of other α-adrenoreceptor agonists (oxymetazoline 0.05 % solution and xylometazoline 0.05 % solution; applied to the skin in their nasal decongestant formulations) showed a reduction of facial erythema over several hours in patients with ETTR.

Nonselective *β-blockers* decrease sympathetic activity and have been reported to reduce flushing. By antagonising β-adrenergic receptors on smooth muscles of cutaneous blood vessels, β-blockers produce vasoconstriction. In addition, their anxiolytic effects may reduce the social anxiety that may lead to blushing in some of these patients. There are only a few reports of β-blocker therapy in patients with rosacea, and patient numbers in these reports are small. However, both propranolol (30–120 mg/day) and carvedilol (titrated from 3.25 mg three times a day to 25 mg/day) have been shown to reduce flushing episodes in these patients.

Laser techniques such as pulsed dye laser, intense pulsed light and potassium titanyl phosphate laser may be useful for the treatment of telangiectasia and erythema.

Table 84.3 Skin care management

Use sunscreens with both UVA and UVB protection, and a sun protection factor of 15 or greater. Sun-blocking creams containing the physical barriers titanium dioxide or zinc oxide are usually well tolerated
Use soap-free, pH-balanced synthetic detergents (syndets) and lukewarm water to wash the face
Use cosmetics and sunscreens that contain protective silicones
Water-soluble make-up containing inert green pigment helps neutralise the perception of erythema. Camouflage make-up may also be useful
Moisturisers containing humectants (e.g. glycerin) and occlusives (e.g. petrolatum) may assist in restoring impaired epidermal barrier function
Avoid astringents, toners and abrasive exfoliators and procedures such as dermabrasion
Avoid waterproof cosmetics and heavy foundations that are difficult to remove without irritating solvents or physical scrubbing
Avoid cosmetics that contain alcohol, menthols, camphor, witch hazel, fragrance, peppermint and eucalyptus oil
Avoid environments which may overheat and/or dry the skin such as saunas, heater fans in cars and open fireplaces

Medical Treatment of PPR

Topical and/or systemic antibiotics play an important role in this subtype.

Topical agents can be used as initial therapy in grade 1–2 disease or as maintenance therapy following clearance with systemic antibiotics. A recent Cochrane review confirmed the effectiveness of topical azelaic acid and metronidazole for the treatment of PPR. In comparative studies, azelaic acid 15 % gel was more effective than metronidazole 0.75 % gel in reducing erythema and inflammatory lesions but produced more adverse effects such as stinging and burning. Sodium sulphacetamide 10 % and sulphur 5 % have been shown to be more effective than placebo in reducing erythema and inflammatory lesions. Other topical treatment options for the management of PPR are listed in Table 84.4.

For more severe cases of PPR, *oral antibiotics* should be considered. Specifically, the anti-inflammatory role played by tetracyclines in the management of rosacea is well recognised. Oral tetracyclines have been used in the treatment of rosacea since the 1950s. Data pooled from three studies of oral tetracycline versus placebo involving 152 participants showed that, according to physicians, tetracycline was effective in treating rosacea (OR 6.06, 95 % CI 2.96–12.42). Tetracyclines have many mechanisms of action which may contribute to their effectiveness in their treatment of rosacea. They have been shown to inhibit matrix metalloproteinases (MMPs); downregulate the inflammatory cytokines TNF-α, IL-1β, IL-8 and IL-10; and inhibit cell movement and proliferation, in particular neutrophil migration

Table 84.4 Topical treatments for PPR

FDA approved	Non-FDA-approved topical treatments	Alternatives not commonly used clinically
Metronidazole	Erythromycin b.i.d.	Permethrin
(0.75 % gel or cream; 1 % cream) q.d. or b.i.d.	(2 % solution)	(5 % cream q.d–q.w.)
	May be a useful treatment in pregnant patients where other treatments are contraindicated	Topical antiparasitic agents aimed at reducing the *Demodex* mite population on the skin. Shown to be as effective as metronidazole for the treatment of papules and erythema. May have future role in combination with antibiotics – further studies needed (Kocak et al. 2002)
Azelaic acid	Clindamycin q.d.	Crotamiton 10 % cream/lotion b.i.d.
(15 % gel) b.i.d.	(1 % lotion)	Shown in a retrospective study to be useful in patients with rosacea-like *Demodex* dermatitis. May be irritating (Bikowski and Del Rosso 2009)
Sodium sulphacetamide (10 %) and sulphur (5 %) in cream or lotion q.d. or b.i.d. May include urea	Benzoyl peroxide 5 % and clindamycin 1 % q.d.	Oxymetazoline
		Positive clinical response shown in case reports of ETTR patients using this α-agonist
	Azelaic acid	Pimecrolimus
	(20 % cream b.i.d.)	(1 % cream b.i.d.)
		Although some studies show improvement in erythema with these immunomodulatory agents, there have been case reports of exacerbations, so caution is advised until further studies are performed (Karabulut et al. 2008)
	Tretinoin	
	(0.025 % cream; 0.01 % gel q.d.)	

Table 84.5 Systemic antibiotics for papulopustular rosacea

Doxycycline (only FDA-approved antibiotic treatment for rosacea)	40 mg once daily (30 mg immediate release and 10 mg delayed release)
Doxycycline	50–100 mg once or twice daily
Minocycline	50–100 mg twice daily or sustained action formula once daily
Oxytetracycline	250–500 mg twice daily
Erythromycin	250–500 mg once or twice daily
Metronidazole	200 mg once or twice daily (for 4–6 weeks)

(Golub et al. 1984; Cazalis et al. 2008; Gabler and Creamer 1991). They have also been shown to inhibit granuloma formation, reactive oxygen species and angiogenesis.

In 2006, a once-daily controlled-release formulation of doxycycline monohydrate (40 mg) became the first FDA-approved oral antibiotic treatment for rosacea. Clinical studies have shown this sub-antimicrobial dose of doxycycline to be as effective as the 100 mg dose but with less adverse effects and less bacterial resistance.

Alternative antibiotic treatments include metronidazole or a macrolide (Table 84.5). Antibiotic courses are generally given for 6–12 weeks, and repeated courses may be necessary for future exacerbations.

Isotretinoin has been shown to reduce erythema and papulopustules in treatment-resistant patients, as well as reducing nasal volume and halting the progression of rhinophyma. One study showed that low-dose isotretinoin (10 mg once daily for 4 months) reduced inflammatory lesions, erythema and telangiectasia after 9 weeks. Although further studies are needed, low-dose isotretinoin may be a viable useful alternative, particularly in men and women past child-bearing years.

Medical Treatment of Phymatous Rosacea

Surgical excision, electrosurgery or CO_2 laser can be used to debulk and resculpt the nose. The possibility of recurrence should be explained to the patient. Isotretinoin may help to slow the progression of rhinophyma.

Medical Treatment of Ocular Rosacea

Eyelid hygiene, artificial tears, fusidic acid, metronidazole gel and cyclosporin 0.5 % ophthalmic emulsion are useful treatments for this subtype of rosacea. Systemic antibiotics may be required for the treatment of more severe or persistent disease, and these patients should be referred to an ophthalmologist.

Patient Education

While the chronicity of disease and the likelihood of exacerbations should be explained to the patient, reassurance of the benign nature of rosacea is also important. Advice should be given on the avoidance of triggers as well as the importance of photoprotection. Direct patients to information websites such as those of the National Rosacea Society (www.rosacea.org) or the American Academy of Dermatology (www.aad.org). Finally, acknowledging the psychosocial impact of this disorder may help to guide patients in need of psychological support towards the appropriate services such as counselling or cognitive behavioural therapy.

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Sarcoidosis

85

Sven R. Quist

Key Points

- A multisystemic granulomatous disease of unknown cause that most commonly involves the lungs but also the skin (around one-third of cases).
- Cutaneous manifestations could appear as the first sign of sarcoidosis and present as red-brown or violaceous plaques or papules on the head, face, neck, back and extremities.
- Variants include lupus pernio, angiolupoid, ichthyosiform, subcutaneous and ulcerative sarcoidosis, and scars can also be affected.
- Erythema nodosum is a non-specific inflammatory skin finding associated with subacute, transient sarcoidosis.
- Noncaseating epithelioid granulomas without surrounding lymphocytic inflammation characterise histology.
- A complex interaction between genetic factors, antigens and immune response is believed to affect the host susceptibility to sarcoidosis.

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Definition and Epidemiology

Sarcoidosis was first described by Sir Jonathan Hutchinson in 1875 and later in the skin as lupus pernio by Besnier in 1889 and as "multiple benign sarkoid of the skin" by Boeck in 1899. Sarcoidosis is a systemic granulomatous disorder of unknown cause. By Even the lung is most commonly affected, lymph nodes, lungs, liver, spleen, bones and eyes and especially the skin can be involved. Skin lesions could frequently appear as the first sign of disease (in up to 35 %) emphasising the important role of the dermatologist for the diagnosis and further investigations. Typically noncaseating epithelioid granulomas without surrounding lymphocytic infiltration can be found within affected organs histologically.

Basic Concepts of Pathogenesis

The current knowledge is that the development of sarcoidosis requires an interplay between infectious and environmental causes and individual genetic factors (HLA phenotype, ACE gene polymorphism) that trigger the disease and affects the cell-mediated immunity. The following events are involved: (a) exposure to an antigen; (b) acquired cellular immunity directed against this antigen and mediated through antigen-presenting dendritic cells or macrophages that recognise, process and present the antigen to a T-lymphocyte receptor via HLA

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_85, © Springer-Verlag Berlin Heidelberg 2015

class II molecules; and (c) antigen-specific T lymphocytes together with immune effector cells finally lead to formation of noncaseating granulomas. Effector cells include $CD4^+$ T-helper 1 cells that promote a non-specific inflammatory response including cytokines interleukin 1, interleukin 2 and interferon gamma. Activated macrophages produce interleukin 10, interleukin 12 and tumour necrosis factor alpha. In this microenvironment various T-cell clones including the gamma-delta subtype are expanded, and monocytes initiate the formation of epithelioid granulomas. Genetic factors are related to the different HLA phenotypes (HLA-1, HLA-B8, HLA-DR3, HLA-DRB1, HLA-DQB1) that determine the severity of sarcoidosis since it has a crucial role in antigen presentation, following cytokine production and granuloma formation. In case the disease is chronic, it progresses to fibrosis in up to 30 % of cases with severe and irreversible tissue damage, whereas granulomas are still reversible.

The potential antigen is still unknown and may also depend on the individual immune constitution, but antibodies to *Mycobacterium tuberculosis* have been detected in serum of affected patients; even cultures are negative in most cases. Other antigens that have been associated with sarcoidosis include *Mycobacterium marinum*, *Propionibacterium* acnes, Epstein Barr, herpes (simplex, zoster or HHV6) and HIV virus infection and non-infectious agents such as mouldy wood or mineral dust from titanium, iron or silica, skin tattoo pigmentation, aluminium and zirconium in cosmetic preparations or dermal fillers for cosmetic use.

Clinical Presentation

In general, this disease has a great variation of manifestations that can involve the skin or other organs that might be affected at different time points during the course of this low predictable disease.

Cutaneous sarcoidosis can be with (specific) or without (non-specific) granulomas. Variants include the following forms:

- Papular or plaque types, often larger lesions, red to brown (some variation in colour exists: diascopy is helpful showing an apple-jelly colour), mostly a sign of a chronic disease (Figs. 85.1a, 85.2a and 85.2e)
- Nodular: annular or angiolupoid (most frequently at the nose), lupus pernio (indurated violaceous mostly on the nose, ears, lips and cheeks), also appearing subcutaneously (Darier-Roussy disease) (Fig. 85.2b–d)
- Erythematous (erythema nodosum), maculopapular
- Scar sarcoidosis (appearing also in tattoos), may indicate systemic involvement
- Miscellaneous: hypopigmented, ulcerative, psoriasiform, ichthyosiform, mucosal, ungual, verrucous, discoid, erythrodermic, necrotising, morphoea-like, with cicatricial alopecia

Non-cutaneous sarcoidosis mostly affects the intrathoracic area but can also affect other different organs:

- Pulmonary involvement: 90 % of cases, bilateral hilar or paratracheal lymphadenopathy without (stage 1 according to X-ray classification) and with infiltration (stage 2), pulmonary infiltration (stage 3) or fibrosis (stage 4), alveolitis and infiltration of bronchioles, blood vessels, pleura and septa leading to air flow dysfunction (FEV, FVC reduction) (Fig. 85.3a, b).
- Ocular involvement: granulomatous uveitis (Heerfordt syndrome: uveoparotid); involvement of iris and lacrimal gland (together with parotid swelling: von Mikulicz syndrome), retina, choroid and sclera; optic nerve neuropathy; danger of vision loss; and development of glaucoma (Fig. 85.3c).
- Liver and spleen involvement: liver involvement mostly silent; cholestasis or portal hypertension can occur; elevation of liver enzymes; very rarely this can lead to liver cirrhosis; fever, night sweat and weight loss are unspecific signs but may indicate liver sarcoidosis.
- Renal involvement can lead to calcium dysregulation of overproduction of vitamin D and hypercalcaemia or hypercalciuria.
- Neurologic involvement: facial nerve or peripheral neuropathy, parenchymal brain

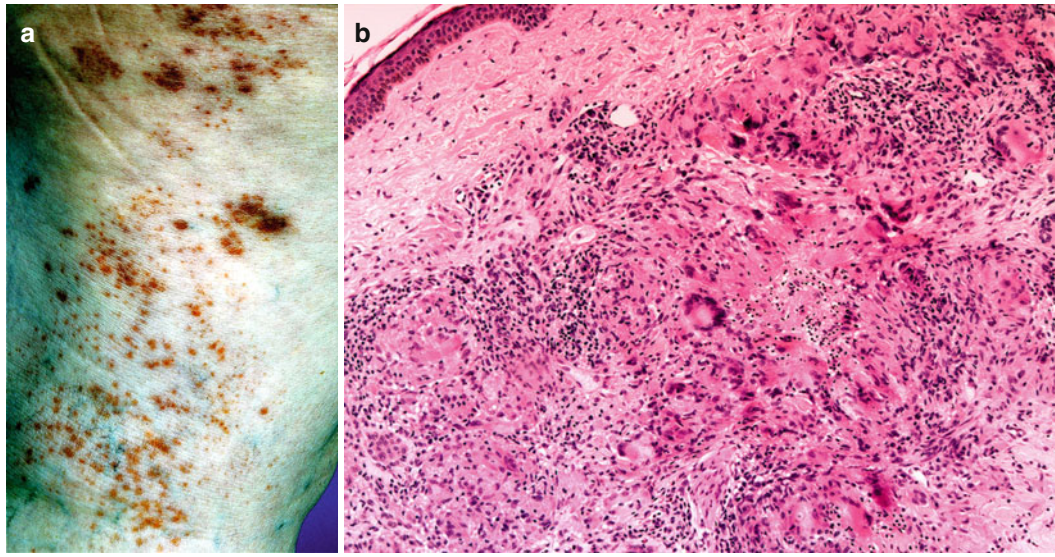

Fig. 85.1 (**a**) Papular cutaneous sarcoidosis after infection with herpes zoster, manifestation in the same dermatome. (**b**) Histopathology of cutaneous sarcoidosis with the presence of noncaseating epithelioid cell granulomas, giant cells and infiltration of lymphocytes

lesions, myopathy, spinal lesions, seizures, stroke, vision loss (Uhthoff phenomenon).

- Cardiac involvement: left ventricular wall or septum frequently affected; often asymptomatic and remains undetected; cardiomyopathy, arrhythmia, palpitations, atrioventricular block, tachycardia, pericardial effusions and heart failure depending on the area involved can occur.
- Bone and joint involvement: chronic mono- or polyarthritis, cystic lesions in bones mostly asymptomatic detectable via MRI or PET (Jüngling ostitis multiplex cystoides).

In general, the occurrence of cutaneous lesions and systemic involvement is considered the most unfavourable condition.

Histopathology

Histology of sarcoidosis is almost identical in affected tissues. This includes the presence of noncaseating epithelioid cell granulomas and infiltration of lymphocytes or plasma cells. Giant cells may be visible, sometimes with inclusions such as asteroid bodies or Schaumann bodies. Granulomas are present in the dermis or subcutis and can occur periadnexal or perineural, and necrosis is detected rarely. More frequently mucin can be found as well as fibrosis in subcutaneous lesions. Whereas CD8+ lymphocytes can be detected in the perigranulomatous area, CD4+ lymphocytes can be detected in the granuloma (Fig. 85.1b).

Systemic Diseases Associated with Sarcoidosis

Several systemic diseases have been reported to be associated with sarcoidosis propagating a common autoimmune pathogenesis which, however, might be to some extent coincidental: dermatomyositis, pyoderma gangrenosum, progressive systemic sclerosis, systemic lupus erythematosus, vitiligo, Wegener's granulomatosis, Sjögren's syndrome, diabetes mellitus, ulcerative colitis, biliary cirrhosis, autoimmune thyroiditis, polycythaemia vera, pernicious anaemia, cutaneous lymphoma and B-cell lymphatic leukaemia.

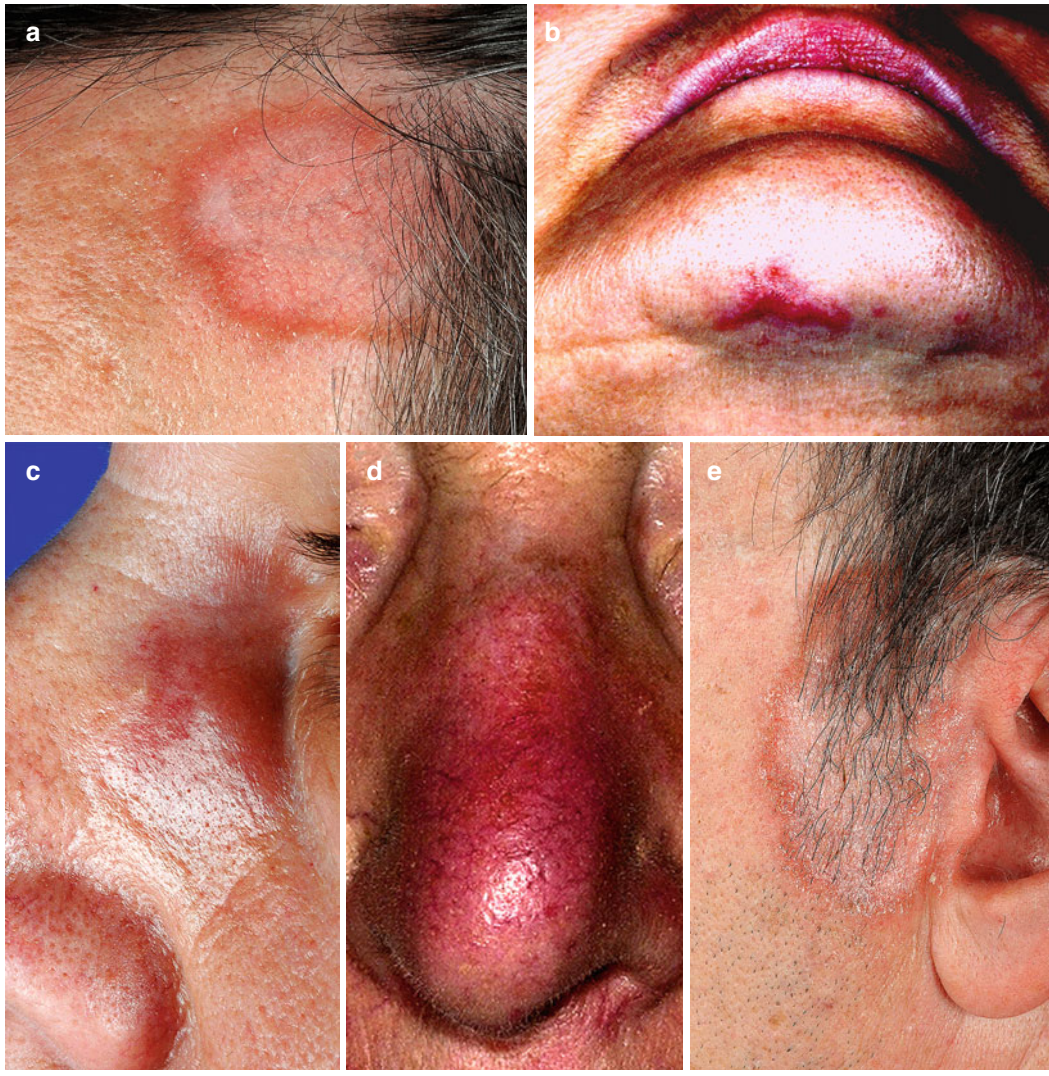

Fig. 85.2 Clinical signs of cutaneous sarcoidosis: (**a**) Annular plaque, hypopigmented. (**b**) Scar sarcoidosis. (**c**) Erythematous. (**d**) Lupus pernio. (**e**) Annular plaque, psoriasiform

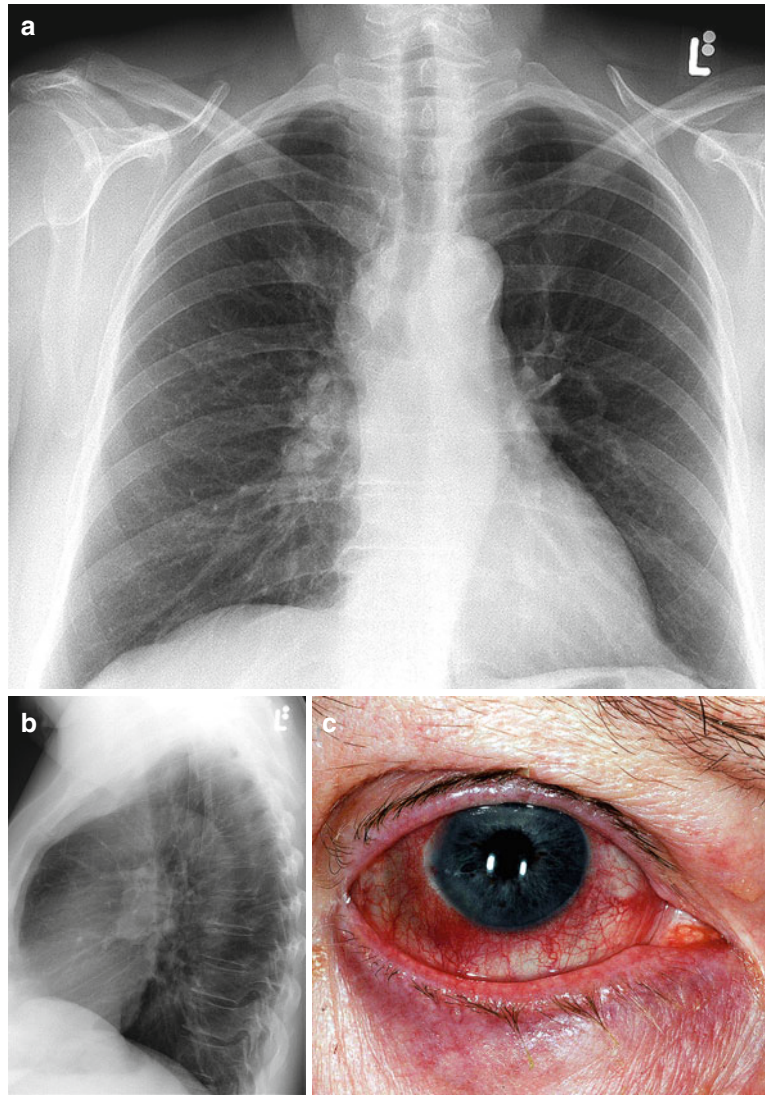

Fig. 85.3 (**a**, **b**) Pulmonary sarcoidosis with bilateral hilar involvement (stage 1). (**c**) Ocular sarcoidosis with Heerfordt syndrome and prominent uveitis

Differential Diagnosis

Similar to syphilis, cutaneous sarcoidosis can mimic other skin diseases stressing the importance of anamnestic, clinical, radiographic, laboratory and histopathological criteria to come to the correct diagnosis:

- Erythema annulare centrifugum, erythema marginatum and urticaria can present annular lesions.
- Tuberculosis, cutaneous lymphomas, histiocytosis, psoriasis vulgaris, discoid lupus erythematosus, prurigo, Sweet syndrome and Well's disease can present papules or plaques.
- Hypertrophic scars or keloids must be differentiated from lupus pernio.
- Onychomycosis, psoriasis vulgaris and lichen planus must be considered for dystrophic nail involvement.
- Vitiligo can present hypopigmented skin lesions.

General Principles of Treatment

Treatment should be cautious since sarcoidosis often spontaneously remits or remains stable, and several treatment options are associated with significant side effects. Furthermore several drugs used are not approved for this disease, so weighing up risks and benefits for each kind of treatment is strongly recommended. Especially cutaneous sarcoidosis is frequently asymptomatic, but in case of organ involvement, especially pulmonary, neural, liver, renal, ocular or cardiac involvement, and when symptoms such as persistent fever, weight loss or hypercalcaemia occur, systemic treatment should be considered.

The main problem is that there are almost no well-controlled and randomised clinical trials that show a clear benefit for a certain treatment in cutaneous sarcoidosis. Most recommendations are generally based on a small number of cases or single case reports which have to be considered. Treatment recommendations will be given based on the best treatment options to cutaneous sarcoidosis.

Topical Treatment

Topical treatment for cutaneous sarcoidosis is recommended if patients have symptoms and feel cosmetically compromised.

Corticosteroids

Treatment with potent topical corticosteroids or repeated (two to three times/week) intralesional injection with triamcinolone acetonide suspension (up to 10 mg/ml, 2) is useful for isolated and thinner cutaneous sarcoidosis lesions. In case lesions do not respond to topical treatment, a switch to oral corticosteroid treatment (prednisolone starting dose 20–40 mg/day) is recommended. Corticosteroids suppress the immune infiltration, the cytokine disbalance and the fibrosis.

Other Options

Cryotherapy, radiotherapy, PUVA treatment, photodynamic therapy and calcineurin inhibitors such as topical tacrolimus have been reported to be beneficial in the treatment of cutaneous sarcoidosis.

Topical Treatments at a Glance

- Topical treatment mainly consists of potent topical corticosteroids.
- Intralesional injection with triamcinolone acetonide suspension can be used for isolated lesions.
- Topical tacrolimus as well as PUVA treatment and cryotherapy might be an additional option for isolated lesions.
- Lesions resistant to topical treatment should be treated systemically starting with corticosteroids.
- Additional cosmetic camouflage might be a helpful advice for patients with cutaneous lesions on the face.

Systemic Treatment

Systemic treatment is recommended when organ involvement and/or symptoms are present. Systemic treatment options range from corticosteroids to several other immunosuppressants that have severe side effects.

Corticosteroids

Systemic corticosteroids should be initiated between 0.5 and 1 mg/kg per day and tapered to 5–10 mg per day when response to treatment is observed. Re-evaluation of treatment should be done after 4–6 weeks and long-term treatment with lower doses for months to years. Short-term treatment is likely to relapse and not recommended. Lack of response within 3 months indicates irreversible changes such as fibrosis or nonresponsiveness to corticosteroids.

Systemic corticosteroids such as prednisone represent the standard treatment in case of rapid progressive skin involvement and/or in case of organ involvement such as the lungs and lymph nodes. They should be initiated between 0.5 and 1 mg/kg per day and tapered to 5–10 mg per day when response to treatment is observed.

A dose of 0.5–1 mg/kg body weight prednisone (or equivalent) for the first month is followed by a slow reduction over the next months, which is recommended. Treatment is likely to continue for years (Baughman et al. 2006a, b), especially in case of lupus pernio. Short-term treatment is likely to relapse and is not recommended. Side effects of corticosteroids include infections, diabetes, hypertension, gastric ulcer and osteoporosis.

Therefore, cortisone-sparing second-line agents such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, chloroquine and TNF-α inhibitors should be initiated to reduce the daily dose of cortisone which will be also the choice in case of steroid-resistant sarcoidosis. Lack of response to corticosteroids within 3 months indicates irreversible changes such as fibrosis or nonresponsiveness.

Chloroquine/Hydroxychloroquine

Antimalarial agents such as chloroquine or hydroxychloroquine have been used successfully in sarcoidosis for decades. Inhibition of antigen presentation and formation of granuloma seems to be their rationale for treatment. Efficacy was tested in small cohorts up to 17 patients. It seems helpful in patients with hypercalcaemia and neurologic and skin involvement. They can be used either as steroid-sparing agent or as monotherapy. Doses used for chloroquine are 50–500 mg and for hydroxychloroquine 200–400 mg/day. Major side effects are nausea and ocular disease resulting in retinopathy or even blindness. Therefore, regular eye evaluation on an at least yearly basis is crucial.

Already in 1961 and 1964, it was shown that chloroquine improved cutaneous and pulmonary sarcoidosis. In a randomised prospective double-blind trial using hydroxychloroquine 2–3 mg/kg/day, a significant improvement after 3–6 months was recognised but not after 12 months, indicating resistance when used long term. Twelve of seventeen patients were able to discontinue all other therapies (Jones and Callen 1990).

Chloroquine has been more tested to be effective than hydroxychloroquine but the latter has a lower incidence of retinopathy.

Methotrexate

Methotrexate is one of the best studied drugs in sarcoidosis. It is given in weekly doses of 10–30 mg, but haematological, gastrointestinal, pulmonary and hepatic side effects are limiting and blood and liver enzymes should be checked regularly. However, it might be tapered to doses as little as 2.5 mg. Response rates can be up to 80 % for cutaneous sarcoidosis when using 10 mg per week orally (Lower and Baughman 1990). In a randomised controlled trial, it has been shown that patients with new onset of disease received prednisone for 4 weeks and were then randomised to receive either methotrexate or placebo the following year. Methotrexate was able to reduce the dose of corticosteroids significantly compared to placebo (Baughman et al. 2000). Symptoms, lung function tests and chest X-ray results did not differ between methotrexate and placebo but in another small case series by 15 % under methotrexate including reduction of skin infiltration. Patients who discontinued methotrexate relapsed, indicating its immune suppressive role.

Thalidomide

Thalidomide has been withdrawn from the market because of its teratogenic effects. However it has been used successfully for a wide range of autoimmune diseases based on small case series. Its main effect is suppression of TNF-α and interleukin 12. In most cases, the starting dose was 200 mg/day in most cases which was either reduced to 100 mg/day after 3–4 weeks, kept at 200 mg/day or had to be increased to 400 mg/day. In a study of 19 patients, feasibility and efficacy of prolonged treatment with thalidomide for cutaneous sarcoidosis associated to pulmonary involvement in patients resistant to corticosteroid treatment has been evaluated. Lower skin scores occurred after 3 and 6 months, serum ACE levels decreased over time at the third month and chest X-ray as well as lung function tests improved during the first 6 months. Minor side effects forcing the suspension of the drug were drowsiness and sedation, constipation, weight gain and axonal sensitive peripheral neuropathy which resulted in discontinuation of the drug in eight

patients (Fazzi et al. 2012). In another case series of 12 patients, complete remission was observed in four patients and partial response in six patients (Nguyen et al. 2004). Due to its safety profile, thalidomide must be regarded as second- or third-line therapy. In another dose-escalation trial where patients received 50 mg initially, doubling the dose each month to a maximum of 200 mg for the treatment of lupus pernio, all 14 patients responded to thalidomide. However, side effects were somnolence, numbness and constipation in lower doses and numbness and rash in higher doses, but only in two patients the maximum dose had to be reduced due to toxicity. Obviously contraception must be strictly performed in women of childbearing potential.

Leflunomide

Leflunomide blocks the synthesis of pyrimidine and the proliferation of T cells. Leflunomide is used orally 10–20 mg/day. It seems to be similarly effective as methotrexate with lower toxicity, but larger clinical trials to test this seem necessary. Leflunomide was tested in a small cohort of 32 patients. Complete or partial response was observed in 12 of 17 patients treated with leflunomide alone and in 13 of 15 patients treated with the combination of leflunomide and methotrexate mostly with chronic ocular and lung involvement (Baughman and Lower 2004).

Fumaric Acid

Even fumaric acids such as a mixture between dimethylfumarate and monoethylfumarate, remains an excellent choice for the treatment of moderate to severe psoriasis, fumaric acids have been used successfully for other autoimmune diseases such as lupus erythematosus, granuloma annulare, lichen planus, necrobiosis lipoidica and cutaneous sarcoidosis. Its effect is to inhibit proliferation of T cells, keratinocytes and fibroblasts and suppress cytokine production. In recalcitrant cutaneous sarcoidosis, it has been used in cases of unsuccessful treatment with corticosteroids and chloroquine. Clinical improvement started only after 2 months and was more evident after 4 months, and complete remission can take as long as 1 year. It can be regarded as a third-line therapy considered for chronic or disseminated skin involvement if other treatments have failed (Klein et al. 2012). Side effects include flush, lymphopenia and minor gastrointestinal complaints.

Tetracyclines and Other Anti-infective Drugs

Since there is evidence that bacteria play an important role in the pathogenesis of sarcoidosis, the use of antibiotics has been suggested in the treatment of cutaneous sarcoidosis. However, modulation of the immune system and anti-inflammatory effects rather than antimicrobial activity may be the main mechanism behind these treatment options. In addition, increasing interleukin-2 production in monocytes and decreasing chemotaxis of neutrophils are observed (Drake et al. 2013). Most experience exists with tetracyclines such as minocycline (Schmitt et al. 2012) which is also effective against propionibacterium acnes, a well-known antigen in sarcoidosis. In a prospective, open-label, non-randomised clinical trial, cutaneous sarcoidosis recalcitrant to corticosteroids and/or quinolones was treated with minocycline 100 mg twice a day for a medium duration of 1 year. Complete response in 8 and partial in 2 (African American with a history of sarcoidosis for several years) of 12 patients was observed, and clinical improvement was observed after 3.2 months. Three patients relapsed after discontinuation of minocycline but responded well to doxycycline (Bachelez et al. 2001). In a retrospective trial, 27 patients with extensive skin lesions (but no lupus pernio) including two ulcers and systemic involvement in 18 patients received minocycline as first-line treatment (18 patients) or second-line treatment (nine patients, most of them had quinolones prior to minocycline). Six patients (22 %) had a complete remission (100 % of the affected body surface), 14 patients (52 %) had a partial remission (50 % of the affected body surface) and seven patients (26 %) did not respond to minocycline (Steen and English 2013). Poor responses to tetracycline have been reported for lupus pernio. The main effects include hyperpigmentation,

dizziness and nausea. However, compared to other treatments for cutaneous sarcoidosis, tetracyclines have a relatively benign safety profile which makes them an attractive choice for a first-line treatment. Treatment could be initiated with minocycline as monotherapy for the first 3 months. In case of an unsatisfactory response, quinolones or low-dose methotrexate might be added as well as additional topical or intralesional corticosteroids for recalcitrant skin lesions.

Since mycobacteria are frequently found in patients with sarcoidosis, antimycobacterial therapy seems another treatment option. Oral treatment with levofloxacin, ethambutol, azithromycin and rifampicin (CLEAR regimen) was tested in a randomised, placebo-controlled, single-masked trial in 30 patients with chronic cutaneous sarcoidosis (Drake et al. 2013). A significant decrease in lesion diameter and reduction in granuloma burden and lesion severity were observed for the CLEAR-treated cohort (14 patients) compared to treatment with placebo (15 patients). Immune transcriptome analysis via gene expression profiles of sorted CD4+ and CD8+ T cells showed activation of interferon signalling pathway, Jak-Stat signalling and mitogen-activated protein kinase.

Anti-TNF-α Agents

Granulomas are composed of macrophages, epithelioid cells, multinucleated giant cells and CD4+ T cells that are surrounded by monocytes, mast cells, CD8+ T cells and B lymphocytes. The finding was that TNF-α plays an important role for the formation and maintenance of granulomas by interfering with the maintenance of these cells at the location of granulomas and microenvironment. This gave the rationale for treatment with drugs that inhibit the production or action of TNF-α, biologic anti-TNF-α inhibitors such as adalimumab, infliximab or etanercept. Treatment with etanercept, even successfully reported in some single cases (Tuchinda and Wong 2006), does not seem very convincing compared to infliximab or adalimumab and is clearly inferior in cutaneous and pulmonary sarcoidosis. Overall, etanercept is not recommended for the treatment as in addition to inferior responsiveness compared to infliximab and adalimumab, it might induce non-infectious sarcoid-like granulomas (Burns et al. 2012).

Overall, there are more reports on the use of infliximab than for adalimumab for treatment of sarcoidosis. Both have achieved favourable results after other treatments were unsuccessful. In a small case series of patients with recalcitrant cutaneous sarcoidosis and multiple organ involvement (lung, lymph nodes, eye) but with multiple unsuccessful systemic pretreatments (corticosteroids, minocycline, thalidomide, methotrexate, quinolones), the patients received infliximab 5 mg/kg at 0, 2, 6 and 8 weeks (three patients) or adalimumab 40 mg every week or every other week (two patients) after a loading dose of 80 mg. All patients improved after three doses over a 2-month period and were still clear after 4 months at least (Wanat and Rosenbach 2012).

It has been demonstrated that infliximab is the most effective drug for treating lupus pernio in recalcitrant cases in one large retrospective series of 54 patients (Stagaki et al. 2009). The objective response rate regarding achieving resolution, near resolution or improvement of lesions was best for infliximab (77 %) and superior to corticosteroids plus noncorticosteroids (29 %), corticosteroids alone (20 %) and noncorticosteroids (11 %). In another case series of ten patients with skin, lung, liver, bone and muscle involvement, all patients responded to infliximab.

In a retrospective clinical trial investigating the efficacy of long-term use of infliximab in 26 patients with proven pulmonary and extrapulmonary sarcoidosis, sustained improvement was observed in 58.5 % of assessed organs whereas in 35.8 % no clinical change, and in 5.7 % a progression was observed. Infliximab has also been used in a large multicentre randomised double-blind, placebo-controlled clinical trial which included 138 patients with pulmonary sarcoidosis. (Patients receive infliximab (3–5 mg/kg) or placebo at weeks 0, 2 and 6 and then all 6 weeks up to 1 year).

Nineteen of these patients had lupus pernio, which generally seems to respond well to infliximab treatment. A significant improvement in the

forced vital capacity was noticed, and even no statistically significant difference in the appearance of facial lesions was evident. Further analysis of the study results suggested that infliximab therapy was most helpful in the severe cases. In a double-blind, randomised, placebo-controlled, open-label clinical trial of adalimumab in the treatment of cutaneous sarcoidosis, adalimumab was administered to ten patients and placebo to six patients. Treatment was given randomly and double-blinded for 12 weeks, followed by an open-label additional 12 weeks and an 8-week no-treatment period. At the end of the 12-week, double-blind phase, there was a significant improvement in the skin lesion in adalimumab-treated patients relative to placebo-treated patients. At the end of the additional 12-week open-label phase, significant improvement relative to placebo was found for target lesion area, target lesion volume and Dermatology Life Quality Index score, whereas no significant changes were seen in pulmonary function tests, radiographic findings or laboratory studies. After the 8-week off-treatment period, there was some loss of this improvement. Overall anti-TNF-α inhibitors might be an interesting option in steroid-resistant sarcoidosis (Denys et al. 2007).

For both anti-TNF-α agents, there is the risk of activation of tuberculosis and the induction of anti-TNF-α antibodies or other autoimmune diseases (systemic lupus erythematosus, vasculitis). Typical side effects include headache, musculoskeletal symptoms, infection, vision problems and dizziness.

Mycophenolate Mofetil

Mycophenolate mofetil was used in doses of 30–45 mg/kg/day to improve skin lesions up to 70–90 % of patients with cutaneous and systemic sarcoidosis that had been refractory to other systemic therapies within 3–6 months. Treatment allowed to taper prednisone. It has been reported also to be effective in neurosarcoidosis, renal sarcoidosis and sarcoidosis uveitis.

Retinoids

Isotretinoin has been used for cutaneous sarcoidosis in same cases in doses of 0.5–2 mg/kg/day. Due to its teratogenic potential, it is problematic since a cohort of patients that develop sarcoidosis include women of childbearing potential.

Azathioprine

There is only little data on the use of azathioprine in sarcoidosis. It is mainly used as a corticosteroid-sparing agent with a dose of 2 mg/kg daily together with prednisolone 0.1 mg/kg. However, experience with azathioprine in sarcoidosis is limited. Side effects include hepatotoxicity, haematotoxicity and gastrointestinal problems.

Cyclophosphamide

Cyclophosphamide is a cytotoxic agent that is used systemically (500–1,500 mg i.v.) every 2–4 weeks. There are no larger case series that have tested the efficacy of cyclophosphamide in cutaneous sarcoidosis. Case reports indicate efficacy in the treatment of neurosarcoidosis or myocardial sarcoidosis (Demeter 1988). Adverse effects include stomatitis, nausea, hepatotoxicity, bone marrow suppression, haemorrhagic cystitis or bladder carcinoma.

Cyclosporin A

Cyclosporin A is attractive regarding its potent inhibition of interleukin2 and suppression of Tlymphocyte proliferation and reduction of monocytes' chemotaxis. However, the clinical benefit is rather low as observed in large patient cohort studies. Patients were randomised in an openlabel study to receive prednisolone alone or in combination with cyclosporin A for 18 months. The use of cyclosporin A did not confer an additional benefit given that the combination group was characterised by an increase in the number of relapse infections and adverse events (Wyser et al. 1997). Pia and colleagues observed a complete and lasting remission in patients treated with the combination of methotrexate, cyclosporin and flucortolone, but the exact role of each agent cannot be determined (Pia et al. 1996).

Allopurinol

Some authors have observed remission of pulmonary and cutaneous sarcoidosis in patients treated with allopurinol that was used originally to treat

hyperuricaemia. Allopurinol is used in doses of 300 mg/day. Its main indication is cutaneous sarcoidosis, and it might be used for recalcitrant cases that are resistant to corticosteroids and quinolones. Side effect profile is low and includes gastrointestinal problems and skin rash. However, larger clinical trials are missing as in a lot of other drugs used for sarcoidosis.

Treatment Algorithm

A potential treatment algorithm of cutaneous sarcoidosis in case of cosmetically significant, symptomatic skin lesions without systemic involvement could start with topical treatment using corticosteroids, either topical potent corticosteroids or in case of recalcitrant single lesions also corticosteroids via intralesional injection.

In case of recalcitrant skin lesions or a rapid advancing disease and/or organ involvement, treatment could start with chloroquine or hydroxychloroquine or systemic corticosteroids and addition of steroid-sparing agents such as chloroquine, hydroxychloroquine or methotrexate. In case there is no improvement after 6–9 months or in case of lupus pernio, the option would be the anti-TNF-α drugs infliximab or adalimumab.

If an antimicrobial trigger is present or assumed, antimicrobial treatment with minocycline or tuberculostatic treatment is an option.

Allopurinol is a third- or fourth-line drug with a low side effect profile.

Systemic Treatments at a Glance

- Glucocorticoids in doses of 0.5–1 mg/kg are recommended in rapid progressive skin and organ involvement.
- Steroid-sparing agents include antimalarial drugs chloroquine and hydroxychloroquine, methotrexate and the less frequently reported drugs azathioprine and mycophenolate mofetil that could be used together with corticoids or alone.
- Chloroquine/hydroxychloroquine and methotrexate are the drugs with the longest experience and have been proven to be successful in treating cutaneous sarcoidosis.
- Anti-TNF-α drugs infliximab and adalimumab are effective in recalcitrant sarcoidosis, and infliximab is a good choice especially for recalcitrant lupus pernio.
- Etanercept was less successful than infliximab and adalimumab and would not be recommended.
- Antimicrobial treatment with minocycline and antimycobacterial treatment regimens are useful when microbial antigens are suspected.
- Thalidomide, fumaric acid, cyclosporine A and allopurinol have shown some efficacy reported in case series and might be used as third- or fourth-line therapy or if the other drugs are less tolerated.

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Scabies

86

Anna Górkiewicz-Petkow

Key Points

- Scabies is a contagious skin infestation caused by the human mite *Sarcoptes scabiei*.
- It remains a significant public health problem worldwide. Scabies infestation is independent of socioeconomic situation, age or sex.
- Epidemics of scabies occur in hospitals, nursing homes and schools. Spreading of the disease often depends on late and incorrect diagnosis especially for hyperkeratotic scabies.
- Treatment should be applied preferably after the confirmation of the clinical diagnosis.
- Effectiveness of the medications depends not only on the drugs but also on the proper use according to instructions.

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Definition and Epidemiology

Scabies is an ectoparasite skin infestation. The role of mites as a cause of ectoparasite skin infestations in man has often been underestimated. In the presence of a pleomorphic, pruritic and papular eruption, the possibility of mite infestation should be taken into account. Scabies has been recognized for thousands of years. The causative mite was discovered in the seventeenth century.

Basic Concepts of Pathogenesis

The causative mite is *Sarcoptes scabiei* var. hominis. The scabies infestation is independent of socioeconomic situation (although in underdeveloped countries, prevalence is very high). It affects more often younger population. Scabies occurrence rate varies from 2.71 per 1,000 to 46 %. About 300 million people are infected with scabies globally at any given time (accuracy of this estimate is impossible to verify). Epidemics of scabies still occur in schools, hospitals and nursing homes, within families and between immunosuppressed patients. Frequently inadequate epidemiological recognition, and consequent inadequate treatment, is the cause of the spread of disease. Scabies is easily transmitted by skin-to-skin contact or through contaminated environment (dust, chairs, curtains, sheets,

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_86, © Springer-Verlag Berlin Heidelberg 2015

pillows, toys). Adult female mites can survive 24–36 h at room temperature. The incubation period varies from 4 days to 6 weeks. The number of mites living on an infected host varies from 50 mites to several million in crusted (hyperkeratotic) scabies and human immunodeficiency syndromes.

Clinical Presentation

The skin lesions associated with scabies result from a type I and type IV immunological hypersensitivity reaction to the mite or its faecal pellets. Skin lesions are various, depending on local and general immunological response.

The primary complaint of a patient with scabies is itching, particularly at night (it has been suggested that it may be connected with increased activity of the female mite in warmer and darker conditions or to an immune response to the mite and its products). The onset of symptoms is gradual. Pruritus begins slowly (in some varieties of scabies, it is not pronounced); the patient is unable to point the exact date of symptoms or rash. Symptomatic pruritus can persist for 2–4 weeks after treatment, while the dead mites in the outer layers of stratum corneum are sloughed off with normal exfoliation. Conversely in reinfestation, symptoms reappear almost immediately. The most characteristic features of scabies are burrows and vesicles, and the less characteristic are papules, pustules, excoriations, nodules and bullae. Affected areas include the hands (interdigital areas and palms), lateral borders of feet, ankles, elbows, breasts, periumbilical area, genitals (particularly penis and scrotum) and buttocks. In children under 2 years of age, possible involvement of the face and soles is observed. In severe cases or in immunosuppressed patients, scabies can involve the entire skin surface. There have been reports on subungual and nail involvement in persons with crusted scabies or in neonatal scabies. Scabies can coexist as an additional infection with sexually transmitted diseases and different skin diseases like psoriasis, atopic dermatitis and dermatitis herpetiformis, making the diagnosis more difficult.

Complications of Scabies

These include urticarial reactions, persisting dermatitis and pruritus after treatment, nodular lesions and psychological problems (parasitophobia). There are reports on pemphigoid-like eruption and histiocytosis-like lesions in patients treated for scabies. Not recognized scabies infestation is complicated by chronic pyodermas, possibly with MRSA, or streptococcal strain bacterial infection, which can cause renal or heart disease. This problem is emerging in underdeveloped countries.

Clinical Variants of Scabies

Crusted (Hyperkeratotic, Norwegian) Scabies

This is a distinctive form of scabies with a predilection for the physically disabled, mentally ill individuals and immunosuppressed patients, and can, although seldom, also occur in healthy individuals. Keratotic scabies is not very rare and can mimic other skin conditions such as psoriasis, exfoliative dermatitis and T-cell lymphoma, and therefore is often misdiagnosed. The increased use of immunotherapies may also predispose to crusted scabies. The most characteristic lesions are hyperkeratotic plaques (due to excessive keratinocyte proliferation) involving scalp, ears, knees, palms and soles. The lesions are heavily infested with mites, which can be detected also in the patient's environment (bed, linen, floor, carpets). Pruritus is rare but occasionally may be severe. These patients are often a source for scabies epidemics in nursing homes and hospitals.

Neonatal Scabies

Neonatal scabies differs from that seen in older patients by its generalized character involving all body areas. Lesions consist of papules, vesicles and crusts. It often occurs with secondary infection with weeping and desquamation. The itch is not always present.

Diagnosis

There is no standardized method to diagnose scabies. Scabies should be suspected in patients with nocturnal itch, erosions and pleomorphic lesions in typical distribution. A definite diagnosis requires identification of the mite or eggs in the presence of burrows. Burrows may appear as elevated lines or erythematous or oedematous linear lesions, sometimes with vesicle formation at the top. The brownish to black discoloration of the burrows is due to the presence of faeces, eggs or the mite itself. Burrows may be better seen by applying mineral oil on the skin and liquid tetracycline preparations or by burrow ink test. The next possibility to confirm scabies infestation is to demonstrate the scabies mite by extracting the mite by scrapings from the burrows with a sterile needle, by shaving or stripping the lesion with cellophane tape and by examining the obtained material under the microscope (Fig. 86.1).

Other methods include standard dermoscopy of the lesions. Mites appear as small triangular objects within the burrow area. Epiluminescence microscopy requires expensive technically setting. There are reports of using PCR and serological test for scabies-specific IgE and IgG antibodies.

Differential Diagnosis

Skin Eruption Caused by Other Mites

Domestic animals (birds, dogs, cats, and rabbits), dust and grain may be the source of infestation. The main difference in the clinical picture is the lack of burrows. The eruption consists mainly of papules, urticarial lesions and vesicles with no characteristic distribution. The itch persists all day. To confirm the diagnosis, a detailed history about work conditions, hobbies, domestic animals and detection of mites in the environment may be helpful.

Differentiation from Other Skin Diseases

These include allergic dermatitis, pyoderma, ecthymatosis, Darier's disease and dermatitis herpetiformis.

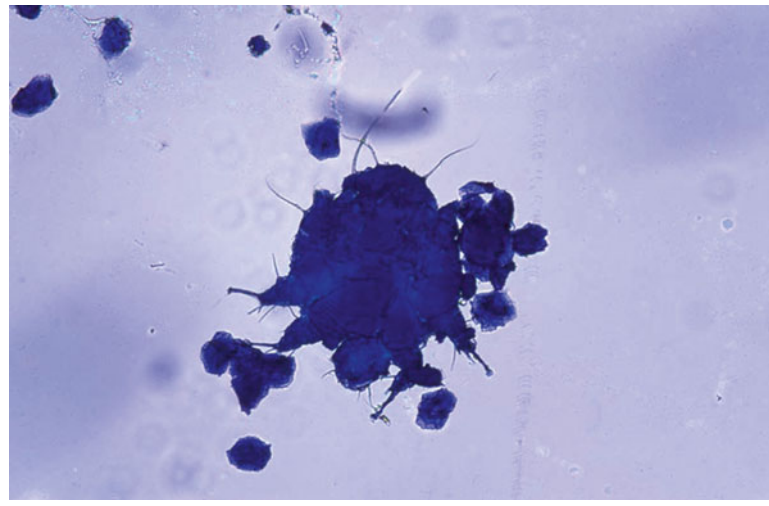

Fig. 86.1 Diagnosis of scabies by scrapings from the burrow

Special Considerations

- Proper diagnosis and choice of adequate treatment of scabies is vital.
- Treatment of endemic disease in nursing homes, schools, large hospitals and communities (ethnic groups, army).
- Diagnosis of crusted scabies.

General Principles of Treatment

General Therapeutic Guidelines

There are a variety of various scabicides so the choice of treatment depends often on the personal preferences of the medical officers, availability of the drug or economic situation of the patient. In each case it is necessary to confirm diagnosis and source of infestation, which relates also to non-human mite infestations. There are several questions to be addressed before starting the treatment. Because the use of scabicides can cause irritation, patients should be warned against overtreatment, and only physicians, in cases of persistent infestation or reinfestation, should decide about repeated applications. If secondary infection is present, antibiotics should be prescribed. Sometimes pruritus persists for several weeks after completion of the treatment. In these patients the antihistamines and emollients may be helpful. Treatment should always be carefully supervised since most failures are due to inadequate application of scabicide. All members of the family and all contacts should be treated, even where there is no evidence of infection. The environment should be decontaminated, especially in cases of crusted scabies. All personal clothing and bed linen should be changed and washed. In large-scale epidemics, it is advisable to establish treatment centres.

Scabicides are also described in the relevant chapter.

Remember:

- To start treatment after confirmation of diagnosis
- To give all instructions and explanations to the patient
- To treat all contacts
- To treat the whole body including intertriginous areas, toenails and subungual areas
- To follow strictly the instructions of the manufacturer
- To choose adequate medication for children, pregnant women or immunocompromised patients
- To be aware of greater permeability of scabicides in patients with impaired skin barrier
- To remove hyperkeratosis before starting topical treatment in crusted scabies

Recommended Therapies (Table 86.1)

Topical Treatments

Pyrethrins

Commercial Preparation: Lyclear Dermal Cream 5 % Permethrin

Permethrin synthetic pyrethroids are well tolerated, adverse reactions are rare, and irritation of the skin is infrequent. For the treatment of scabies in adults, a single application, after a bath, for 8–12 h, repeated in 1 week apart is recommended. Permethrin can be used in neonates and children under 2 years of age in reduced amounts and in pregnant women with caution.

Table 86.1 Recommended topical treatment for scabies

Scabies	
Adults	Permethrin 5 % cream
	Malathion 0.5 % aqueous sol.
	Benzyl benzoate 25 % sol.
	Sulphur 6–15 % ointment
	1 % ivermectin lotion
Pregnant women	Sulphur 6–10 % ointment, crotamitone, (permethrin 5 % cream, benzyl benzoate 10 % – with caution)
Children	Sulphur 6 % ointment, crotamitone
	Permethrin 5 % cream after 2 months of age in reduced amounts
	Benzyl benzoate 10 % (excluding neonates and under 4 months of age)

Treatment schedules in the chapter on scabies and pediculosis

Chlorinated Insecticides

- Gamma-hexachlorocyclohexane – lindane 1 % emulsion
- Commercial preparations – Jacutin, Quellada lotion, Aphtiria

Adverse reactions are possible. Central nervous system (CNS) toxicity occurs only if not properly used or ingested. It is not recommended for neonates, small children under 4 years of age or pregnant women. The following recommendations have been proposed to minimize the potential risk of lindane treatment: it should not be applied after a hot bath which can enhance absorption, in very slim, cachectic patients (atrophy of fat tissue is facilitating absorption) or in patients with massive excoriations or dysfunction of epidermal barrier. Lindane should be washed off the skin after 8–12 h, with only two applications possible in 1 month. Treatment schedule is one or two applications on two consecutive nights. Recently lindane has been withdrawn from the treatment of scabies in many countries due to possible neurotoxicity.

Benzyl Benzoate

- Commercial preparations – Ascabiol 10 % solution for children, 25 % for adults
- Adverse reactions – locally irritant
- Treatment schedules (not unified) – after bath two to three applications with 12-h intervals. May be used in children, excluding neonates, those under 4 months of age and pregnant women in concentration

Anticholinesterase Inhibitors

- Commercial preparation – Derbac-M (malathion 0.5 % aqueous sol.)
- Treatment schedule – single application for 12 h, not preceded by the hot bath. May be used with caution in children and in pregnant women

Sulphur

- 5 %, 10 % in petrolatum base, 25 % in zinc base.
- Adverse reactions – local irritation.
- Treatment schedules – after bath 3 to 4 applications with 12-h intervals. For children lower concentration is indicated. The major disadvantages of sulphur are its unpleasant smell and messy consistency.

Crotamitone

- Commercial preparations – Eurax, Euraxil.
- Crotamitone has lower potential as scabicide but has in addition some antipruritic activities.
- Treatment schedule – after bath on 4–5 consecutive nights. May be used in children and pregnant women. Also used for the treatment of postscabietic pruritus or pruritus of other origin.

Systemic Treatments

Ivermectin

- Commercial preparation – ivermectin (Stromectol).
- Ivermectin is an antiparasitic agent with a structure similar to the macrolide antibiotics, but without antibacterial activity. It is a synthetic derivative of abamectin. The drug has an endectocidal effect causing paralysis by suppressing the conduction of the nervous impulses in the interneuronic synapses of parasites. Ivermectin is widely used for the treatment of onchocerciasis.

Since 1992 there have been reports on systemic administration of this drug for uncomplicated scabies infestations in humans (Polynesia, India, Sierra Leone, Mexico, and the USA) or scabies in HIV-positive patients. A single oral dose of 100 or 200 fg of ivermectin/kg or two repeated doses in weekly interval are given in HIV-positive patients, crusted scabies or epidemics in nursing homes. Sometimes the use of concomitant topical treatment is recommended, e.g. benzyl benzoate. The benefits of oral ivermectin are high therapeutic efficacy (quick relief of pruritus), good tolerance, administration once a weak, lack of local irritation and action on the whole body surface. There are reports on topical use of ivermectin 1 % lotion for

scabies with an effect comparable to 5 % permethrin cream.

Further clinical studies are necessary to evaluate optimal regimen of treatment, to exclude possible interactions with topical treatments (e.g. lindane) and to assess the incidence of serious adverse reactions.

Thiabendazole

Thiabendazole has a broad spectrum of anthelmintic action (strongyloidiasis, cutaneous larva migrans). In South America, there are reports on oral administration of thiabendazole in the treatment of scabies (25 mg/kg for 10 days) and on thiabendazole 5 % cream for topical treatment of scabies applied for 5 consecutive nights.

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Seborrheic Dermatitis

87

Andrea Kovacikova Curkova and Maria Simaljakova

Key Points

- Seborrheic dermatitis is a chronic, relapsing, papulosquamous inflammatory skin disorder.
- The etiology is still not completely understood. *Malassezia* yeasts have a major role.
- Satisfactory therapeutic results are achieved with topical antifungal agents of the azole class, which are considered as the first-choice treatment for seborrheic dermatitis offering more sustained relapse-free periods as compared with corticosteroids and without their side effects.
- Topical glucocorticosteroids are also effective, but long-term use should be avoided due to side effects.
- Other topical agents with proven efficacy may be used as complementary therapy.
- Narrowband UVB phototherapy should be considered for severe, widespread, and/or resistant disease.
- Oral antifungals carry the potential risk of serious hepatotoxic side effects from repetitive use.
- Severe and therapy-resistant forms of seborrheic dermatitis can be predictors of some serious conditions such as HIV infection.

Definition and Epidemiology

Seborrheic dermatitis is a chronic recurrent inflammatory skin disorder frequently occurring in infancy and adulthood. It clinically presents with sharply demarcated erythematous papules, patches, and plaques with greasy scales primarily affecting areas of high sebaceous gland activity, namely, the scalp, face, upper chest, upper back, and flexures. Itching can be present. The estimated prevalence of adult seborrheic dermatitis is 3–5 %, with a predilection in men. It has two incidence peaks, the first in the first 3 months of life and the second beginning at puberty and chronically relapsing until the third and fourth decade of life. A higher incidence can be found among patients with HIV infection or neurologic disorders like Parkinson's disease or mood disorders. The etiology and pathogenesis of seborrheic dermatitis remains controversial. However, the focus is put on the involvement of *Malassezia* yeasts or fatty acid metabolites of *Malassezia*, hormones (androgens), sebum levels,

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_87, © Springer-Verlag Berlin Heidelberg 2015

and immune response. Additional factors including drugs, winter temperatures, and stress may exacerbate the disease. The diagnosis is usually clinical, based on history and the appearance and site of skin lesions. A variety of treatment modalities are available, mainly consisting of antifungal agents, topical corticosteroids, keratolytics, and calcineurin inhibitors (immunomodulators). Due to the chronicity of the disease with frequent relapses, a treatment strategy in which effectiveness and potential side effects are weighed should be used.

Basic Concepts of Pathogenesis

Despite a high prevalence of seborrheic dermatitis, the exact cause is not clearly understood. The exact pathogenetic mechanism also remains controversial.

Malassezia Yeasts

Growing evidence indicates that *Malassezia* species (spp.) are a major etiologic factor in the development of seborrheic dermatitis. *Malassezia* yeasts are lipophilic microorganisms that are most often found on skin areas rich in sebaceous glands – the scalp, face, and upper trunk. *Malassezia* spp. yeasts use fats as principal food source and are normal skin commensals of humans of any age. There is an observed variability in the microscopic morphology of *Malassezia* spp. depending on the species. *Malassezia* spp. are dimorphous fungi that are able to exist in both yeast and mycelial forms.

Species distribution of the *Malassezia* yeasts in seborrheic dermatitis shows some geographical characteristics. *Malassezia obtusa* are the most frequent species in patients with seborrheic dermatitis from Eastern Europe. *Malassezia globosa* and *Malassezia restricta* are the predominant species in seborrheic dermatitis in the USA and Japan. In Greece, *Malassezia globosa* and *Malassezia sympodialis* are isolated from patients with seborrheic dermatitis. In Germany and in Bulgaria, *Malassezia furfur* is the most prevalent species. The geographical variations of *Malassezia* spp. are constantly being updated with new data.

The number of *Malassezia* spp. decreases after antifungal therapy with vanishing of skin lesions. The number of the spores is reduced, which in turn increases the relapse-free intervals of the disease. This is probably the strongest evidence for the importance of *Malassezia* yeasts in the development of seborrheic dermatitis.

Malassezia spp. have the ability to produce lipases that can initiate inflammatory response by releasing unsaturated fatty oleic and arachidonic acid from the sebum lipids. Both of these acids have direct irritative and desquamative effects on keratinocytes. Arachidonic acid metabolized by cyclooxygenase produces proinflammatory eicosanoids (specifically prostaglandins), which lead to inflammation and consequent damage of stratum corneum. Keratinocytes in affected areas are stimulated to produce proinflammatory cytokines that further intensify and maintain the inflammatory response. Elevated levels of cytokines were observed from seborrheic dermatitis lesions – IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α, and IFN-γ. These inflammatory mediator molecules were measured from punch biopsy samples using immunohistochemistry. Also nonlesional skin from patients with seborrheic dermatitis showed elevated levels of proinflammatory cytokines compared to normal skin. These data support the inflammatory component of seborrheic dermatitis.

Hormones and Sebum

Despite the fact that seborrheic dermatitis is not always associated with excessive secretion of sebum, 50 % of patients have an oily skin. Sebum lipids are essential for *Malassezia* proliferation and synthesis of initial proinflammatory factors. Therefore, seborrheic dermatitis is most common in puberty and adolescence, during periods of highest sebum production. The occurrence of seborrheic dermatitis in puberty and more commonly among males suggests an influence of androgens on the pilosebaceous unit.

Immune Response

The lipid-rich layer around the yeast seems to play an important role in its transformation from saprophyte to pathogen. The lipids in the cell wall protect *Malassezia* yeast from the host defense mechanisms in the scenario of normal cutaneous commensalism. However, the lipid layer may be altered in seborrheic dermatitis, which leads to a better detection by the immune system of the host followed by an inflammatory reaction. The pathogenesis of the disease is complex. Both nonimmune and immune mechanisms – specific and nonspecific – are involved. Which of the mechanisms will dominate in each individual patient and what will be the degree of severity of the disease with a certain profile of stimulated inflammatory interleukins will depend on the yeast itself (type, amount, pathogenicity) as well as on the individual reactivity of the organism.

There is an increase in the number of natural killer 1+ (NK1+) T cells and CD16 cells associated with complement activation in seborrheic dermatitis lesions, suggesting an intense, irritative, nonallergic immune response. Understanding the ability of *Malassezia* to either upregulate or suppress the individual immune response directed against it may be the key to understanding how *Malassezia* spp. occur both as commensals and as pathogens.

Despite the presence of hypergammaglobulinemia (IgA and IgG antibodies) in patients with seborrheic dermatitis, there are no detected elevated titers of antibodies specific to *Malassezia* antigens. This suggests that the increased immunoglobulin production occurs as a response to yeast toxins and lipase activity.

The strongest evidence for immunodeficiency as an etiologic factor in seborrheic dermatitis is associated with findings that the prevalence of the disease is significantly higher (34–83 %) among HIV-positive and AIDS patients compared to the general population (approximately 3 %). A more severe clinical presentation of seborrheic dermatitis (often affecting extremities) has been observed in HIV-positive patients. Seborrheic dermatitis occurs most often in individuals with a CD4+ T-lymphocyte count of 200–500 and is considered as an early skin manifestation of AIDS. Seborrheic dermatitis in these patients is considered by some authors as a distinctive entity – seborrheic-like dermatitis of acquired immunodeficiency syndrome. Response to antiretroviral therapy is variable with contradictory reports in the literature.

Neurogenic Factors

There have been long clinical observations of the frequent occurrence of seborrheic dermatitis in patients with Parkinson's disease, who may have increased plasma levels of α-melanocyte-stimulating hormone (α-MSH), probably due to the lack of MSH-inhibiting factor as a consequence of insufficient dopaminergic neuronal activity. Treatment with L-dopa restores the synthesis of MSH-inhibiting factor and reduces sebum secretion in patients with Parkinson's disease. The masklike face in Parkinson's disease patients can secondarily lead to the increased accumulation of sebum, thus contributing to the development of seborrheic dermatitis.

Seborrheic dermatitis frequently occurs in patients treated with neuroleptic drugs, as well as in patients with tardive dyskinesia, central nervous system trauma, and facial nerve palsy.

Frequent occurrence of seborrheic dermatitis is also among patients with depressive disorders. This could also be attributed to the altered lifestyle of such patients, to remain indoors, as well as to poor hygiene habits.

Other Factors

Familial predisposition is observed in 28 % of the patients. The only description of HLA typing in non-Caucasian patients with seborrheic dermatitis was published in 1976 by Tsuji et al. The investigators typified an increase in the frequency of HLA-AW30 and/or AW31 and HLA-B12 in seborrheic dermatitis. The oily secretion of the skin and seborrheic status are genetically determined. Stress and urbanization have an unfavorable

effect on the spread of seborrheic dermatitis. Relapses of the disease have a seasonal aspect and are more common in winter. Exposure to sun has a positive effect on the skin lesions. This improvement could be explained with the seasonal changes in the lipid secretion. Changes in pH of the skin may be triggered by hyper- and dysseborrhea. Many shampoos and cosmeceuticals change the pH on the skin surface. In patients with dandruff, neutral to alkaline pH (6.0–7.0) is found in the area of the lesions. The optimal pH for growth of *Malassezia* is between 5.5 and 6.5.

Seborrheic dermatitis can be triggered by emotional stress and sleep deprivation. Diet rich in sugar intake is also blamed for the development of seborrheic dermatitis. A severe seborrheic dermatitis-like rash can be produced by zinc deficiency in patients with acrodermatitis enteropathica and acrodermatitis-like conditions. However, a supplementary zinc therapy usually does not relieve the symptoms of seborrheic dermatitis.

Clinical Presentation

Typical lesions for seborrheic dermatitis are erythematous macules or thin plaques with well-defined borders with fine, dry white or greasy yellowish scales of varying extent and degree of intensity. The predilection areas consist of numerous sebaceous glands, such as the scalp, hairline, eyebrows, glabella, nasolabial folds, external ear, retroauricular region, neck, upper chest, back, axillae, umbilicus, and groins. The disease may either be limited to small areas of the body, or there may be generalized forms and even forms of erythroderma. Patients may often report pruritus of the lesions, predominantly on the scalp and in the ear canal. Complications of the lesions are secondary bacterial infection, which increases the erythema and exudate, local discomfort, and lymphadenopathy close to the affected areas.

Depending on the age group affected, the pediatric form is self-limiting, whereas in adults the disease is chronic. The pediatric form is more prevalent in the first 3 months of life with yellowish adherent scales on the scalp being the most common clinical manifestation. The scales may also develop on the face and in the body folds. If seborrheic dermatitis in an early infancy (first 2 months of life) presents with a generalized form, it is often associated with immunodeficiency. This condition is called erythroderma desquamativa of Leiner. Symptoms include scaling on the trunk and limbs, red patches in the flexural folds, recurrent local and systemic infection, fever, reduced blood protein levels, peeling of the skin, itching, corneal ulcers, wasting of the lymph nodes, anemia, severe diarrhea, wasting, and nervous system deficiency. Greasy scaling is present on the scalp, behind the ears, nose, or eyebrows or around the mouth. If left untreated, the skin infections will cause loss of protein and electrolytes. This disease is caused by a deficit of the complement protein C5. However, case reports have described also deficits in either C3 or C4. Hospitalization is recommended to prevent nutritional deficiencies and infections.

In adults, seborrheic dermatitis is a chronic, relapsing dermatosis that may range from a mild erythema to papular, exudative squamous lesions with periods of exacerbation related to stress, sleep deprivation, and winter months. Scalp lesions extend from a mild desquamation (pityriasis simplex capillitii) to honey-colored crusts firmly affixed to the scalp and hair, which may provoke areas of alopecia (pseudo-tinea amiantacea). Scalp lesions may extend into the forehead skin and form a scaly erythematous border called "corona seborrheica." On the face, involvement of the glabella, the nasolabial folds, and the eyebrows is characteristic (Figs. 87.1 and 87.2). Blepharitis is another symptom of seborrheic dermatitis with honey-colored crusts on the eyelids. In men, the beard area may also be affected with lesions of seborrheic dermatitis. In some individuals, chronic dermatitis of the ear canal may be the only manifestation of seborrheic dermatitis. In the body folds, lesions may acquire a moist, macerated appearance with erythema at the base and around the lesions. They may progress with fissures and secondary infection. On the chest, in the presternal area, lesions of seborrheic

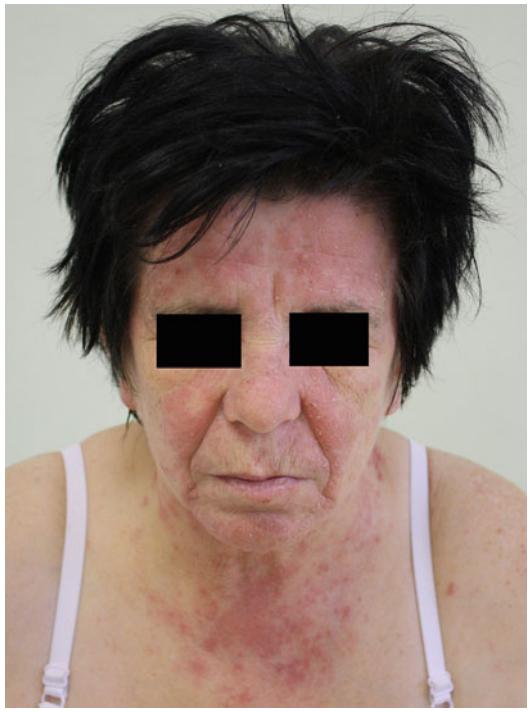

Fig. 87.1 Seborrheic dermatitis in a patient with neurologic disorder

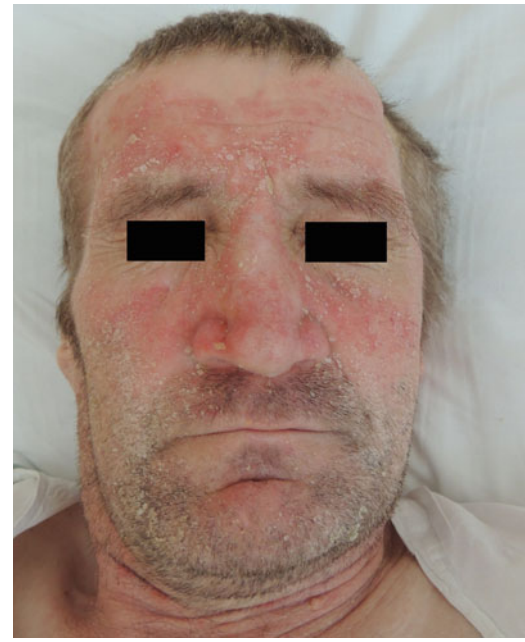

Fig. 87.2 Seborrheic dermatitis on the face and on the chest

dermatitis may occur in two forms: a common petaloid type and a rare pityriasiform type. The petaloid type starts with red to brown follicular and perifollicular papules, which develop to patches that resemble the shape of flower petals, and the scales are over the lesions. The pityriasiform type is probably an acute form of petaloid seborrheic dermatitis, which presents with generalized macules and patches following the skin lines mimicking pityriasis rosea. A generalized exfoliative erythroderma (seborrheic erythroderma) is a serious variant of seborrheic dermatitis.

Differential Diagnosis

The patient's age, gender, affected skin sites, presence of concomitant disorders (especially immunocompromising, neurologic, psychiatric), and family history as well as the patient's daily routine must be taken into consideration when performing differential diagnosis.

The key clinical features to establish diagnosis of seborrheic dermatitis are erythematous and scaling plaques in the scalp, nasolabial folds, eyebrows, and retroauricular regions.

These clinical features may be confused with psoriasis.

Skin biopsy is rarely needed to verify the diagnosis, and associated histologic changes may vary from acanthosis and parakeratosis to spongiosis.

Psoriasis: sharply demarcated erythematosquamous plaques, typical distribution on the scalp, elbows, knees, and lumbosacral area on the back, white-silver color of scales, nail pitting, and distal onycholysis. In the body folds, inverse psoriasis should be differentiated from seborrheic dermatitis. In case of infantile psoriasis, which is very similar to seborrheic dermatitis, it is almost impossible to differentiate between the two conditions. The occurrence of so-called seborrhiasis could be found, indicating a condition with overlapping psoriasis and seborrheic dermatitis on the face.

Atopic dermatitis: history, distribution – extensor surfaces, itch, elevated serum IgE.

Diaper dermatitis: does not affect the body folds, whereas seborrheic dermatitis affects these areas predominantly.

Primary irritant contact dermatitis: history, patch tests.

Dermatophytosis: microscopy with KOH solution, mycology cultivation.

Erythrasma: examination with Wood lamp – coral red fluorescence, bacterial cultivation.

Tinea capitis: microscopy with KOH solution, mycology cultivation.

Pityriasis (tinea) versicolor: on the trunk and upper back. Examination with Wood light – golden yellow fluorescence. Microscopy with KOH solution, mycology cultivation.

Generalized pityriasis rosea: begins with a single "herald patch" lesion most commonly on the abdomen, followed in 1 or 2 weeks by a generalized body rash following the rib line in a characteristic "Christmas-tree" distribution lasting up to 12 weeks. An upper respiratory tract infection may precede all other symptoms.

Acute cutaneous lupus erythematosus: bilateral malar eruption, butterfly erythema; immunologic assessment is required.

Rosacea: chronic erythema on the central face – nose, cheeks, forehead – with telangiectasia, red papules, and pustules. Treatment with topical corticosteroids can aggravate the condition.

Cutaneous lymphoma: skin biopsy (histology), immunohistochemistry, clonal T-cell population, Sezary syndrome (erythroderma), circulating malignant T lymphocytes, and generalized lymphadenopathy.

Cutaneous Langerhans cell histiocytosis: may affect the body folds and the scalp; however, there is a presence of purpuric component in the lesions.

Drug-induced dermatitis similar to seborrheic dermatitis: induced by drugs (gold, buspirone, chlorpromazine, ethionamide, griseofulvin, haloperidol, IL-2, interferon-α, lithium, methoxsalen, methyldopa, phenothiazines, psoralens, and stanozolol, among others).

Nutritional deficiency: riboflavin, pyridoxine, niacin, zinc.

Seborrheic-like dermatitis due to dermatomyositis: severe pruritus of the scalp, Gottron's papules, and a photodistributed poikiloderma.

General Principles of Treatment

Seborrheic dermatitis is a therapeutic problem because of the high incidence of reappearance due to the presence of various predisposing factors. The patient has to be aware of the course of the disease. The objective of treatment consists of controlling the inflammation, the proliferation of the microorganisms, and the oiliness.

Topical treatments are the mainstay of therapy considering the fact that the condition is recurrent, usually mild, and well responding to these agents. The combination of various active ingredients in one single product and the use of rotational therapy are the most effective treatment options.

Recent therapeutic approach is commonly based on topical antifungal, anti-inflammatory, and immunomodulatory agents, thus emphasizing the key underlying pathogenetic mechanisms including excessive proliferation of *Malassezia* spp. with consequent induction of skin inflammatory response. Keratolytics are also highly effective because desquamation is regularly present.

Systemic therapy is required in severe cases with outspread lesions, as well as in cases unresponsive to topical treatments.

Topical Treatments

Antifungal Treatment

Recently, it is generally accepted that initial therapy for seborrheic dermatitis should include topical antimycotics. Topical antifungal agents of the azole class that are usually well tolerated without significant side effects are currently considered as the first-choice treatment. Azole class of antifungal agents (lanosterol 14 alpha-demethylase inhibitors) proved to be most effective in the inhibition of growth of *Malassezia* spp.

Ketoconazole in various vehicles (e.g., cream, foam, gel, and shampoo) showed superior effects

on seborrheic dermatitis among the azole class of antifungals. Ketoconazole shampoo 2 % used twice weekly is effective for scalp seborrheic dermatitis. Intermittent use of ketoconazole 2 % shampoo has been shown to have a significant prophylactic effect. Ketoconazole 2 % cream used twice daily significantly improves lesions of seborrheic dermatitis on the face and chest (similar effect to hydrocortisone 1 % cream). If used intermittently, it is effective in maintaining remission. Ketoconazole also has slight anti-inflammatory properties.

Bifonazole 1 % cream, used once daily, also represents an effective treatment option for seborrheic dermatitis of the scalp and face. A combination ointment containing 1 % bifonazole and 40 % urea reduces seborrheic dermatitis on the scalp.

Miconazole is another effective azole antifungal agent proven to be effective in the treatment of seborrheic dermatitis, either as monotherapy or in combination with hydrocortisone.

Ciclopirox has both antifungal and anti-inflammatory effects. Ciclopirox 1 % cream used twice daily provides a reduction of symptoms of seborrheic dermatitis on the face. Combinations of ciclopirox 1.5 % shampoo with salicylic acid 3 % or zinc pyrithione 1 % are also beneficial. Recent studies report a statistically non-inferior effect of ciclopirox compared to ketoconazole.

Corticosteroids

Corticosteroids (clobetasol propionate) promote anti-inflammatory effect. Long-term use should be avoided because of their well-known side effects. In severe forms of seborrheic dermatitis, low to mild potency topical corticosteroids are effective especially in rapid clearing of visible symptoms, thus limiting inflammation. There is a consensus that topical corticosteroids are useful when applied over a short period, mainly to control erythema and itching. Topical corticosteroids may be used alone or in combination with antifungal agents. Prolonged use is not recommended due to their side effects, such as skin atrophy, telangiectasias, hypertrichosis, and perioral dermatitis. Based on the fact that ketoconazole 2 % foaming gel has been shown to be superior to betamethasone dipropionate 0.05 % lotion in reducing symptoms and lowering the number of *Malassezia* spp., it is still the therapy of first choice.

Calcineurin Inhibitors

Pimecrolimus 1 % cream and tacrolimus 0.03 and 0.1 % ointment decrease cutaneous inflammation by inhibiting the cytokine production driven by T lymphocytes. Calcineurin inhibitors do not have the side effect profile of corticosteroids. In a randomized, double-blind, vehicle-controlled 4-week efficacy clinical trial of twice-daily pimecrolimus 1 % cream in 96 patients, topical calcineurin inhibitor therapy proved to be effective and well tolerated in the treatment of facial seborrheic dermatitis. In another two randomized clinical trials, pimecrolimus 1 % cream proved similar efficacy to topical corticosteroids (hydrocortisone acetate 1 % cream or betamethasone 17-valerate 0.1 % cream). Treatment with topical pimecrolimus also demonstrated longer periods of remission and milder relapses when compared with betamethasone. Pimecrolimus has also been used in comparison to ketoconazole 2 % cream in an open randomized study that showed comparable efficacy. Topical tacrolimus 0.1 % ointment was tried in an open-label 4-week randomized trial against betamethasone 17-valerate lotion and zinc pyrithione 1 % shampoo in 83 patients with scalp seborrheic dermatitis. Tacrolimus ointment showed prolonged efficacy than topical corticosteroids, but the duration of improvement was shorter compared to zinc pyrithione shampoo. Tacrolimus ointment has a highly viscous consistency, which makes it inconvenient to use on the scalp. Application should be limited to lesions of seborrheic dermatitis.

Metronidazole

The effectiveness of 0.75 % topical metronidazole gel is contradictory. In two trials, metronidazole showed greater efficacy than placebo and was equally effective as ketoconazole 2 % cream, while in another study by Koca et al., metronidazole was not found to be superior over placebo in patients with seborrheic dermatitis.

Zinc Pyrithione

Zinc pyrithione has both antifungal and antimicrobial effects. This agent is a common active ingredient in many of the over-the-counter antidandruff shampoos. The available concentration in shampoos is 1 and 2 %, as well as a 1 % cream formulation. In several trials, zinc pyrithione showed lower efficacy compared to ketoconazole. A satisfactory effect was proven when used in combination with ketoconazole.

Lithium Salts

Topical lithium succinate and lithium gluconate may have anti-inflammatory effects. They are effective in treating seborrheic dermatitis in areas other than the scalp. Lithium succinate 8 % ointment showed greater efficacy compared to placebo in the treatment of seborrheic dermatitis in HIV-positive patients. Lithium gluconate 8 % ointment seems to be more effective than ketoconazole 2 %. In an 8-week trial involving 129 patients with facial lesions, lithium gluconate 8 % ointment used twice daily showed better efficacy compared to placebo.

Selenium Sulfide

In a randomized double-blind trial involving 246 patients with moderate to severe dandruff, selenium sulfide 2.5 % shampoo was tested against ketoconazole 2 % shampoo and placebo. Ketoconazole medicated shampoo was better tolerated. Both medicated shampoos showed better efficacy compared to placebo.

Keratolytics

Keratolytics based on salicylic acid (2–6 %) with or without sulfur (2–5 %) help the removal of adherent scales.

Other Topical Treatments

There are few reports of successful treatment of seborrheic dermatitis with benzoyl peroxide, azelaic acid, tacalcitol cream, and MAS064D cream (a nonsteroidal preparation containing multiple active ingredients such as emollients, anti-inflammatory agents, keratolytics, and an antimycotic agent).

Topical Treatments at a Glance

- Topical treatments are the mainstay of therapy.
- The combination of various active ingredients in one single product and the use of rotational therapy are the most effective treatment options.
- The initial and first-choice therapy for seborrheic dermatitis should include topical antimycotics (ketoconazole, bifonazole, miconazole, ciclopirox).
- Topical corticosteroids are useful when applied over a short period, mainly to control erythema and itching.
- Calcineurin inhibitors do not have the side effect profile of corticosteroids. Application should be limited to lesions of seborrheic dermatitis.
- The effectiveness of topical metronidazole gel is contradictory.
- Combination of zinc pyrithione with ketoconazole has proven to be effective.
- Topical lithium salts are effective in treating seborrheic dermatitis in areas other than the scalp.
- Keratolytics are recommended for the removal of adherent scales.

  Selenium and zinc are effective in combination with topical corticosteroids, topical antifungals, or topical immunomodulators.

Systemic Treatments

Orally administered drugs may be used in cases of extensive seborrheic dermatitis and cases resistant to topical treatments.

Oral Antifungal Treatment

Data on the effectiveness of systemic antifungal therapy are limited and not consistent.

The antifungal agents used and their recommended doses are:

- Ketoconazole 200 mg/day for 14–28 days according to the clinical presentation
- Itraconazole 100 mg/day for 21 days
- Terbinafine 250 mg/day for 4 weeks
- Pramiconazole in a single 200 mg dose

Oral ketoconazole 200 mg daily has proven to significantly improve facial seborrheic dermatitis. However, oral fluconazole in a 300 mg single weekly dose has not shown any significantly therapeutic effect.

Itraconazole at an initial dose of 200 mg daily for 1 week, followed by a maintenance single dose of 200 mg every 2 weeks, was useful in patients with moderate to severe seborrheic dermatitis.

Oral terbinafine 250 mg daily has shown greater efficacy on lesions of seborrheic dermatitis in areas other than the face. Due to the possible hepatotoxic effect of systemic antifungals, the benefit of the treatment must be carefully considered.

Pramiconazole is a new triazole agent with potent in vitro antifungal activity against *Malassezia* spp. A single 200 mg dose of pramiconazole shows in vivo efficacy in controlling clinical symptoms of seborrheic dermatitis.

Isotretinoin

Oral isotretinoin as a regulator of seborrhea was suggested for the control of seborrheic dermatitis. Scientific studies on the use of isotretinoin for seborrheic dermatitis have become rare, with the last published in 2003. The doses of the drug used in the study were low (2.5 mg, three times weekly and up to 5 mg/day) with good efficacy. There has been a report on seborrheic dermatitis-like eruption in patients taking isotretinoin for acne.

Systemic Treatments at a Glance

- Oral antifungals are recommended for severe and topical-therapy-resistant seborrheic dermatitis.
- Ketoconazole 200 mg/day for 14–28 days is recommended for seborrheic dermatitis of the face.
- Itraconazole at an initial dose of 200 mg/day for 1 week followed by a maintenance single dose of 200 mg every 2 weeks is recommended for moderate to severe seborrheic dermatitis. An alternative regimen of itraconazole 100 mg/day for 21 days is another option.
- Terbinafine 250 mg/day for 4 weeks is recommended for lesions of seborrheic dermatitis on the trunk.
- Pramiconazole in a single 200 mg dose has shown efficacy in controlling clinical symptoms of seborrheic dermatitis.
- Liver enzymes must be carefully monitored when using systemic treatment with antifungals.
- Isotretinoin in low doses (2.5 mg, three times weekly and up to 5 mg/day) showed good efficacy in seborrheic dermatitis.

Other Treatment Options for Seborrheic Dermatitis

Phototherapy

Ultraviolet B (UVB)

Many patients often notice improvement during the summer months. UVA and UVB light directly inhibit *Malassezia* yeasts cultured from the skin. Narrowband UVB 311 nm is usually used three times per week until clearance or upon completing 2 months of therapy. Patients with widespread seborrheic dermatitis benefit from narrowband UVB phototherapy. The limitations of UVB phototherapy are the frequent visits to a phototherapy unit, a rapid disease relapse appearing usually 2–6 weeks after treatment, burning and itching sensations during phototherapy, and the risks associated with exceeding the maximum lifetime cumulative dose.

Psoralen Plus Ultraviolet A (PUVA)

There have been reports of clearance of seborrheic dermatitis in HIV patients who were administered PUVA treatment (30–262 J/cm^2 every 2–4 weeks). However, there have also been reports of new cases of seborrheic dermatitis appearing during PUVA therapy in patients with psoriasis.

Red and Blue LED Light

Inhibit the growth of *Malassezia* spp. and reduce seborrheic inflammation.

Alternative Therapeutic Approaches

Tea-Tree Oil

Tea-tree (*Melaleuca alternifolia*) oil-based soaps have proven effective in the topical treatment of seborrheic dermatitis due to their potential antifungal effect. They are also available in shampoos for seborrheic dermatitis of the scalp. Rare adverse events have consisted of an occasional irritant dermatitis.

90 % Honey Diluted in Warm Water

Honey is recommended to be gently rubbed in the seborrheic dermatitis lesions for 2–3 min every other day, left on for 3 h before gentle rinsing with warm water.

Fish Oil Supplements

Taking fish oil supplements that contain omega-3 fatty acids may help seborrheic dermatitis. Up to 3 g of fish oil per day is generally considered safe. Fish oil can cause nausea and diarrhea. High doses may increase the risk of internal bleeding.

Patients should be educated to always consult a doctor before adding any alternative treatment of seborrheic dermatitis.

Principles of Treatment at a Glance

- The aim of treatment consists of controlling the inflammation, proliferation of the microorganisms, and the oiliness.
- First-line therapy for seborrheic dermatitis includes local antifungals.
- Topical corticosteroids used for a short course can temporarily relieve itching and erythema.
- Topical calcineurin inhibitors do not have the side effect profile of corticosteroids. Topical application should be restricted to lesions of seborrheic dermatitis.
- Narrowband UVB phototherapy (311 nm) may be efficacious in widespread seborrheic dermatitis.
- Systemic therapy may be used in cases of severe seborrheic dermatitis not responding to topical treatments.
- Wearing smooth-textured cotton clothes helps in avoiding irritation and sweating of seborrheic dermatitis lesions.
- Avoid scratching. Scratching can increase irritation and the risk of infection.
- If one type of medicated anti-dandruff shampoo works for a certain period and then loses its efficacy, try alternating between other types.
- Leave the shampoo on the scalp for the full recommended length of time to allow its ingredients to work.
- Rinse soaps and detergents completely off the body and scalp.
- Use treatments for seborrheic dermatitis exactly as described by the physician.

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Seborrhoeic Keratosis

88

António Picoto

Key Points

- Seborrhoeic keratosis, also known as seborrhoeic wart, verruca seborrhoeica senilis or basal cell papilloma, appears as macules and papules, brownish to grey or black, usually symmetrical and predominantly on the face, trunk and extremities.
- It is common in whites and uncommon in black people and Indians.
- The aetiology is unknown.
- Seborrhoeic keratosis is only of cosmetic concern, so treatment should provide a satisfactory cosmetic result. Curettage, cryosurgery, shaving and chemical peeling are among the recommended treatments.

Definition and Epidemiology

Seborrhoeic keratosis, also known as seborrhoeic wart, verruca seborrhoeica senilis or basal cell papilloma, appears as macules and papules, brownish to grey or black.

Sometimes they are polypoid with a "stuck on" appearance and greasy surface with plugged horns, predominantly on the face, chest and back of adult whites.

They are common in whites (third decade onwards) and uncommon in black people and Indians; probably many cases are dominantly inherited. Males and females are equally affected. Black and Asian patients can develop a variant of seborrhoeic keratosis called dermatosis papulosa nigra. This consists of heavily pigmented papules, some pedunculated, on the face, developing as early as adolescence.

While the aetiology is unknown, there are many clinicopathological variants:

- Reticulated seborrhoeic keratosis
- Stucco keratosis
- Clonal seborrhoeic keratosis
- Irritated seborrhoeic keratosis
- Melanoacanthoma
- Dermatosis papulosa nigra

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_88, © Springer-Verlag Berlin Heidelberg 2015

Clinical Presentation

Seborrhoeic keratosis appears exclusively on hair-bearing skin, often in a "Christmas tree" pattern, and mainly on skin rich in sebaceous glands (Fig. 88.1).

It begins as flat brown maculae that slowly transform into greasy papules, with multiple grey or black plugged follicles. The lesions are often located bilaterally and are symmetrical, predominantly on the face, trunk and extremities.

The sudden appearance of a large number of lesions with pruritus may be associated with internal malignancy, and this is the so-called Leser-Trélat sign.

The associated malignancy is typically aggressive and carries a poor prognosis. GI adenocarcinomas are responsible for approximately one-third of the cases and lymph proliferative disorders for about one-fifth of the cases. The entity is controversial because of a simultaneous increased incidence of seborrhoeic keratosis and malignancy in the elderly.

The lesions are benign. There is no evolution towards malignancy, and they become symptomatic when irritated.

They are of cosmetic concern and may cause difficulties when dressing and undressing. There is no spontaneous resolution (Fig. 88.2).

Diagnosis is usually not difficult looking at the characteristics and distribution of the lesions, but on the face early lesions can be difficult to diagnose. One can press the surface of the lesions with the fingernail and confirm their greasy nature.

Dermoscopy is mandatory. We will look for milia-like cysts, pseudofollicular openings and cerebriform structures. There are two different types of milia-like cysts: large ones (cloudy) and smaller ones (starry). Starry milia cysts are prevalent both in seborrhoeic keratosis and melanomas. Cloudy ones are said to have 99.1 % specificity for seborrhoeic keratosis.

Differential Diagnosis

This includes:

- Pigmented nevi
- Actinic keratosis
- Verruca vulgaris
- Pigmented basal cell carcinoma
- Acanthosis nigricans
- Lentigo and lentigo maligna
- Melanoma

Clinical inspection, better done with the help of a dermatoscope, is usually sufficient to establish a firm diagnosis. Reflectance confocal microscopy apparently has a distinct set of criteria for seborrhoeic keratosis.

When doubt persists there should be no hesitation to biopsy for a histological examination.

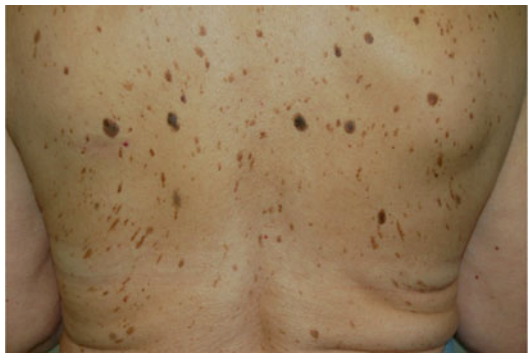

Fig. 88.1 Seborrhoeic keratoses of the trunk

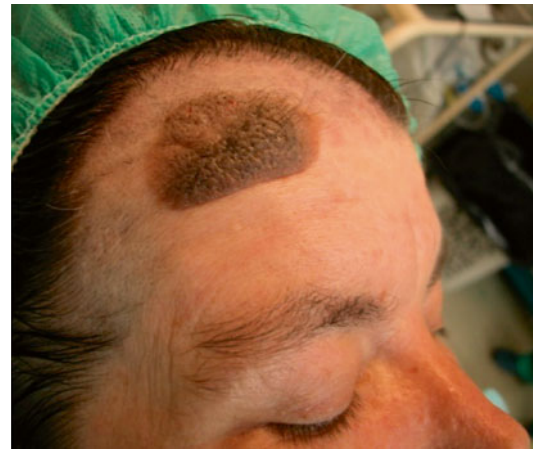

Fig. 88.2 Seborrhoeic keratosis of the forehead

General Principles of Treatment

It has been mentioned before that seborrhoeic keratosis is only of cosmetic concern, so treatment should provide a satisfactory cosmetic result. The treatment should be explained to the patient and consent obtained. Recommendations for home treatment should be given, preferably in writing.

The aim of the treatment will be to destroy the lesions completely, avoiding recurrence, without much pain and leave a cosmetically acceptable scar.

Recommended Therapies

Curettage

You need a sharp curette and local anaesthesia – lidocaine buffered with potassium bicarbonate. Anaesthetic cream before local injection is also a good option, but you will have to wait 60 min.

If the lesions are multiple and this is generally the case, a plan should be done to act in several sessions.

After curettage there is the problem of stopping the bleeding, and for this pressure with a little peroxide, cautery and CO_2 laser are good options. Observe caution to avoid an ugly scar. Some authors recommend the use of aluminium chloride or Monsel's solution, but there is the risk of staining the skin.

Disposable curettes are best suited for the job, but there is a learning curve with their use.

After the procedure the wound is dressed with an antibiotic or Vaseline.

If the lesion is very thick and papillomatose, then the lesion can be first "cooked" with electrodessication or CO_2 laser followed by curettage.

Cryosurgery

Freezing with liquid nitrogen (about 12 s spray) is also a treatment modality useful for multiple lesions.

Shaving

Shaving excision with scalpel or Gillette blue razor is another possible technique, mainly for thick lesions.

Chemical Peeling

Peeling with TCA from 25 to 35 % can be useful in early thin seborrhoeic keratosis of the face.

In conclusion, there is not a perfect treatment so far for this vexing problem.

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Sjögren's Syndrome

89

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Key Points

- Sjögren's syndrome (SS) is a common, chronic autoimmune disorder of unknown origin. The disease affects mainly the exocrine glands, particularly the salivary and lacrimal glands, resulting in dry mouth and eyes.
- In more than a half of patients, it extends beyond the exocrine glands affecting parenchymal organs and small-size arteries producing extraglandular manifestations, including (1) nonspecific, (2) parenchymal organ involvement with periepithelial infiltrates, and (3) vasculitis.
- Skin involvement includes dry skin, flat or palpable purpura, annular erythema, and Raynaud's phenomenon.
- The principal goal in treating the impaired lacrimal and salivary production associated with SS is the successful replacement of glandular secretions.
- Systemic therapy should be considered in patients exhibiting systemic features and tailored to the organ affected and severity including hydroxychloroquine for arthralgias, myalgias, and joint inflammation, methotrexate for florid inflammatory or persistent arthritis, and rituximab. TNFα blockade (infliximab and etanercept) has been proven inefficacious in primary SS in terms of subjective and objective measures of salivary and lacrimal function as well as joint inflammation. Cytotoxic drugs such as cyclophosphamide along with systemic steroid administration (0.5 mg/kg daily) are considered for severe extraglandular manifestations including severe cutaneous vasculitis, glomerulonephritis, and peripheral neuropathy.

Definition and Epidemiology

Sjögren's syndrome (SS) is a chronic autoimmune, systemic disorder. It is characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes. More than 50 % of patients present with systemic manifestations including arthritis; Raynaud's phenomenon; kidney, liver, and lung involvement; as well as vasculitis. A small (around 5 %) but significant number of patients may develop malignant B-cell lymphoma. The disease presents alone (primary Sjögren's syndrome) or in association

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_89, © Springer-Verlag Berlin Heidelberg 2015

with other autoimmune rheumatic diseases including rheumatoid arthritis and systemic lupus erythematosus.

The two major autoimmune phenomena observed in pSS are (a) lymphocytic infiltration of the affected tissues and (b) B-cell hyperactivity. The latter is manifested by hypergammaglobulinemia and the presence of serum autoantibodies including antinuclear antibodies, rheumatoid factor, cryoprecipitable monoclonal immunoglobulins with rheumatoid factor activity, and antibodies against two ribonucleoproteinic complexes named Ro/SSA and La/SSB, as well as against immunoglobulins (rheumatoid factors).

SS primarily affects women (nine women to every man), mainly in the fourth and fifth decades of life. However, it can occur in people of all ages including children and elderly persons. Epidemiological studies in the general population have shown that SS is a rather common disease since it affects approximately 0.5 % of the total population. Indeed, a thorough review of published epidemiology studies disclosed that the prevalence of the disease ranges from 0.1 % to 4.8 %, with increasing rates in advanced age. Heterogenicity in inclusion criteria, ethnic origin, sample size, and sex distribution between studies contributes to the observed variability.

Basic Concepts of Pathogenesis

As for the vast majority of autoimmune diseases, the leading etiopathogenetic events are yet unknown. It appears that all the interplay between environmental contributors (such as viruses, stress, or hormones) and host's genetic background can lead to inflammatory responses against epithelial tissues. It is highly likely that the disease may develop in three stages: (1) autoimmunity can be triggered by an environmental factor, acting on given genetic background, (2) perpetuation of the autoimmune reactivity becomes chronic through normal immune regulatory mechanisms, and (3) tissue injury occurs as a consequence of the ongoing inflammatory process.

The main body of infiltrating cells in the affected exocrine glands are activated T and B lymphocytes. T cells predominate in mild lesions, and B cells in more severe lesions. Macrophages and dendritic cells also are found. The number of interleukin (IL)-18 positive macrophages is correlated with parotid gland enlargement and low levels of the C4 component of complement, both adverse predictors for lymphoma development. Glandular epithelial cells undergo apoptotic death by signals provided from T cells. Ductal and acinar epithelial cells are activated, playing a significant role in the initiation and perpetuation of the autoimmune injury. In fact, they express class II major histocompatibility complex (MHC) and costimulatory molecules. In addition, the intracellular autoantigens are expressed on cell membranes, thus being able to prime an autoimmune response. Importantly, the epithelial cells produce also inappropriately proinflammatory cytokines and lymphoattractant chemokines necessary for sustaining the autoimmune lesion. In around 20 % of patients, the lesion is organized to ectopic germinal centers containing autoreactive B cells. The epithelial cells express also functional receptors of innate immunity, particularly TLR 3, 7, and 9, that may account for the perpetuation of the autoimmune response. B-cell-activating factor (BAFF) has been found to be elevated in patients with Sjögren's syndrome, especially those with hypergammaglobulinemia. Glandular epithelial cells seem to have an active role in the production of BAFF, since it may be expressed and secreted after stimulation with type I interferon, as well as with viral or synthetic dsRNA. These properties of the epithelial cell introduced the term "autoimmune epithelial," which is the etiologic name of the syndrome.

The triggering factor for epithelial activation appears to be a persistent enteroviral infection (possibly by coxsackievirus strains).

Clinical Presentation

The majority of SS patients display an indolent benign course. The initial manifestations can be nonspecific and usually 6–8 years elapse from the initial symptoms to the full blown development of the disease. The clinical features of SS

can be largely divided into those related to exocrine dysfunction (glandular) and to those affecting other organs beyond the exocrine glands (extraglandular or systemic).

Glandular Manifestations

The principal oral symptom of SS is dryness. Patients describe this as difficulty in swallowing dry food, inability to speak continuously, and a burning sensation. The physical examination shows a dry, erythematous, sticky oral mucosa and atrophy of the filiform papillae. Enlargement of the parotids or other major salivary glands can be seen in 50–60 % of patients.

Ocular involvement is the other major glandular manifestation of SS. Diminished tear secretion leads to the destruction of the corneal and bulbar conjunctival epithelium termed keratoconjunctivitis sicca. The patients describe a burning, foreign-body feeling or a sandy or scratchy sensation under the lids, itchiness, redness, and photosensitivity. Clinical signs include dilatation of the bulbar conjunctival vessels, pericorneal injection, irregularity of the corneal image, and sometimes enlargement of the lacrimal glands.

Involvement of other exocrine glands occurs less frequently and includes a decrease in mucous gland secretions of the upper and lower respiratory tree, resulting in dry nose, throat, and trachea (xerotrachea), and diminished secretion of the exocrine glands of the gastrointestinal tract, leading to esophageal mucosal atrophy, atrophic gastritis, and subclinical pancreatitis. Dyspareunia due to dryness of the external genitalia and dry skin also may occur.

Extraglandular Manifestations

Extraglandular manifestations are seen in many patients with primary SS and divided into (1) nonspecific, (2) parenchymal organ involvement with periepithelial infiltrates, and (3) vasculitis, resulting from the deposition of immune complexes. Nonspecific symptoms include easy fatigue, low-grade fear, myalgias, and arthralgias. Arthritis is seen in 70 % of patients and is nonerosive, leading in some patients to Jaccoud's arthropathy. Raynaud's phenomenon is seen in around 30 % of patients and in some patients may precede sicca manifestations by many years. Pulmonary involvement includes dryness of the tracheobronchial mucosa (xerotrachea) and small airways obstruction. Interstitial disease or pleurisy is uncommon. Acute or chronic pancreatitis is rarely reported. In that case IgG4-related syndrome should be ruled out. Chronic liver disease, resembling stage I of primary biliary cirrhosis, is seen in 2–3 % of patients. Renal involvement includes interstitial renal disease and occasionally glomerulonephritis. Vasculitis is found in approximately 10 % of patients with SS. It affects small, primarily sized vessels. The skin is most commonly affected in the form of palpable purpura, but cases with visceral organ involvement such as the kidney, lungs, and gastrointestinal tract have been described. Neurological manifestations of SS include peripheral sensory or sensorimotor neuropathy as a consequence of vascular involvement. Some cases of myelitis associated with antibody to aquaporin-4 have been described.

Lymphoma is a well-known sequela of Sjögren's syndrome and usually presents later during the course of the illness. Persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, low C4 complement levels, and the presence of IL-18, macrophages, and B cells as well as ectopic germinal centers in minor salivary gland biopsies are predicting factors suggesting the development of lymphoma. Interestingly, the risk factors predicting glomerulonephritis and lymphoma are the same with those that confer increased mortality. Most lymphomas are extranodal, low-grade marginal zone B-cell lymphomas and are usually detected incidentally upon evaluating the labial biopsy. The affected lymph nodes are usually peripheral. Survival before the introduction of B-cell-depleting therapy with chemotherapy is decreased in patients with B symptoms, lymph node mass >7 cm in diameter, and high or intermediate histologic grade.

Skin Involvement

Apart from the eyes and mouth, other mucous membranes as well as the skin may exhibit dryness. Nasal dryness with crusting, vaginal dryness with dyspareunia, cheilitis, and xerosis (dry skin) have been described. Patients with dry skin frequently experience dermal stinging and itching.

Skin biopsy and direct immunofluorescence (DIF) show a pattern consisting of IgG deposits in the basal and suprabasal layers of the epithelium, widespread in the intercellular space and demarcating cell surface membranes.

Purpura is a rather common finding in primary SS patients. Flat purpura is usually seen in hypergammaglobulinemic patients, while palpable purpura is a manifestation of dermal vasculitis. The latter is a predictor factor for lymphoma development in the future.

In recent years, numerous reports from Japan claimed hitherto unreported skin lesions in patients with SS. Annular erythemas consisting of wide elevated erythematosus borders with central pallor are located on the face (especially cheek and periocular skin), upper extremities, and back, occasionally coalescing to form polycyclic patterns. The erythema fades within a few months, leaving no scars or pigmentary changes. There is a striking clinical resemblance to Sweet's syndrome. The most conspicuous histologic finding is the lymphocytic infiltration throughout the dermis around blood vessels and appendices. Annular erythema in primary SS is significantly associated with the presence of serum antibodies against Ro/SSA (100 %) and La/SSB (75 %). The annular erythema in SS differs clinically from the polycyclic annular and papulosquamous erythemas in subacute cutaneous LE (SCLE), especially in its edematous borders without significant scaling.

Raynaud's phenomenon occurs in about 30 % of patients with primary SS and usually precedes the sicca manifestations by many years. SS patients with Raynaud's phenomenon present with swollen hands, but in contrast to scleroderma, they do not experience digital ulcers and telangiectasias.

Pernio-like lesions (chilblain) on the distal extremities were noted in Japanese patients. Reports on other skin disorders are rare: one case in which SS and Sweet's syndrome developed simultaneously and one in which a woman developed poikiloderma atrophicans vasculare after 12 years of SS. Two cases of lipodystrophy have also been reported in patients with SS.

Diagnosis

The diagnosis is made after a careful clinical evaluation in every patient presenting with symptoms of oral and/or ocular dryness. The diagnostic approach consists of a complete systems review, including specific questionnaires to assess oral and ocular dryness, clinical examination, and tests evaluating the degree of exocrine gland dysfunction, the presence of relevant immunological abnormalities, and the extent of organ involvement. Since sicca symptoms can be attributed to several different diseases, the differential diagnosis is rather broad. In clinical practice, investigations that should be offered in patients presenting with sicca symptoms include: (1) assessment of lacrimal gland function by measuring tear production using Schirmer's test (wetting on paper strip of less than 5 mm per 5 min; sensitivity and specificity 76.9 and 72.4 %, respectively) and by staining of the cornea and conjunctiva using rose bengal or the less irritating lissamine green staining, which reveals punctuate or filamentary keratitis lesions, typical of keratoconjunctivitis sicca (KCS) (sensitivity 64.3, specificity 81.7), (2) measurement of unstimulated saliva secretion in a graded tube (less than 1.5 ml/15 min is considered abnormal) (sensitivity 56.1, specificity 80.7), and (3) minor salivary gland biopsy assessing the presence of lymphocytic infiltrates around salivary gland epithelium which is the SS hallmark (sensitivity and specificity 82.4 and 86.2 %, respectively). An average focus score >1 in salivary gland biopsy is considered as a classification criterion for SS. It is calculated as the number of lymphocyte foci per 4 mm^2 surface based on a survey of at least four lobules. A focus is a cluster of at least 50 lymphocytes. Patients should undertake full blood count, serum biochemistry tests, protein electrophoresis, antinuclear antibodies,

antibodies against Ro/SSA and La/SSB autoantigens and rheumatoid factor, as well as viral testing for HCV, HIV, and HTLV-1 virus, infections which can produce a clinical picture resembling SS. Anti-Ro/SSA and anti-La/SSB antibodies can be detected in 70–100 and 35–70 % of patients with SS, with anti-La/SSB being considered a highly specific diagnostic marker for the diagnosis of SS. According to classification criteria for SS, which will be discussed below, the presence of these antibodies along with other features implying the presence of SS is sufficient for establishing SS diagnosis, even in the absence of a positive salivary gland biopsy.

Once SS diagnosis is established, additional investigational tests as cryoglobulins, complement levels, and immunofixation should be also asked, particularly in patients with palpable purpura, peripheral neuropathy, salivary gland enlargement, or in situ demonstration of salivary gland lymphoma. Upper gastrointestinal tract endoscopy; CT scans of the neck, thorax, and abdomen; and bone marrow biopsy should be further offered in order to detect the development and extent of the potentially existing lymphoma.

In order to aid in the classification of the syndrome, the international research community proposed the "European-American consensus group criteria" (EACG), which require the presence of either focal lymphocytic infiltrates in minor salivary glands with a focus score of 1 or more or anti-SSA/SSB autoantibodies in the presence of features suggesting salivary and/or lacrimal gland involvement.

Differential Diagnosis

Differential diagnosis must include other diseases responsible for KCS, xerostomia, and parotid gland enlargement. Sarcoidosis is one of the diseases which can mimic the clinical picture of SS. However, there is a lack of autoantibodies to Ro/SSA or La/SB, and sometimes the minor salivary gland biopsy reveals noncaseating granulomas. Other medical conditions which can mimic SS are lipoproteinemias (types IV and V), chronic graft-versus-host disease, amyloidosis, HIV infection, as well as hepatitis C infection. Major salivary enlargement, particularly in patients without anti-Ro/SSA and anti-La/SSB autoantibodies, should raise the suspicion of IgG4-related syndrome which may present also as chronic pancreatitis, interstitial nephritis, retroperitoneal fibrosis, and aortitis.

General Principles of Treatment

General Therapeutic Guidelines

SS remains an incurable disease, since no therapeutic modality that can alter the course of the disease has been identified. Careful follow-up of patients, including regular outpatient visits; close collaboration with rheumatology, ophthalmology and oral medicine, concentration on simple measures to relieve desiccation, gives the most satisfactory results in the therapy of SS.

Treatment of patients with SS is divided into two parts: (1) treatment of glandular manifestations and their consequences and (2) treatment of the extraglandular manifestations.

Treatment of Glandular Manifestations

The treatment of xerostomia should accomplish the following:

1. Maintain oral hygiene to prevent dental carries
2. Careful examination to diagnose and treat oral candidiasis
3. Systemic therapy to stimulate glandular secretions
4. Use of saliva substitutes

The principal goal in treating the impaired lacrimal and salivary production associated with SS is the successful replacement of glandular secretions. Therapeutic measures for dry eyes include local stimulators of tear secretion, protective bicarbonate-buffered solutions, artificial lubricants, and supportive operative procedures. Cyclosporin A 2 % in olive solution in the form of eye drops has been shown to be relatively effective in placebo-controlled clinical trials. The

choice of therapeutic procedure used depends on the experience the ophthalmologist may have of the disease. Systemic therapy to stimulate glandular secretions includes the use of cholinergic agonist pilocarpine hydrochloride (5 mg four times daily). Contraindications of pilocarpine include pregnancy, history of gastrointestinal ulcer, arrhythmias, and severe, poorly controlled hypertension. Other agonists such as cevimeline "Evoxac" have been shown to improve symptoms of dry mouth. The recommended dose is 30 mg three times a day, and the drug should be used with caution in patients with cardiovascular disease.

Treatment of Extraglandular Manifestations

Systemic therapy should be considered in patients exhibiting systemic features as previously described and tailored to the organ affected and severity. It should be however emphasized that management of extraglandular manifestations is mainly based on case series, open-label studies, and expert opinion based on biological rational and on experience in other autoimmune diseases, given the lack of robust data from controlled studies. Hydroxychloroquine is effective in improving arthralgias, myalgias, and joint inflammation, while methotrexate can be used in cases of florid inflammatory arthritis; for cases of persistent arthritis, rituximab has been shown to significantly improve the tender and swollen joint count. TNFα blockade (infliximab and etanercept) has been proven inefficacious in primary SS in terms of subjective and objective measures of salivary and lacrimal function as well as joint inflammation with augmentation of the already activated type I interferon/B-cell-activating factor axis possibly accounting for this failure. Cytotoxic drugs such as cyclophosphamide along with systemic steroid administration (0.5 mg/kg daily) are considered for severe extraglandular manifestations including severe cutaneous vasculitis, glomerulonephritis, and peripheral neuropathy. Given that B-cell activation is a major finding of the disease, targeted anti-B-cell therapies are a thoughtful approach in patients with vasculitis. Improvement in fatigue scores in a randomized controlled trial and demonstrable efficacy in extraglandular features including cryoglobulinemic vasculitis and peripheral neuropathy with reduction of disease activity indices suggest that B-cell depletion treatment is a promising therapeutic strategy in SS.

Treatment of Skin Manifestations

Patients with dry skin should refrain from daily use of soap, except for skin creases, and from too frequent bathing, especially in hot water. Bath oils and frequent use of emollients (i.e., greases based on lanolin, lanolin/paraffin mixtures, or creams based on emulsifying wax, Macrogol) are beneficial. Increasing the humidity of the environment may also be helpful. Vasculitis limited to the skin (leukocytoclastic vasculitis), which manifests as palpable purpura, does not require specific therapy. Avoidance of cold exposure or emotional stress, together with nifedipine 5–10 mg three times daily, is indicated for decreasing the severity and frequency of Raynaud's phenomenon. Vaginal dryness is a cause of painful intercourse. Vaginal lubricants such as K-Y jelly or the recently available vaginal inserts are helpful. Patients should avoid cortisone creams. In postmenopausal women, estrogen preparations are recommended.

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Skin Diseases from Metabolic, Endocrinologic Diseases

90

Franco Rongioletti

Abbreviations

ACTH	Adrenocorticotropic hormone
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
DD	Diabetic dermopathy
FSH	Follicle-stimulating hormone
GA	Granuloma annulare
GH	Growth hormone
HMG-CoA	Hydroxy-methylglutaryl coenzyme A
IGF-1	Insulin-like growth factor 1
LH	Luteinizing hormone
MEN1	Multiple endocrine neoplasia type 1
NL	Necrobiosis lipoidica
PTH	Parathyroid hormone
TSH-(R)	Thyroid-stimulating hormone (receptor)
TSI	Thyroid-stimulating immunoglobulin

Key Points

- As skin manifestations may reflect a life-threatening endocrine or metabolic disease, identifying the underlying disorder is important, so that patients can receive corrective rather than symptomatic treatment.
- Skin signs may be also a marker for the success of therapeutic interventions as it occurs for hyperpigmentation in Addison disease.
- Treatment of skin manifestations in hormone-deficiency conditions relies on the management of endocrine disease that consists of replacing the individual peripheral hormones.
- Treatment of specific conditions such as pretibial myxedema (thyroid dermopathy) or diabetes-associated skin diseases such as necrobiosis lipoidica, granuloma annulare, or perforating dermatosis is difficult, and there is no standard of treatment.
- Controlling hypersecretion of pituitary hormones secondary to adenomas with medical or surgical care improves most cutaneous manifestations of acromegaly, Cushing disease, and hyperprolactinemia.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_90, © Springer-Verlag Berlin Heidelberg 2015

- Parathyroid surgery should be considered for all patients with symptomatic hyperparathyroidism and associated skin lesions such as calciphylaxis in chronic renal failure.
- Treatment of xanthomas involves normalization of lipid levels but also surgical procedures.
- Encouraging weight loss and treating metabolic syndrome in obese patients improve also associated skin conditions.

Definition and Epidemiology

Endocrine diseases are any diseases caused by the abnormal function of endocrine glands, including the adrenal, pituitary, thyroid, and parathyroid glands. Metabolic disorders involve the disruption of metabolic processes and are caused by genetic errors, hormonal dysfunction, and/or mineral or vitamin deficiency states. Common metabolic disorders include diabetes, hyperlipoproteinemia, and obesity.

Basic Concepts of Pathogenesis of Endocrine/Metabolic Diseases

Adrenal disease includes Cushing syndrome and Addison disease. Cushing syndrome describes the symptoms related to overexposure to glucocorticoids. Currently, the most common cause of Cushing syndrome is due to exogenous or iatrogenic hypercorticism. The term Cushing syndrome also includes cases of hypercortisolism secondary to functional tumors of the adrenal cortex. The designation "Cushing disease" includes cases of hypercortisolism due to overproduction of ACTH as a result of either pituitary overproduction or ectopic ACTH production. Addison disease is defined as primary adrenal gland insufficiency. In Addison disease, usually of autoimmune origin, the ability of the adrenal cortex to produce glucocorticoids (cortisol) and mineralocorticoids (aldosterone) is compromised, resulting in increased levels of pituitary ACTH.

Two main types of thyroid dysfunction can be encountered: hyperthyroidism (sometimes assimilated to thyrotoxicosis, in which the levels of T_4, T_3, or both are elevated) and hypothyroidism caused by a deficiency of them. Almost 60 % of cases of thyrotoxicosis are represented by Graves' disease that is an autoimmune disorder with a variety of circulating antibodies including thyroid-stimulating immunoglobulin (TSI), which binds to TSH-(R) and activates the thyroid hormone synthesis and release and induces the thyroid to grow. Pretibial myxedema and thyroid acropachy are typical manifestations of hyperthyroidism, in particular of Graves' disease. Pathogenesis of pretibial myxedema is unclear, but it appears that pretibial fibroblasts are targets of the autoimmune attack. Trauma on the legs, which result in cytokine release from inflammatory cells, arterial or venous insufficiency, and smoking may be favoring factors.

Hypothyroidism may result from a primary insufficient hormone production by the gland or from a secondary failure of TSH pituitary secretion from the pituitary gland. The most common cause is Hashimoto thyroiditis. Generalized myxedema is the most common skin manifestation of hypothyroidism.

Pituitary gland diseases include an excessive secretion of pituitary hormones as well as hormone deficiency. The main manifestations of pituitary gland diseases are acromegaly, hyperprolactinemia, Cushing disease, and hypopituitarism. Acromegaly is the clinical syndrome that results from excessive secretion of growth hormone. In more than 95 % of cases, the primary cause is a secreting pituitary adenoma. Tissue hyperplasia is the hallmark of the syndrome and is a consequence of the stimulation of growth hormone that promotes sulfation of collagen and synthesis of RNA and DNA. Prolactin is a pituitary hormone that plays a fundamental role in a variety of reproductive functions. It is an essential factor for normal production of breast milk following childbirth. Hyperprolactinemia is a commonly encountered clinical condition due to a prolactin-secreting adenoma (prolactinoma).

Several drugs may result in a significant increase in prolactin serum concentration such as antipsychotic, antidepressant with serotoninergic activity, prokinetics, opiates, estrogens, antiandrogens, antihypertensive drugs, H2-receptor antagonists, anticonvulsants, and cholinomimetics. The term "Cushing disease" is reserved for the pathological condition that is caused by excessive secretion of ACTH by a pituitary adenoma. Roughly, two thirds of the cases of endogenous Cushing syndrome are caused by "Cushing disease." Hypopituitarism is a condition in which there is diminished or absent secretion of one or more pituitary hormones, resulting either from a primary disorder of the secretory cells of the anterior pituitary gland or as a secondary consequence of reduced stimulation by the releasing hormones of the hypothalamus. When the deficiency of anterior pituitary hormones is generalized, the condition is referred to as panhypopituitarism. The most common cause is a pituitary tumor (chromophobe adenoma, craniopharyngioma), but vascular abnormalities (ischemic necrosis), granulomatous inflammation (sarcoidosis), autoimmune disorders (autoimmune hypophysitis), trauma (stalk destruction), infections (syphilis, tuberculosis), Langerhans cell histiocytosis, congenital disorders (Rathke's cleft cyst), and iatrogenic damage (surgery, radiotherapy, ipilimumab) also cause hypopituitarism. A particular well-described cause of acquired hypopituitarism is postpartum pituitary necrosis or Sheehan's syndrome.

Parathyroid hormone (PTH) is secreted by parathyroid glands as a polypeptide which increases calcium levels in the blood through parathyroid receptors in bones, kidneys, and intestines. The condition of elevated blood levels of PTH is known as hyperparathyroidism. If the cause is the parathyroid gland, it is called primary hyperparathyroidism, which may be caused by parathyroid adenomas, parathyroid hyperplasia, and parathyroid cancer. If the elevated levels of PTH do not involve the gland, it is known as secondary hyperparathyroidism. Tertiary hyperparathyroidism results from hyperplasia of the parathyroid glands with subsequent lack of response to serum calcium levels. Both secondary and tertiary hyperparathyroidism are most often seen in patients with chronic renal failure.

Hypoparathyroidism is an endocrine disorder characterized mainly by hypocalcemia due to inadequate parathyroid hormone (PTH) secretion or less often by unresponsiveness to elevated PTH levels (pseudohypoparathyroidism). It may be congenital or acquired. Postsurgical hypoparathyroidism is the most frequent acquired form, but other causes include autoimmunity.

Diabetes is characterized by high serum glucose levels and disturbances of carbohydrate and lipid metabolism that is estimated to affect 151 million people. Clinically, diabetes mellitus can be classified as type 1 and type 2. Type 1 diabetes mellitus, characterized by a specific autoimmune destruction of the insulin-secreting β cells in the pancreatic islets, comprises 5–10 % of all diabetes. Type 2 diabetes mellitus, which accounts for 80–90 % of all cases, affects older and overweight patients and is characterized by a resistance to the action of insulin and inadequate insulin secretion from the pancreas. Cutaneous manifestations are common in diabetes mellitus, with approximately 30 % of patients experiencing some cutaneous involvement during the course of their illness. They can be classified as (I) noninfectious, (II) infectious, (III) related to complications due to vasculopathy and neuropathy, and (IV) related to complications of diabetes treatment. Patients with type 2 diabetes are more prone to develop skin infections, whereas those with type 1 more often have autoimmune-related diseases. The etiopathogenesis of most of noninfectious skin manifestations of diabetes is unknown. Diabetic microangiopathy and neuropathy, immunologic reactions including antibody-mediated vasculitis and Th1 inflammatory-delayed reaction, trauma, genetic component, and irreversible glycosylation of collagen with resistance to degradation by collagenase can play a role.

Skin manifestations can be found in both primary (hereditary) hyperlipidemia and secondary hyperlipidemia (e.g., hyperlipidemia in hypothyroidism or with protease inhibitor administration). Indeed, many drugs can cause hyperlipidemia, including retinoids such as isotretinoin for acne or bexarotene for mycosis

fungoides. The major dermatologic manifestations in hyperlipidemia are xanthomas, tumors comprised, at least in part, of lipid-laden histiocytes.

Obesity has a profound impact on the development of skin manifestations. It causes abnormalities in skin barrier function, sebaceous glands and sebum production, sweat glands, lymphatics, collagen structure and function, wound healing, microcirculation and macrocirculation, and subcutaneous fat and is implicated in a wide spectrum of dermatologic diseases.

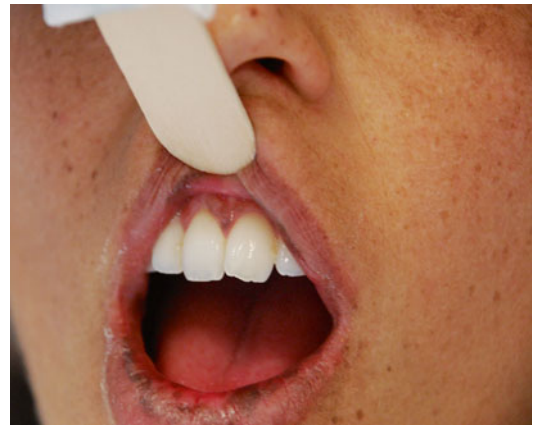

Fig. 90.1 Hyperpigmentation of lips and gums in autoimmune Addison disease

Clinical Presentation of Skin Disease in Endocrinological/ Metabolic Diseases

Adrenal Disease

The cutaneous manifestations of hypercortisolism in Cushing syndrome include an accumulation of fat tissues with a characteristic distribution (facial, truncal, and back of the neck) causing the "moon face" with plethora and rubeosis over the cheeks and "buffalo hump." Violaceous striae extending greater than 1 cm in diameter on the abdomen and lower flanks are a pathognomonic sign. The skin eventually becomes atrophic and fragile. Atrophy results in easy bruising manifesting with petechiae and ecchymoses over the extremities. Hyperpigmentation is a feature of adrenocorticotropic hormone (ACTH)-dependent Cushing disease, while it is not a feature of Cushing syndrome due to primary adrenal hypercortisolism. Other skin manifestations include the increased risk for infection and delayed wound healing. The most common skin manifestation of Addison disease is hyperpigmentation, presenting as scattered hyperpigmented macules, diffuse homogenous hyperpigmentation, or hyperpigmentation of the palmar creases and flexural areas. Isolated hyperpigmentation can also involve friction sites, recent scars, genital skin, areolae, and oral mucosa (Fig. 90.1). Darkening of preexisting nevi and longitudinal pigmented bands on the nails has also been reported.

Thyroid Disease

In hyperthyroidism, the skin is smooth, soft, warm, and moist with increased pigmentation, especially on the palms and soles. There is a flushed face, increased sweating, and accelerated nail growth. Skin manifestations are more prominent in Graves' disease and are typically represented by the triad of pretibial myxedema, thyroid acropachy, and exophthalmos in 30 % of patients. Pretibial myxedema occurs up to 14 years after ophthalmopathy, but it has also been reported in patients with hypothyroidism. Its incidence peaks in the fifth to sixth decades of life. Myxedema may also involve other skin areas, such as the arms, the head, the neck, and elsewhere on the legs. There are four main clinical variants of pretibial myxedema: diffuse, nonpitting edema (43 %), plaque-type (27 %), nodular (18 %), and elephantiasis (5 %).

Thyroid acropachy occurs up to 25 years after the onset of thyroid disease and often after hyperthyroidism has been treated. Women are affected four times as often as men. It consists in digital clubbing and diaphyseal proliferation, which on radiograph appears as irregular, lacy, bubbly new bones. Onycholysis, spoon nails, and hippocratic nails may be observed.

Primary generalized myxedema is the most common skin manifestation of hypothyroidism.

In the adult form, fatigue and weight gain, cold intolerance, hoarseness of voice, physical slowness, mental retardation, and constipation are common features. The face is round with periorbital edema, enlarged and protruding lips, macroglossia, and a broad nose. Cold, nonpitting edema involves also the hands and feet. The skin is usually thick, yellowish (due to carotenemia), cold, and dry with livedo on the extremities. Hairs are dry, coarse, and brittle contributing to the diffuse or partial alopecia of the scalp, groin, and even lateral eyebrows. Nails are brittle and thick and grow slowly. Bruising is easy with poor wound healing.

Pituitary Gland Disease

In patients with acromegaly, the skin is thickened and has a doughy feel due to dermal mucin accumulation and edema. The main clinical features are broadened hands and feet with widened, thickened, and stubby fingers. The facial aspect is typical with coarse features including a widened nose, thick lips, frontal bossing, and deep facial lines. Oily skin with widened skin pores and hypertrichosis are also frequent findings, while acne is a less common feature. The skin is also wet with an offensive body odor due to excessive eccrine and apocrine hyperhidrosis leading to a heightened incidence of abscesses in the axillae and intergluteal cleft. Numerous pigmented skin tags are found in up to 45 % of patients. Occasionally, acanthosis nigricans is also a finding. Cutis verticis gyrata, a scalp condition where there are convoluted folds and deep furrows that resemble the surface of the cerebral cortex, can be another sign of acromegaly. The scalp hairs are usually sparse in late stages. A relationship between psoriasis and acromegaly has been reported, based upon an increase of serum GH in some psoriatic patients and an improvement of the dermatitis after surgical pituitary tumor excision or after treatment with somatostatin or dopamine analogues.

The most frequent symptoms of hyperprolactinemia are decreased libido, infertility, oligomenorrhea/amenorrhea, and galactorrhea in women and decreased libido, infertility, gynecomastia, or impotence in men. The skin in hyperprolactinemia becomes thickened, coarse, and greasy, with enlarged pores. Acne vulgaris and seborrhea may develop; androgenetic alopecia may occur also in children and adolescents, where the straight hairline conforms to the adult configuration (calvities frontalis adolescentium). Hyperprolactinemia is one recognized cause of hypertrichosis or hirsutism occurring on the extremities, anterior chest, abdomen, lower back, and beard area.

The cutaneous manifestations of Cushing disease are superposable to those of adrenal Cushing syndrome. Hyperpigmentation is more frequent with Cushing disease and almost absent with adrenal Cushing syndrome. Hypertrichosis is common as well as acne, but, different from acne vulgaris, the lesions are monomorphic, without comedones and cysts. Associated features in women are clitoridomegaly and androgenetic alopecia with male pattern.

Most of the dermatological signs and symptoms of hypopituitarism are similar to those that occur with a primary deficiency of that gland. Thyroid-stimulating hormone (TSH) deficiency results in signs and symptoms of hypothyroidism. In addition to amenorrhea and erectile dysfunction, deficiency of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) results in loss of body hair, which is observed in all patients early in the course. Scalp hair tends to be fine and dry, and there may be generalized thinning. Growth hormone (GH) deficiency causes atrophic, dry, and pruritic skin that may be easily traumatized with a delayed time of wound healing. ACTH deficiency gives rise to signs similar to those found in adrenal insufficiency except for the absence of hyperpigmentation.

Cutaneous manifestations in parathyroid-related diseases are rare in sporadic cases but not unusual in familial syndromes. Multiple endocrine neoplasia type 1 (MEN1), also known as Wermer syndrome, is an autosomal dominant entity characterized by the combination of tumors of the anterior pituitary gland, parathyroid glands, and endocrine pancreas. MEN1 is caused by the

loss of function germline mutations in the MEN1 gene mapped to chromosome 11q13, which encodes a protein named menin that acts as a tumor suppressor gene. Cutaneous neoplasms include collagenomas, angiofibromas, melanomas, and lipomas.

In hyperparathyroidism, metastatic calcification occurs as a result of hypercalcemia or hyperphosphatemia. Calcium deposits can be found in the skin, subcutaneous tissues, muscle, tendon, and internal organs. Calciphylaxis is a syndrome usually fatal due to infectious complications and is seen in the setting of end-stage renal disease in patients on dialysis or postrenal transplant. Patients initially develop violaceous, mottled patches and plaques that resemble livedo reticularis on the abdomen, thigh, and hips, which frequently ulcerate. Calciphylaxis can also present with acral ischemia of the fingers, toes, or penis. Proximal location of the necrosis is associated with a mortality rate of 63 %. In calciphylaxis the essential feature is the calcification of dermal and subcutaneous small blood vessels (venules and arterioles).

Signs and symptoms of hypocalcemia are the most prominent features of all forms of hypoparathyroidism; nevertheless, most patients with slowly progressive hypocalcemia remain asymptomatic. Dermatological findings related to hypoparathyroidism are usually mild and nonspecific including xerosis, scaling, edema, rough-fragile hair, alopecia, and mild onychodystrophy. Rarely eczematous dermatitis and hyperkeratotic and maculopapular eruptions have been described. Autoimmune polyendocrine syndrome type has also been described under the names of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Its major components are hypoparathyroidism, autoimmune adrenal insufficiency, and chronic mucocutaneous candidiasis.

Diabetes mellitus includes many skin-associated conditions. Necrobiosis lipoidica (NL) is a chronic granulomatous condition that usually appears in the third and fourth decades and is three times more common in women. Although NL occurs in only 0.3–1.6 % of diabetics, it precedes the onset of diabetes mellitus in 15 % of patients, and 75 % of patients with NL have or will develop diabetes mellitus. The lesion is characterized by a non-scaling plaque with a yellow atrophic center, surface telangiectases, and erythematous or violaceous border that may be elevated (Fig. 90.2). In most cases, the lesions are bilateral and confined to the shins. Ulceration occurs in up to 35 % of cases, resulting in pain. Rarely, squamous cell carcinoma has been reported in older, ulcerated lesions.

Diabetic dermopathy (DD) (i.e., shin spots, pigmented pretibial papules) is the most common cutaneous manifestation of diabetes occurring in 7–70 % of all diabetic patients. DD is commonly seen in diabetics with other end-organ damage such as retinopathy, neuropathy, nephropathy, and coronaropathy. Lesions consist of asymptomatic, bilateral, asymmetrical, well-demarcated, annular or irregular atrophic, brownish macules of 4–12 mm in diameter on the shins.

Granuloma annulare (GA) is a benign self-limited, granulomatous inflammatory disease. A weak link with type 1 diabetes has been demonstrated. GA has also been associated with autoimmune diseases, lymphoproliferative conditions, and solid tumors. GA is typically a papular disease which can be divided into a localized, disseminated (more than ten lesions involving

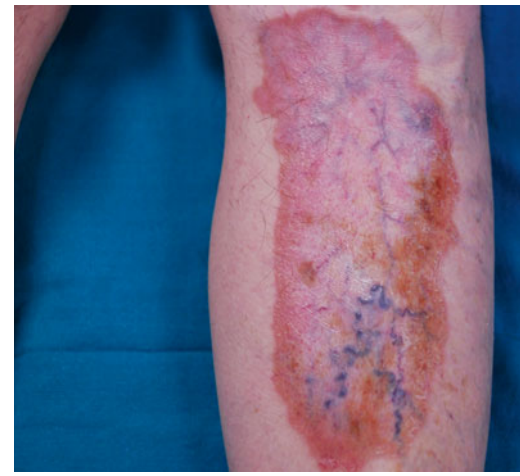

Fig. 90.2 Necrobiosis lipoidica on the shin in a patient with insulin-dependent diabetes

trunk and limbs), or linear type. The most common presentation is the localized, papular form (80 % of cases) that occurs before the age of 30, most commonly in children, and it is twice as often in females. The lesions typically are located on the dorsa of the hands and feet and are characterized by multiple, small, skin-colored or erythematous papules that coalesce into an arcuate or annular pattern. Disseminated, papular GA occurs in 15 % of cases, prevailing in middle-aged and elderly patients. Disseminated GA is the most common clinical pattern in HIV infection. Other main clinical variants include: perforating type with central umbilication or crusts and subcutaneous (deep) type (also known as pseudorheumatoid nodule), most commonly observed in children.

Diabetic thick skin is seen both in type 1 and type 2 diabetic patients. Two forms are described: scleredema and diabetic hand syndrome, which share a common histopathology characterized by thickened dermis and deposition of mucin.

Scleredema diabeticorum occurs in patients with obesity and long-standing, poorly controlled diabetes. The clinical findings are characterized by asymmetric nonpitting induration of the posterolateral aspects of the neck and upper back.

Thickening of the skin on the dorsum of the hands, also known as diabetic hand syndrome or diabetic sclerodactyly, occurs in both diabetic type 1 and diabetic type 2 patients. Clinical presentations start with pebbled knuckles (or Huntley papules) that are multiple minute papules, grouped on the extensor side of the fingers, on the knuckles, or on the periungual surface, and progress to stiffness of the metacarpophalangeal and proximal interphalangeal joints, limiting joint mobility.

Bullosis diabeticorum is a noninflammatory blistering condition occurring in patients with type 2 diabetes. Diabetic bullae most often present as painless, tense, superficial bullae that occur in an acral distribution, mostly on the legs and feet. Direct immunofluorescence studies are negative.

Acquired perforating dermatosis is a rare disorder seen in adult patients, especially those presenting with type 2 and type 1 diabetes mellitus (50 %) and with chronic renal failure (73 %). It is characterized clinically by itching and hyperkeratotic, sometimes umbilicated, or follicular papules and nodules with a central core, situated primarily on the extensor surfaces of the lower and upper extremities, often in a linear fashion. The histological features are not uniform and may resemble any of the four classic perforating disorders: elastosis perforans serpiginosa, reactive perforating collagenosis, perforating folliculitis, or Kyrle disease. This classification is based primarily on the nature of the eliminated material.

Acanthosis nigricans is a cutaneous manifestation of insulin-resistant diabetic patient and may indicate increased risk of type 2 diabetes mellitus. Insulin resistance is the most common association of acanthosis nigricans in the younger age population. Acanthosis nigricans presents as hyperpigmented, velvety plaques involving typical areas such as the posterior neck, axilla, and flexural surfaces.

Hyperlipoproteinemia

The major dermatologic manifestations in hyperlipidemia are xanthomas, tumors comprised, at least in part, of lipid-laden histiocytes including planar xanthomas, tuberous xanthomas, and tendinous xanthomas. Several xanthomas are considered pathognomonic for specific hyperlipidemia disorders, e.g., planar xanthomas in an intertriginous distribution, especially finger web spaces, are pathognomonic for homozygous familial hypercholesterolemia. There are three major subtypes of planar xanthomas: xanthelasmas, intertriginous xanthomas, and palmar crease xanthomas (xanthoma striatum palmare). Eruptive xanthomas are characteristically associated with secondary hyperlipidemia, particularly elevated chylomicrons (of which triglycerides are the principal element) as may be found in poorly controlled diabetes mellitus. Classically they will spontaneously resolve after several weeks. Tuberous xanthomas can involve the elbows, knees, and buttocks. Although familial

dysbetalipoproteinemia (type III hyperlipoproteinemia) is the most common setting, tuberous xanthomas may present in homozygous or heterozygous familial hypercholesterolemia. Tendinous xanthomas present as indurated, flesh-colored nodules that arise slowly over the years and involve the tendons, ligaments, and fascia, in particular the Achilles tendon and extensor tendon of the hands and feet. The most common association is with homozygous familial hypercholesterolemia, for which they are considered a hallmark.

Obesity

Main cutaneous manifestations of obesity include acrochordons, adiposis dolorosa, hidradenitis suppurativa, lymphedema, acanthosis nigricans, striae distensae, and plantar hyperkeratosis. Acrochordons are commonly seen on the neck, axillae, and groin of obese individuals. Adiposis dolorosa, or Dercum's disease, is a rare condition that commonly occurs in obese, middle-aged women. It is characterized by multiple, bilateral, painful lipomas that occur more commonly on the trunk and lower extremities, especially around the knees. Hidradenitis suppurativa is a painful, chronic disease characterized by folliculitis with abscesses, fistulas, and scarring occurring in the apocrine gland-bearing skin of the axillae and groin (Fig. 90.3). Hidradenitis suppurativa affects about 2 % of the population and the majority of patients are obese. Lymphedema can occur secondary to the obesity itself and is seen in the lower extremities and/or large abdominal pannus of extremely obese individuals. Over time, the skin becomes thickened, hyperkeratotic, and fibrotic. Acanthosis nigricans is the most common skin manifestation of obesity, and its incidence and severity tend to increase with the degree of obesity. Plantar hyperkeratosis is a diffuse thickening of the stratum corneum in a horseshoe pattern, affecting the heel, foot arch area, and plantar-medial aspect of the great toe at the level of the interphalangeal joint, and it is considered the most common skin finding in obese patients.

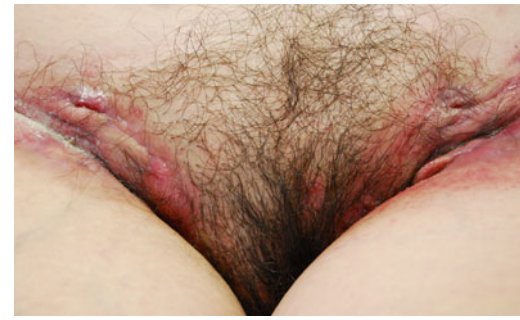

Fig. 90.3 Hidradenitis suppurativa on the groins in an obese patient

General Principles of Treatment

Adrenal Disease

When Cushing syndrome is due to glucocorticoids that are taken for another disease, discontinuing the glucocorticoids will resolve or improve symptoms, with the exception of striae distensae. The hyperpigmentation of Addison disease is very responsive to treatment with physiologic levels of glucocorticosteroids and is one of the more sensitive indices to monitor maintenance therapy doses of replacement glucocorticoids.

Thyroid Disease

Pretibial myxedema may benefit from corticosteroids either in occlusive medication or intralesional injection (10 mg/ml monthly) which are considered the first treatment of choice, especially in early phases. Treatment is less effective as duration and extent of disease is increased. A program of complete decompressive physiotherapy including manual lymphatic drainage, application of multilayered low-stretch bandaging, and intermittent pneumatic compression results in significant benefit. Octreotide, an insulin-like growth factor 1 antagonist, with and without surgical shave removal has been tried, but this is an expensive therapy whose benefit seems questionable. Surgical removal with skin graft can be followed by recurrences. Intravenous

immunoglobulins seem to be a promising therapy especially in the elephantiasic forms. In treatment-resistant elephantiasic thyroid dermopathy, plasmapheresis with and without immunosuppression (e.g., rituximab) has been used in anecdotal cases with variable results. Oral pentoxifylline may be considered only as adjuvant therapy. Treatment for the associated hyperthyroidism does not improve the cutaneous lesions, and, often, localized myxedema develops after treatment. After a follow-up of 25 years, up to 70 % of mild untreated and 58 % of treated severe cases achieved complete or partial remission. Localized myxedema may clear also spontaneously. Tobacco cessation, weight management, and avoidance of skin trauma should always be recommended. Management of thyroid acropachy is similar to dermopathy. Acropachy usually remains stable over the years without complaints in the majority of patients. In 14 % it resolves and in 9 % the condition improves.

In generalized myxedema, symptoms subside with thyroxine administration and recur if it is discontinued. Overall, the most common problem in hypothyroidism is dryness of the skin. It is important to use a gentle cleansing soap with light abrasive properties and to moisturize the skin with petrolatum-based creams, urea (10–20 %), or alpha hydroxy acids.

Hair loss may be a diagnostic problem before becoming a therapeutic challenge. It is essential to distinguish hair problems due to insufficient thyroid hormones (hair dull and brittle) from hair loss as a sign of a paralleling autoimmune attack (telogen effluvium). In the first instance, thyroid hormone administration is mandatory, while in the second a corticosteroid medication, possibly topical, may be beneficial in the long term (at least 4 months).

Pituitary Gland Disease

Controlling GH and insulin-like growth factor 1 (IGF-1) oversecretion improves most cutaneous manifestations of acromegaly, although a full regression is difficult to be attained, especially in patients with long-lasting disease. Facial features improve and puffiness decreases. Ring size decreases along with shoe size, and acanthosis nigricans, cutis verticis gyrata, and psoriasis also improve.

The cutaneous manifestations of hyperprolactinemia improve with systemic therapy. Medical treatment with dopamine agonist drugs (bromocriptine, 10–15 mg daily) is currently the gold standard approach both for microprolactinomas and macroprolactinomas. Bromocriptine as a treatment for prolactinoma has been associated with good therapeutic response of psoriatic lesions on anecdotal basis.

In Cushing disease, the severity of the manifestations does not always correlate with the biochemical indices of the disease. With the exception of striae distensae, cutaneous effects of endogenous hypercortisolism completely heal or improve within the first year after surgical cure of the disease, especially in children.

Concerning hypopituitarism, partial relief from skin dryness can be obtained with emollient creams, but the real treatment is the management of disease that consists of replacing the individual peripheral hormones through oral, transdermal, intramuscular, intranasal, or subcutaneous routes. It is essential that patients are aware about the importance of hormone supplementation and (in the case of cortisol) about the requirement for dosage modifications during acute illness or stress.

Parathyroid Disease

Parathyroid surgery is the standard treatment for all patients with symptomatic hyperparathyroidism in whom there is a reasonable life expectancy. In asymptomatic patients with hyperparathyroidism, surgery is recommended if serum calcium is 1 mg/dL above the upper limit of normal, there is marked hypercalciuria, creatinine clearance is reduced, bone density is reduced, and the patient is younger than 50 years. In sporadic hyperparathyroidism, single-gland parathyroidectomy of the identified adenoma is the recommended approach. For patients with familial hyperparathyroidism, there has to be

balance between the risk of optimal surgical procedures and the morbidity caused by permanent hypoparathyroidism. In the clinical context of renal failure, parathyroidectomy is recommended for symptomatic patients. Recommendations for the treatment of calciphylaxis include the correction of hypercalcemia and hyperphosphatemia, hyperbaric oxygen, appropriate wound care associated with the adequate use of antibiotics, and pain management. Aggressive debridement of cutaneous ulcers improves the outcome of calciphylaxis patients. Recently new medical treatments emerged aiming to reduce the serum concentration of sodium phosphate and to prevent precipitation and calcification. Sodium thiosulfate, a chelating agent with antioxidant efficacy, has been used intravenously in calciphylaxis patients with >90 % of positive result. In hemodialysis patients, improvement in skin ulcers and pain was seen in about 70 %. Nevertheless, sodium thiosulfate was unable to decrease high mortality rate of 71 %. Thrombolytic tissue plasminogen activator has been also tried as a useful adjunctive treatment, and bisphosphonate has also been suggested for mild cases.

Benign cutaneous tumors in the setting of MEN1 including collagenomas, angiofibromas, and lipomas are excised only for cosmetic purposes. Treatment of hypoparathyroidism focuses on correcting the underlying cause, and pharmacologic treatment depends on the nature and severity of the disease. Severe symptoms require intravenous calcium and additional therapy according to each case (oxygen and diuretics for secondary heart failure, etc.). Oral calcium is appropriate for milder cases along with a low-phosphate diet and vitamin D and analogues. Correction of the underlying disease and metabolic imbalances may be a sufficient therapy for skin manifestations, and dermatological basic interventions may be unnecessary other than routine moisturizing for mild cases of xerosis and pruritus. Therapy of chronic candidiasis in autoimmune polyendocrine syndrome involves long-term systemic antifungals (fluconazole, itraconazole) in view of the inadequate response to standard topical medications.

Diabetes Mellitus

NL tends to be chronic. No randomized controlled studies have demonstrated any particularly effective therapy. Topical and intralesional corticosteroids are empirically considered as first-line treatments, lessening the inflammation of early active lesions and the active borders, but worsening the atrophy. Many therapies have been tried with variable success including topical tacrolimus, topically applied bovine collagen, mycophenolate mofetil, cyclosporin A, hydroxychloroquine, UVA1 therapy, photodynamic therapy, and pulsed-dye or fractional CO2 laser. Excision and grafting have been successful, but recurrence may occur. Anti-TNF-α agents such as etanercept and infliximab have been used for refractory, ulcerative NL as well as intravenous immunoglobulin; however, all therapeutical options should be assessed for efficacy and safety by large, randomized, controlled trials. Treatment of the hyperglycemic state does not change the cutaneous lesions, although improvement following pancreas transplantation has been reported. Because localized trauma can cause NL to ulcerate, protection of the legs with elastic support stockings and leg rest is useful.

The evolution of DD is variable and does not appear to be affected by glycemic control. The lesions may persist or resolve spontaneously with scar formation and recur in crops. Treatment is not very effective. Particular attention should be placed on the detection and prevention of diabetic complications such as retinopathy, neuropathy, nephropathy, and coronary heart disease, as patients with DD are more inclined to develop microangiopathies.

No well-designed randomized controlled studies have demonstrated any particularly effective therapy for GA. Localized disease generally is self-limited and resolves within 2 months to 2 years, whereas disseminated disease may last 3–4 years or as long as 10 years. For localized disease, topical or intralesional glucocorticoids, tacrolimus and pimecrolimus, imiquimod, pulsed-dye laser, and cryotherapy have been used with variable success. Because localized GA is self-limited, a “wait and see approach” is also

warranted. For disseminated disease, treatment modalities include retinoids, antibiotics, nicotinamide, dapsone, pentoxifylline, cyclosporine, fumaric acid esters, antimalarials, photodynamic therapy, and ultraviolet therapy including UVA1 phototherapy. Regarding tumor necrosis factor-alpha inhibitors, there are reports reflecting resolution of the disease with this treatment modality, while others show no benefit. Lesions may resolve after biopsy. Recurrences occur in 40 % of cases.

No effective treatment is known for scleredema diabeticorum. Control of the hyperglycemia has little influence on the skin. Many treatments have been tried with variable success. Phototherapy such as UVA1, cyclosporine, low-dose methotrexate, intravenous immunoglobulin therapy, and electron beam therapy have all been reported to be of benefit. Aggressive therapies, however, should be limited to individuals with disabling disease or systemic manifestations.

There is no therapy for diabetic hand syndrome, although strict glycemic control may be helpful. Physical therapy is recommended to prevent limitations in range of motion.

Diabetic bullae heal spontaneously without scarring in 2–6 weeks, but they may be recurrent. Blisters may turn into chronic foot ulcers with complications. Glycemic control does not appear to have a direct correlation with blister formation.

Different treatments have been tried for acquired perforating dermatosis with variable results, such as topical or intralesional steroids, phototherapy including narrowband UVB, topical and systemic retinoids, systemic antihistamines, antibiotics, and allopurinol. Although there have been some reports of the spontaneous disappearance of perforating disorders with the stabilization of diabetes and renal disease, most cases of perforating disease continue for years unless treated.

The most effective treatment for acanthosis nigricans is lifestyle alteration. Weight reduction and exercise can reduce insulin resistance. Keratolytics such as ointments containing salicylic or retinoic acid can be used to reduce thicker lesions in areas of maceration in order to decrease odor. Oral agents that have shown some benefit include etretinate, isotretinoin, metformin, and dietary fish oils. Dermabrasion and laser therapy may also be used to reduce the bulk.

Hyperlipoproteinemia

Many instances of hereditary hyperlipidemia are associated with severe atherosclerotic cardiovascular disease. Secondary hyperlipidemias often abate with correction of the underlying etiology, e.g., cessation of the offending medication, correction of hypothyroidism, etc. Treatment of xanthomas, in particular xanthelasmas, tendinous or tuberous xanthomas, can be surgical, including laser procedures, but additional lesions will likely appear if the underlying hyperlipidemia is not corrected.

Nonsurgical treatment of hyperlipidemia involves pharmacologic agents such as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (more commonly known as "statins"), fibric acid derivatives, bile acid sequestrates, and nicotinic acid. Statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the rate-limiting enzyme for hepatic cholesterol synthesis. This leads to upregulation of LDL receptors and the lowering of plasma LDL cholesterol levels. All statins have this same mechanism of action but vary in their ability to lower LDL. Omega-3 fatty acids are available in a prescription form which has been approved by the United States Food and Drug Administration for use in patients with very high triglyceride levels (greater than 500 mg/dl). The improvement can be greater than with statin monotherapy. Eruptive xanthomas usually resolve spontaneously over the weeks and may result in hyperpigmented scars. Adequate treatment involves controlling the underlying hyperlipidemia with strict dietary therapy. Weight reduction and carbohydrate intake restriction are helpful in cases associated with diabetes. Eruptive xanthomas may herald the risk of atherosclerotic disease and acute pancreatitis. Type III hyperlipoproteinemia (dysbetalipoproteinemia) is typically responsive to pharmacologic therapy, such as fibric acid

agents, nicotinic acid, or statins. Therapy may require a combination of these drugs. It is also important to take note of the genetic counseling ramifications of diagnoses of inherited hyperlipidemia for the individual patient. The potential impact on longevity and family planning can be considerable, and referral to the appropriate genetics specialist, whether a physician geneticist or genetics counselor, should be strongly considered.

Obesity

Acrochordons are benign growths and are removed only for cosmetic reasons. Theoretically, a lower rate of recurrence could be seen in patients who achieve a better control of their diabetes and overweight. However, once an acrochordon is present, it does not seem to regress with weight loss. Treatment is by scissor excision, electrodesiccation, or cryotherapy.

Hidradenitis suppurativa is often a chronic and relapsing condition difficult to treat. The Hurley staging system is often used in clinical practice to document severity and guide treatment. Treatment should include encouraging weight loss and cessation of smoking. Topical steroids and antibiotics such as topical clindamycin 1 %, oral tetracycline (1 g daily), and erythromycin 500 mg twice daily can usually manage mild disease. Retinoids and systemic or intralesional steroids have had variable results. Hormonal contraception of low androgenicity (combined oral contraceptives containing one of the less androgenic progestogens, such as norgestimate, desogestrel, or gestodene) has also been used with better results than antibiotics. Other suggested drugs include oral zinc, metformin for the metabolic syndrome's involvement in the development of hidradenitis, and dapsone that may be an option for maintenance treatment in patients with moderate disease. Anti-TNF-alpha drugs have been shown to be effective, but relapses are common after stopping therapy. However, only surgical excision of all apocrine gland-bearing skin has been shown to effectively treat hidradenitis suppurativa by altering the natural course of the disease.

Lymphedema tends to be a chronic and progressive disease, and patients usually require lifelong treatment. Treatment consists of elevation, elastic stockings, and applying external compression devices. Weight reduction is extremely important in treatment because excess weight decreases the benefit of therapy and worsens the lymphedema. Infection prevention is also important and is accomplished by daily cleansing with mild soap, followed by a moisturizer.

Treatment of striae distensae includes the application of topical tretinoin 0.1 % cream early in the course of the disease. Laser therapy has also shown to be partially effective in the treatment of striae. Early, erythematous lesions respond best to 585-nm pulsed-dye laser, whereas late, hypopigmented scars respond better to the 308-nm excimer laser.

Acanthosis nigricans can be managed by controlling hyperinsulinemia. Weight loss and exercise are thus the best treatment options. Metformin has been shown to be effective. Octreotide, which acts by reducing insulin secretion, has also been shown to be of benefit. Topical antibiotics, retinoids, and keratolytics may also be used for treatment, with variable results.

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Skin Disease from Marine Environment

91

Giuseppe Monfrecola and Gabriella Fabbrocini

Key Points

- Many aquatic organisms are able to produce skin eruptions and occasionally systemic reactions.
- These dermopathies are very common among people who sunbathe and work in these conditions.
- Coelenterates are responsible for a wide range of skin reactions due to their poison in the tentacle.
- Injuries from sea urchin spines, which can be broken into the skin, cause local tissue reactions.
- Treatment should be prompt and appropriate and it should be done on the site of contact or sometimes in a systemic way.

Definition and Epidemiology

Many aquatic organisms are able to produce skin eruptions and occasionally systemic reactions. No data are available about the prevalence of marine-related diseases, but it is well known that these dermopathies are very common among people who sunbathe and work in these conditions.

Illnesses and accidents related to the aquatic environment have increased during the last decades, thus leading up to a rapid development of *Aquatic Dermatology*. Oceans, lakes, rivers, ponds, swimming pools, and aquariums contain numerous plants and animals that may be harmful to humans.

Excluding other aquatic dermatological conditions such as infection (i.e., mycobacteriosis), aquagenic urticaria or pruritus, irritant or allergic dermatitis, and barotrauma, cutaneous lesions can be caused by accidental contact with the organisms listed below. During the years, many marine animals have developed some defense towards their natural predators but, on the contrary, they sometimes can use them to attack. These mechanisms are also used against occasional and often unintentional attackers, such as bathers and divers. The venomous bites and stings of various aquatic animals are able to induce not only local skin manifestations, more or less serious, but also systemic reactions with severe shock and possible fatal evolution. Treatment should be prompt and appropriate and

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_91, © Springer-Verlag Berlin Heidelberg 2015

it should be done on the site of contact or sometimes in a systemic way.

Basic Concepts of Pathogenesis

Cnidarians (or Coelenterates)

In recent years, coelenterates are responsible for the most frequent poisoning reactions with respect to other marine species. Among 9,000 species, about 100 are toxic for humans. Jellyfish (Scyphozoa), anemones and coral (Anthozoa), and the Portuguese man-o'-war and fire corals (Hydrozoa) belong to this phylum. Jellyfish, anemones, corals, and hydroids are characterized by the presence on their tentacles of thousands of stinging organelles (nematocysts) containing poison. Nematocysts are sacciform structures containing a spirally coiled thread tube that can be shot quickly with a very high force of ejection. The released thread, like a harpoon, sticks into the enemy tegument and releases its poison. The nematocyst's release can be stimulated by mechanical or chemical stimulus. The cnidarian venoms are mixtures of peptides or proteins (enzymes) with inflammatory, necrotic, hemolytic, and neurological activities. The human skin can be affected by contact with the whole organism or parts of it (disconnected tentacles) and also by contact with other marine species using the cnidarian nematocysts as a weapon (i.e., nudibranchs or the Mediterranean octopus).

The coelenterates, including corals, sea anemones, jellyfish, and hydroids, have tips that can pierce human skin. The nematocysts are particularly abundant on the tentacles of the animal and, after contact, a tentacle can drain thousands of nematocysts in the skin. Typically, the initial lesions appear as small linear papular eruptions that develop rapidly in one or more discontinuous lines, sometimes surrounded by an erythematous area. The pain can be intense and itching is common. The papules may turn into blisters, sometimes evolving into pustules and finally into scab. The systemic manifestations include weakness, nausea, headache, muscle spasms and pain, watery eyes and runny nose, increased sweating, changes in pulse rate, and pleural chest pain.

Regarding the man-o'-war, it looks like a particular jellyfish or a colony of interdependent polyps forming a single body, but it is a siphonophore, whose distinctive appearance is the air pocket which, emerging from the sea, acts as a sail following the wind; hence the name of "caravel." Cubomedusae are the most dangerous among coelenterates, especially the sea wasp (*Chironex fleckeri*) and the square jellyfish (*Chiropsalmus quadrigatus*), and have been responsible for several deaths in the Atlantic, Indian, and Pacific oceans. It is interesting that a specimen of the Portuguese man-o'-war has been found also in Sicily by a surfer. This organism is particularly dangerous for human beings as its tentacles. Reaching 30 m in length, it contains millions of stinging cells with more than 10 different types of poisons. Each poison has its own specific color, and antidotes against the effects of some of them are not well known. The contact with the man-o'-war may cause severe burns, but also just a drop in blood pressure which could provoke collapse and in severe cases anaphylactic shock, cardiac arrest, and death may occur.

Other factors can influence the intensity of human reaction after contact with cnidarians: the patient's sensitivity, the size of the involved body surface, the anatomical site of contact, and the behavior of the patient after the contact. The reaction usually has a toxic nature, but immune-mediated mechanisms have been also described.

Venomous Fish

The poisoning from fish spines are defined as ichthyoacanthotoxicosis. A lot of species of fish, not only in tropical or subtropical areas but also in temperate climates (i.e., the Mediterranean sea), can induce severe injuries after the injection of the poison secreted by their cutaneous glands such as weever fish (*Trachinus* spp.), scorpion fish (*Scorpaena* spp.), zebra fish (*Pterois* spp.), stonefish (*Synanceia* spp.), stargazers (*Uranoscopus scaber*), stingrays, catfish, toadfish (*Thalassophryne* spp.), leatherbacks

(*Scomberoides sanctipetri*), moray (*Murenidi* spp.), and boxfish (*Ostraciontidae* spp.).

Fish reactions were calculated in about 750 bites/year along the US coasts, but the actual incidence is unknown. Poison is contained in one or more pins on the dorsal surface of the animal or in a spine located in the proximal portion of the tail. The lesions usually occur when a diver or a swimming sunbather tread on the dorsal spine (or spines) of the fish, causing the injection of the poison in the foot or leg. Although it is often limited to the affected area, the pain may spread rapidly, reaching its maximum intensity in less than 90 min and gradually decreasing within 6–48 h. Swelling and edema are usually present. Syncope, asthenia, nausea, and anxiety are frequent and may be due, in part, to peripheral vasodilatation. Lymphangitis, vomiting, diarrhea, sweating, generalized cramps, pain, and respiratory difficulty have been described.

Mollusks

The mollusks include conical shells, octopus, and bivalve shells. The *Conus californicus* is the only recognized conical dangerous shell in the waters of North America. Its sting causes localized pain, swelling, redness, and numbness. The bites of American octopus are rarely dangerous. The paralytic shellfish poisoning, caused by the ingestion of some bivalves, "dinoflagellates," is treated with special attention. The treatment is largely empirical.

Echinoderms and Sea Urchins

Echinoderms include several classes of poisonous fish. Some sea urchins have venomous organs (pedicellaria globose) with calcareous jaws with the possibility to pierce human skin, but injuries are rare. Much more common are injuries from sea urchin spines, which can break into the skin and cause local tissue reactions (Fig. 91.1). If not removed, the plugs can migrate into deeper tissues, resulting in a particularly severe granulomatous nodule. Recent cases from the Mediterranean Sea showed the local reaction in the bone and nerve.

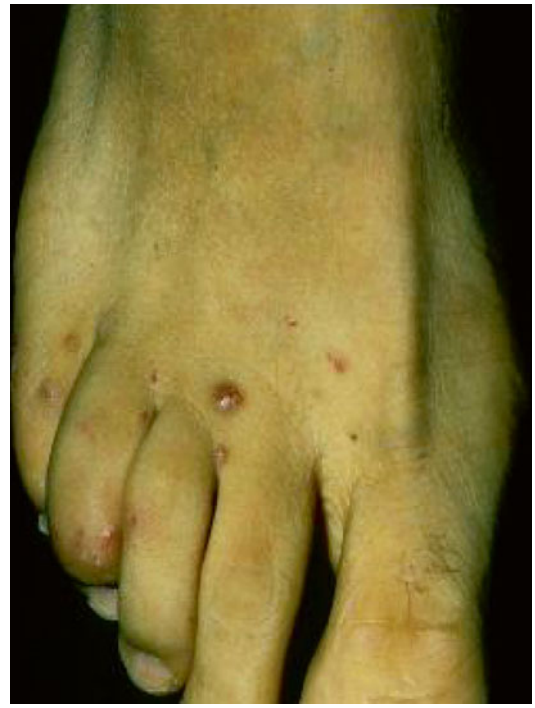

Fig. 91.1 Local skin reaction due to injuries from sea urchin spines

General Principles of Treatment (Table 91.1)

Cnidarians (or Coelenterates)

In some parts of the world, it is not recommended any treatment. However, some substances are used, such as vinegar to stop the sting, for the jellyfish square; baking soda in a 50:50 mixture, for the nettles of the sea; and seawater, for the man-o'-war. The tentacles must be removed, preferably with pliers or with gloved hands. The use of aspirin, an NSAID, or other analgesics can be useful. More severe cases may require O_2 or cardiorespiratory assistance. The painful muscle spasms can be mitigated with 10 ml of calcium gluconate 10 % IV. Narcotics are the drugs of choice for intense pain. In the few cases in which

Table 91.1 Etiology, clinical manifestations, and treatment of the most common skin diseases from the marine environment

	Causative agent	Skin reaction	Treatment
Coelenterates	Tentacles, stinging organelles (nematocysts)	Papular eruptions, hemorrhage, scab, weakness, headache, muscle spasms and pain, watery eyes, anaphylactic shock, cardiac arrest	Evaluation of the dermatologist, removed tentacles, seawater, aspirin, analgesic, calcium gluconate and cardiorespiratory assistance, adrenaline
Venomous fish	Pins, plugs	Syncope, asthenia, lymphangitis, vomiting, sweating, and respiratory difficulty	Evaluation of the dermatologist, remove integumentary sheath, antimicrobial and surgical closure of wound, anesthetized with lidocaine
Echinoderms and sea urchins	Plugs, thorns	Granulomatous nodule, tissue reactions	Evaluation of the dermatologist, washing the area and applying a mentholated balm, remove the plugs, vinegar compress

a shock occurs, adrenaline and intravenous fluids can be used. There is an antidote to the bites of some Australian species of coelenterates, but it is useless for the stings of the species in North America.

Venomous Fish

Wounds localized on limbs should be irrigated with salt water if available. It is necessary to remove the integumentary sheath, if it is visible, and the tourniquet could be useful. There are pump-shaped syringes which, causing a depression, are helpful for extracting the most part of the poison. Then the limb should be soaked for 30–90 min in water as hot as the patient can tolerate without receiving damage because it is very sensitive to heat. The wound should be reexamined to check for the presence of residues of the spine. You may need the use of an antimicrobial and surgical closure of wound. The initial measures are taken in case of emergency and, if the pain persists, the wound can be locally anesthetized with lidocaine. Narcotics can be useful too. The primary shock that sometimes immediately follows a sting usually responds to simple measures of support. The bites on the trunk should be evaluated carefully by the dermatologist for the possibility of perforation of internal organs. Strict surveillance of systemic symptoms is necessary. Taking into account that the plugs and stingers remain poisonous for some hours after the death of the fish, it is therefore necessary to avoid taking them full hand when lying on the beach or on the boat. Among fishmongers this risk does not exist because the sellers are obliged to remove thorns and stings before the sale.

Mollusks

Topical measures seem to have low effectiveness. It had been suggested that local injection of adrenaline and the subsequent use of neostigmine could be useful. The serious bites from *Conus* may require mechanical ventilation and measures against shock.

Echinoderms and Sea Urchins

The stings of *G. pedicellariae* are treated by washing the area and applying a mentholated

balm. The spines of the sea urchin must be removed immediately. A bluish discoloration at the site of entry can help to locate the spine, which is sometimes visible on X-ray. Vinegar dissolves most of the spine's surface, but it may be sufficient to wet the wound with vinegar several times a day and apply a vinegar compress. Rarely a small incision to remove the spine can be useful, but as this is very fragile, the operation is not easy. A spine that has migrated into deeper tissues may require surgical removal.

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Spitz Nevi

92

Susana Puig, Pedro Zaballos, Cristina Carrera, and Josep Malvehy

Key Points

- A Spitz nevus is a benign melanocytic nevus, with specific clinical and pathological features.
- Spitz nevi pose substantial diagnostic difficulty.
- Dermoscopy increases diagnostic accuracy.
- There are six main dermoscopic patterns associated with these lesions, five ascribed to pigmented Spitz nevi (starburst, globular, reticular, homogeneous, and atypical patterns) and one to the classical variant (vascular pattern).
- Spitz nevus is a benign tumor of spindled and epithelioid melanocytes.
- The main differential diagnosis of atypical Spitz is malignant melanoma.
- No evidence-based treatment recommendations can be made but complete excision is recommended, always in adulthood.

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Definition

The pathologist Sophie Spitz described this lesion in 1948 as juvenile melanoma; in her honor, it is named Spitz nevus.

A Spitz nevus (also known as "epithelioid and spindle-cell nevus," "benign juvenile melanoma," and "Spitz's juvenile melanoma") is a benign melanocytic nevus, with specific clinical and pathological treats. The latter terms are generally no longer used as they are misleading: Spitz nevus is a benign lesion and not a melanoma, and it does not only occur in children but also in adults.

In this chapter we will include two close entities, Spitz nevi (including classical and pigmented Spitz nevi) and Reed nevi (pigmented fusocellular nevi).

Epidemiology

Spitz nevi are uncommon. Their annual incidence was estimated in Queensland to be 1.4 cases per 100,000 people (Crotty 1997), where the annual incidence of melanoma in the same population is 25.4 cases per 100,000 people, one of the highest by world standards (Ries et al. 2003).

Although they are most commonly found on people in their first two decades of life, the age range for people with Spitz nevi is from early childhood to elderly, with a mean age of 22 years and a median age of 19 years in one large report.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_92, © Springer-Verlag Berlin Heidelberg 2015

Even though there is an association with sunburn, the cause of Spitz nevi is not yet known.

Clinical Presentation

They are usually small (6 mm or less), raised, pink, red, or light-brown papules that sometimes may resemble hemangioma or pyogenic granuloma (Figs. 92.1, 92.2, and 92.3). Pigmented Spitz nevi have similar characteristics but darker in color (Figs. 92.4, 92.5, 92.6, 92.7, and 92.8). They are usually single but may be multiple and clustered (agminate) or multiple and disseminated (Fig. 92.9). In a recent study performed by Requena and coworkers (2009) including 349 excised Spitz nevi, only 18 % were correctly clinically diagnosed.

Dermoscopy

Dermoscopy is a noninvasive and valuable method for improving the diagnosis of Spitz nevi. An increase in diagnostic accuracy from 56 to 93 % has been reported previously. Spitz nevus can clinically and dermoscopically present either in the classical (reddish pink) variant or the pigmented variant, and dermoscopy has demonstrated that the pigmented variant is much more frequent than the classical one. There are six main dermoscopic patterns associated with these lesions, five ascribed to pigmented Spitz nevi (starburst, globular, reticular, homogeneous, and atypical patterns) and one to the classical variant (vascular pattern) (Figs. 92.1, 92.2, 92.3, 92.4, 92.5, 92.6, 92.7, 92.8, 92.9, and 92.10). Remarkably, the starburst, globular, and atypical patterns accounted for 80 % of cases, representing the major dermoscopic patterns of Spitz nevi.

The starburst pattern is characterized by a prominent black to blue homogeneous pigmentation located in the center of the lesion and pigmented streaks (pseudopods or radial streaming) distributed regularly in a radial arrangement at the edge of the lesion (Fig. 92.4). This pattern is observed in 42–53 % of Spitz nevi (Ferrara et al. 2005).

The globular pattern is characterized by the presence of brown to bluish to black globules distributed throughout the lesion (Fig. 92.10). On occasion, the globules can be arranged in a centrifugal fashion, reminding of an exploding star. These peripheral globules are usually distributed in multiple rows forming the tiered globular pattern which is considered by many authors as a variant of starburst pattern (Ferrara and Argenziano 2012). This pattern is observed in 19–22 % of Spitz nevi.

The reticular pattern is observed in 9–10 % of cases (Fig. 92.5). There is a distinctive type of pigment network associated with pigmented Spitz nevi which is called superficial black network (Fig. 92.6). The black color is due to the presence of excessive amounts of melanin in the stratum corneum which can be removed by tape stripping.

The homogeneous pattern is characterized by a diffuse dark brown to black-bluish color, which lacks evidence of clear-cut streaks at the periphery (Fig. 92.7). This pattern is observed in 6 % of cases.

The atypical (or multicomponent) pattern is observed in 18–25 % of cases and is composed of different colors and structures irregularly distributed, giving a melanoma-like pattern (Fig. 92.8). Because of that, Spitz nevi with this pattern should be excised irrespective of the patient's age.

It is believed that most of these different dermoscopic patterns probably represent different phases in the natural evolution process of Spitz nevi and not distinct clinical and pathological entities. It has been described that pigmented Spitz nevi can evolve from a globular pattern to a starburst pattern and from this starburst pattern to homogeneous pattern (considered a state of senescence). Some authors have observed that the final stage in the natural evolution of Spitz nevi is complete involution of the lesion (Pizzichetta et al. 2002).

The vascular pattern is associated with classical (or hypopigmented) Spitz nevi and is usually composed of dotted vessels, which tend to be monomorphic and regularly distributed throughout the lesion, over a pink background (Figs. 92.1, 92.2, and 92.3). However, it is not uncommon to find vessels with varied morphology

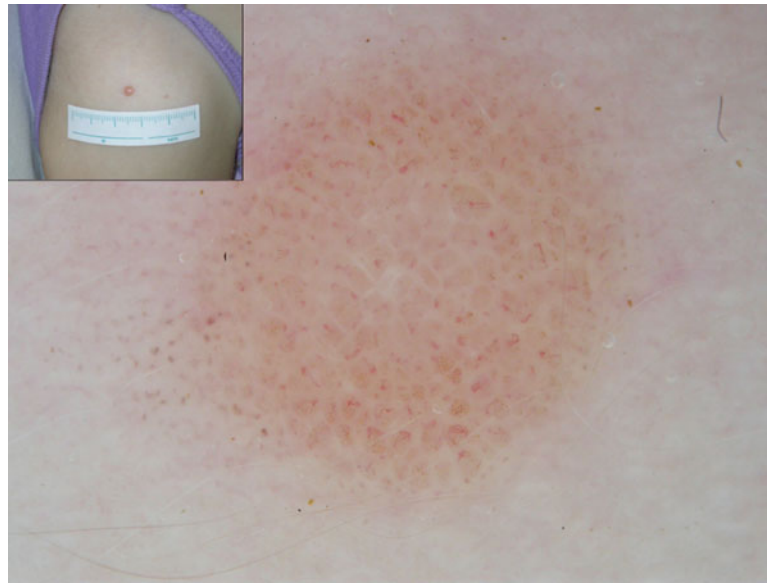

Fig. 92.1 Spitz nevus with a globular pattern located on the arm of an 8-year-old girl

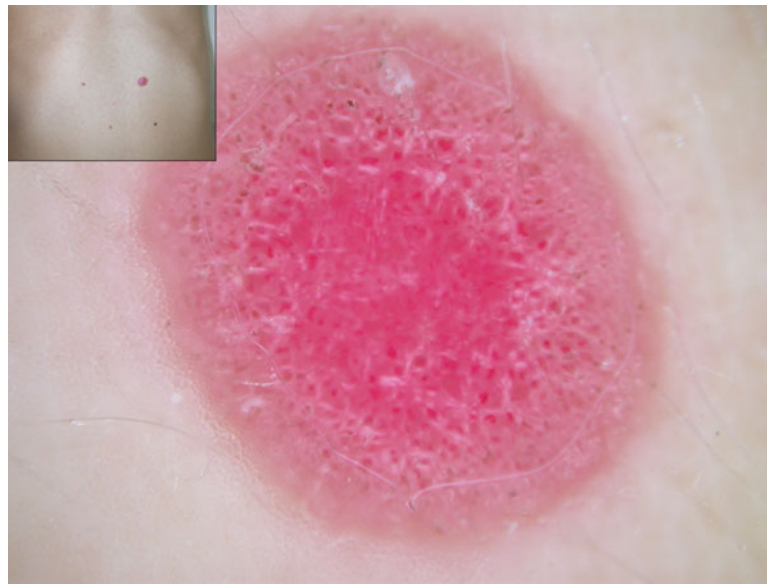

Fig. 92.2 Classical Spitz nevus with a vascular pattern located on the abdomen of a 26-year-old woman

(glomerular, comma, linear, or hairpin vessels), and therefore it is difficult to rule out the diagnosis of melanoma. These "pink" nodular Spitz nevi usually have the highest chances of showing atypical histological features, making it difficult to differentiate them from amelanotic melanomas.

In addition, it is not uncommon for Spitz nevi to show a negative pigment network (also called white network or reverse pigment network) (Figs. 92.1 and 92.3). This reticular structure consists of light areas making up the cords of the network and darker areas filling the holes and was found in 28.8 % of Spitz nevi. Other intersecting

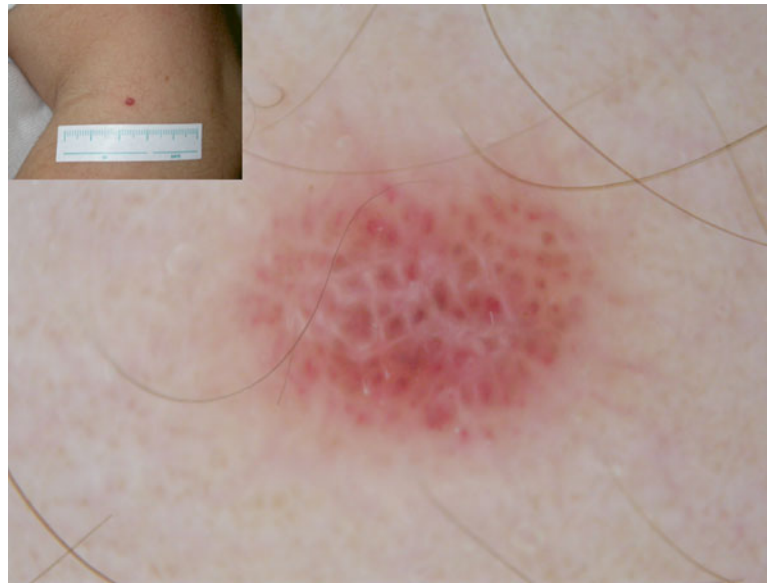

Fig. 92.3 Negative pigment network in a Spitz nevus located on the leg of a 13-year-old girl

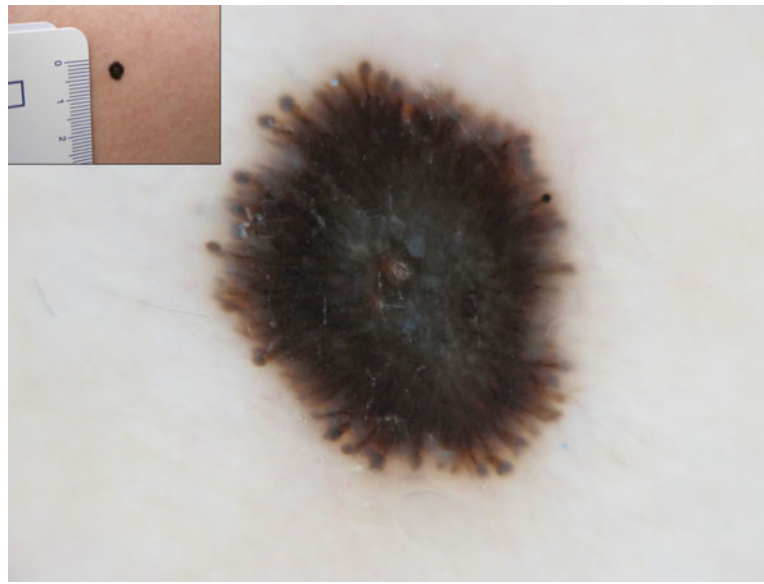

Fig. 92.4 Pigmented Spitz nevus with a starburst pattern located on the buttock of a 15-year-old girl

white lines which can be seen using polarized dermoscopy in some Spitz nevi are chrysalis (also called crystalline or shiny white lines) (Figs. 92.1, 92.2, 92.3, and 92.8). Finally, other dermoscopic structures found in Spitz nevi are regression structures and bluish or reddish halo.

Confocal Microscopy

In vivo reflectance confocal microscopy is a noninvasive imaging technique with cellular resolution that improves the diagnosis of melanocytic and nonmelanocytic tumors.

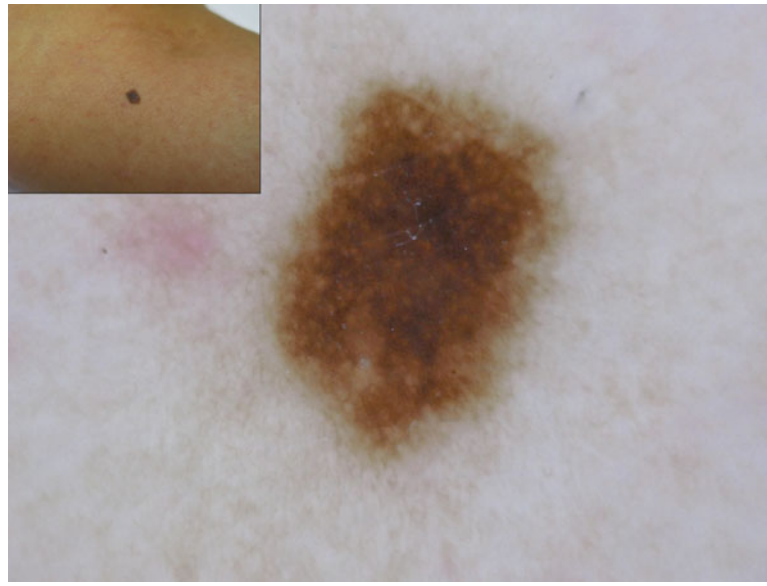

Fig. 92.5 Pigmented Spitz nevus with a reticular pattern located on the leg of a 36-year-old woman

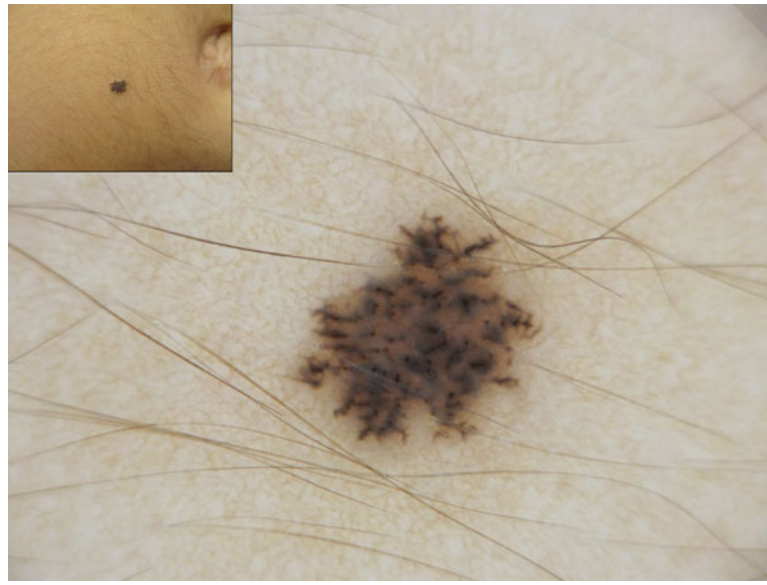

Fig. 92.6 Pigmented Spitz nevus with a reticular pattern (superficial black network) located on the abdomen of a 20-year-old woman

Pellacani and coworkers (2009) studied 40 Spitz nevi by in vivo confocal microscopy compared with 40 MMs and 40 Clark nevi. Some confocal features characteristic for Spitz nevus diagnosis were correlated with histological aspects as the most main features for differentiating Spitz nevi from melanomas: the presence of sharp border cutoff, junctional nests, and melanophages (Fig. 92.10). A limitation of reflectance confocal microscopy was the impossibility to evaluate dermal criteria suggestive of malignancy as lack of maturation or deep mitosis in atypical cells.

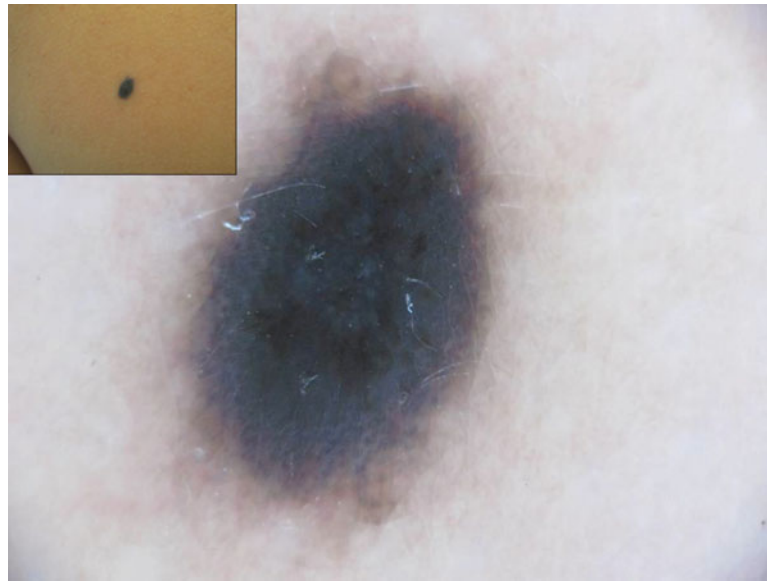

Fig. 92.7 Pigmented Spitz nevus with a homogeneous pattern located on the leg of a 17-year-old man

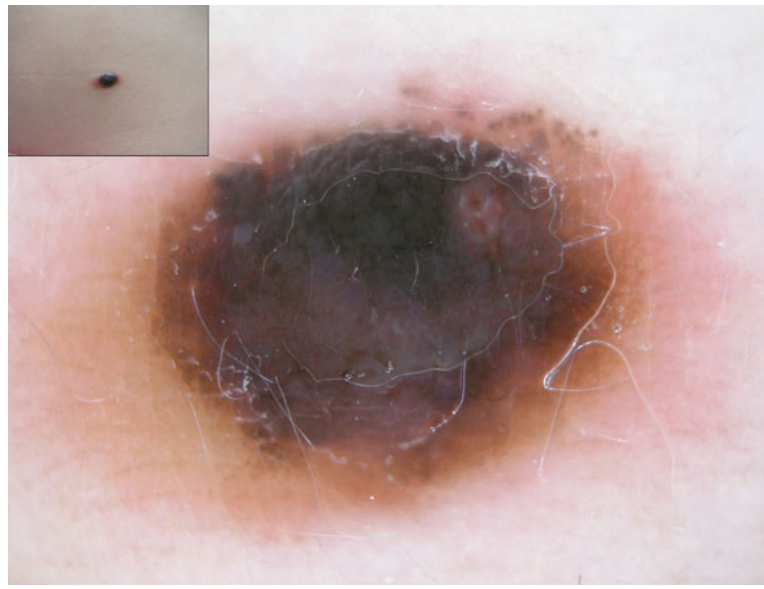

Fig. 92.8 Pigmented Spitz nevus with an atypical pattern located on the abdomen of a 11-year-old boy

Basic Concepts of Pathogenesis

Spitz nevus is a benign tumor of spindled and epithelioid melanocytes. They are symmetric with sharp lateral borders, usually compound nevus with prominent intraepidermal component, but 5 % are junctional and 20 % are dermal.

Spitz nevi characteristically have vertically arranged nests of nevus cells that have both an epithelioid and a spindled morphology (Figs. 92.10 and 92.11). Apoptotic cells may be seen at the dermoepidermal junction, presenting large and well-formed Kamino bodies (eosinophilic hyaline PAS-positive bodies along the

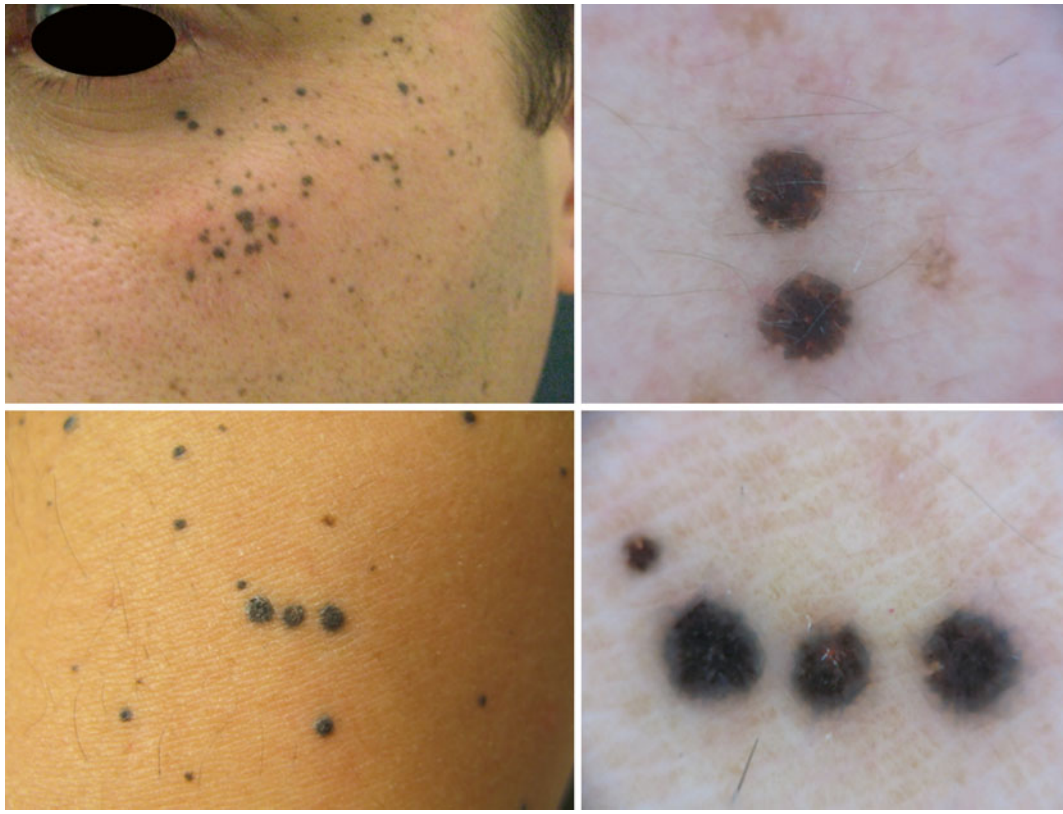

Fig. 92.9 Clinical (*left*) and dermoscopy (*right*) images of a patient with multiples agminated disseminated pigmented Spitz nevi

dermoepidermal junction). Fascicles of spindle cells, perpendicular to epidermis, may be arranged in dermal papillae. These cells have cigar-shaped large nuclei with prominent nucleoli. Epithelioid cells with abundant eosinophilic cytoplasm, distinct cell borders, large nuclei, and prominent nucleoli are dispersed individually. Variable mitotic figures can be seen. Occasional multinucleation and often marked atypia may be present although most cells appear benign and cell maturation occurs in deep portion of tumor.

These lesions may have pagetoid growth, lymphatic invasion, prominent vasculature, and lymphocytic infiltrate. "Consumption of epidermis" (also associated with melanoma) is seen in 10 % of them, defined as thinning of the epidermis with attenuation of basal and suprabasal layers and loss of rete ridges in areas of direct contact with neoplastic melanocytes.

The main histological differential diagnosis is malignant melanoma and common cause of malpractice claims is misdiagnosis as melanoma or melanoma misdiagnosis as Spitz.

Staining may help, being S100, HMB45, and MART1/MelanA positive in Spitz nevi. Spitz nevi also have positive expression of p16 while this could be lost in melanoma. On the contrary, neuropilin-2 (NRP2) is negative in 74 % of Spitz nevi while positive in melanoma. Spitz nevi also show low Ki-67 staining.

Genetic studies of Spitz nevi have shown that most cells have the normal number of chromosomes; however a minority (25 %) of cells have been shown to contain extra copies of parts of some chromosomes, such as the short arm of chromosome 11 (11p).

Occasionally H-RAS mutations were described in Spitz nevi, while usually no N-RAS or B-RAF mutations were identified (van Dijk et al. 2005). Recently B-RAF mutations were found in some classic and atypical Spitz nevi (Fullen et al. 2006).

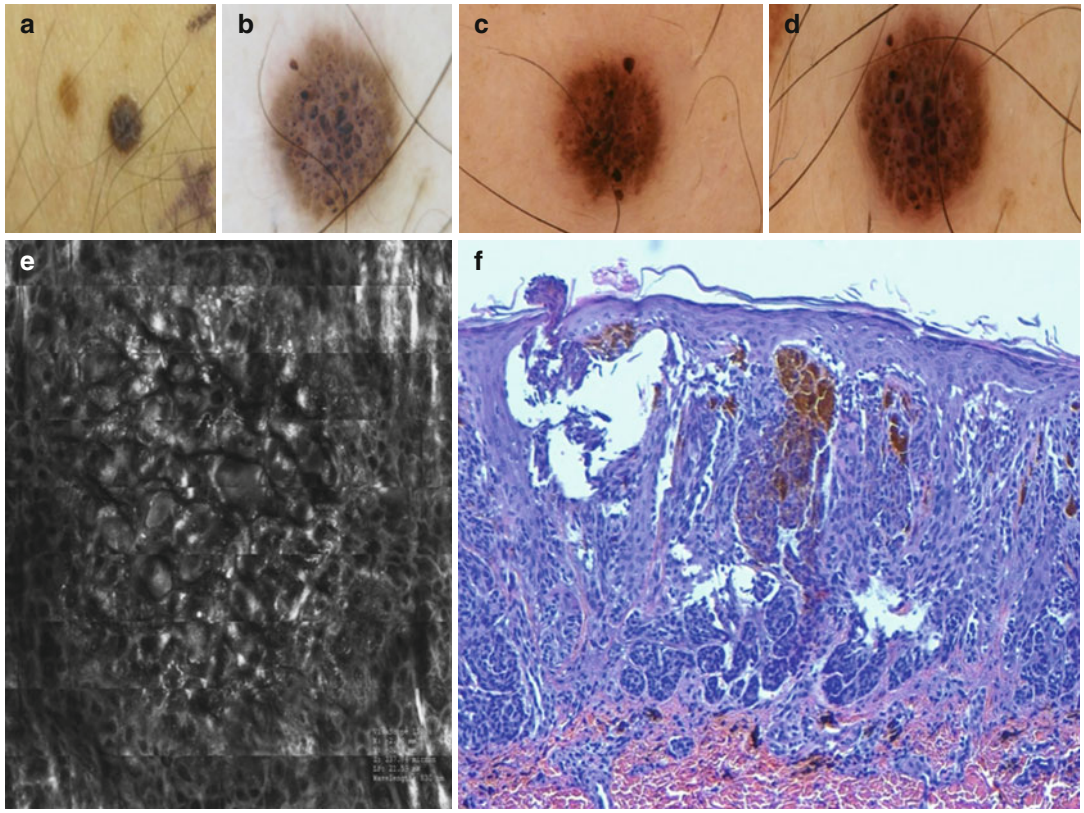

Fig. 92.10 Clinical (**a**) and dermoscopy (**b**) image of an atypical Spitz nevus with globular pattern showing increase in size and change in the distribution of the globules at the periphery between January 2013 (**c**) and January 2014 (**d**). Reflectance confocal microscopy mosaic at dermoepidermal junction (**e**) showing the presence of sharp border cutoff, junctional nests, and melanophages. Hematoxylin and eosin staining ×20 (**f**)

In a study by Díaz and coworkers (2011), fluorescence in situ hybridization (FISH) using probes targeting 6p25 (RREB1), 11q13 (CCND1), 6q23 (MYB), and centromere 6 showed a sensitivity of 73 % and a specificity of 93 % in the diagnosis of spitzoid melanoma in front of pigmented spindle cell nevus because Spitz nevi usually are not showing FISH abnormalities (Horst et al. 2012).

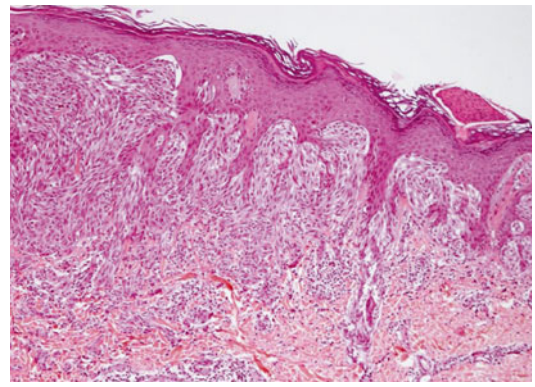

Fig. 92.11 Spitz nevus showing characteristic vertically arranged nests of nevus cells that have both an epithelioid and a spindled morphology. Apoptotic cells may be seen at the dermoepidermal junction, presenting large and well-formed Kamino bodies

Differential Diagnosis

The main differential diagnosis as previously discussed is spitzoid melanoma. Inside spitzoid lesions, there is a spectrum of tumors of difficult

diagnosis. In this setting, even expert pathologists have difficulties to classify such a lesion as benign or malignant. These lesions are classified as atypical Spitz tumors (ASTs) and show some worrisome treats and uncertain biological behavior.

Spitzoid melanoma is exhibiting under histopathology asymmetry, irregular lateral borders, uneven base, pagetoid scatter of melanocytes, uneven nests of melanocytes, lack of maturation, spindle cells not perpendicular to surface, epidermal spread, and ulcerated surface, and most cells show malignant characteristics.

General Principles of Treatment

No clear consensus exists for the management of Spitz nevi (SN) or atypical Spitz tumors (ASTs), particularly in the pediatric population. In adults all lesions with "spitzoid" features should be completely removed with limited margins for a correct pathological evaluation. Even in the case of symmetrical lesions, spitzoid melanomas cannot be ruled out based on clinical examination in adults. In young children (less than 7 years), most dermatologists consider that Spitz nevus can be monitored based in clinical and dermoscopical recognition of the characteristic patterns. However some dermatologists recommend the removal of all suspected Spitz tumors independently of the age of the patient, whereas others perform partial biopsy (Metzger et al. 2013). In the case of excision due to equivocal diagnostic features, a partial excision is not recommended due to the risk of insufficient sample for diagnostic assessment and recurrence. Shaving biopsies should be avoided in raised lesions where the pathologist may have difficulties for the final diagnosis of benignity, and the most important criteria are based in the examination of the deep part of the tumor that can be missed in a superficial biopsy.

ASTs may involve regional lymph nodes but distant metastases are rare. In AST there is controversy on the benefit of performing sentinel lymph node biopsy especially in young patients. In addition the significance of the presence of spitzoid cells in the sentinel node is not equivalent to malignant metastasis. The indication of the surgical and staging of these difficult lesions should be accomplished in experienced multidisciplinary centers and discussed with the patient. In the absence of any demonstrated benefit in overall survival with sentinel node biopsy, most authors consider that overtreatment should be avoided, especially in children. Complete excision and monitoring of regional lymph nodes with sonography in ASTs is considered a good option in these atypical tumors. In the case of regional subclinical or clinical metastasis in lymph nodes detected by sonography, the treatment should follow the melanoma guidelines and complete lymphadenectomy has to be considered.

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Squamous Cell Carcinoma

93

Marta Grazzini and Vincenzo De Giorgi

Abbreviations

5-FU	5-Fluorouracil
AK	Actinic keratosis
5-ALA	5-Aminolevulinic acid
AMM	Amelanotic malignant melanoma
BCC	Basal cell carcinoma
COX	Cyclooxygenase
EGFR	Epidermal growth factor receptor
NMSC	Nonmelanoma skin cancer
PDT	Photodynamic therapy
PpIX	Protoporphyrin IX
PUVA	Photochemotherapy
SCC	Squamous cell carcinoma
SK	Seborrheic keratosis

Key Points

- Malignant tumors of the epidermis are referred to as nonmelanoma skin cancer (NMSC). NMSC is the most frequent type of malignancy in humans and comprehends two major entities: squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).
- SCC is more common in older men, but besides older age and male sex, major risk factors are light skin, family history, residence at latitudes near the equator, and exposure to ultraviolet radiation.
- The initial manifestation of SCC is known as actinic keratosis.
- Invasive SCCs are generally larger, more advanced plaques or nodes, often covered with a thick, irregular, horny material, and sometimes with ulceration.
- The dermatoscopic features of SCC are a nonspecific pattern with scales and grouped glomerular blood vessels surrounded by a whitish halo.
- The usual therapies for individual SCC and actinic keratosis (AK) work destructively by surgically removing the lesion.

Definition

Malignant tumors of the epidermis are referred to as nonmelanoma skin cancer (NMSC). NMSC is the most frequent type of malignancy in humans and comprehends two major entities: squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). SCC arises on sun-exposed areas of the skin and mucosa but they can also occur in covered parts of the body, particularly in patients that have other predisposing factors.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_93, © Springer-Verlag Berlin Heidelberg 2015

SCC arises from epidermal keratinocytes that grows in a destructive way and typically manifests as a spectrum of progressively advanced malignancies, ranging from a precursor actinic keratosis (AK) to invasive SCC and finally to metastatic SCC. SCC may spread to regional lymph nodes and in late stages cause death.

Epidemiology

Although NMSCs are the most common cancers, they are regularly excluded from national cancer registries and cancer databases because they usually do not affect survival; therefore, the exact incidence and the associated mortality rate cannot be determined precisely.

However, the incidence of SCC has increased noticeably over previous decades. NMSC is considered the most common human malignancy, and nearly 30 % of white people living in areas of exposure to high ultraviolet radiation will acquire an NMSC in their lifetime. The age-adjusted incidence of this cancer among whites is 100–150 per 100,000 persons per year, and the age-specific incidence among persons over the age of 75 years is approximately 10 times that rate.

SCC is more common in older men, but besides older age and male sex, major risk factors for development of NMSC include light skin, family history, residence at latitudes near the equator, and exposure to ultraviolet radiation. Indoor tanning, which is already an established risk factor for malignant melanoma, is recently added in the list of SCC risk factor for both squamous cell carcinoma and basal cell carcinoma.

Basic Concepts of Pathogenesis

There are a number of factors (acquired and genetics) that can play a key role in predisposition to SCC (Table 93.1). Patients often have multiplicity of factors that are sufficient to induce SCC development.

Sun exposure is considered the principal cause for NMSC. In particular a history of exposure to sunlight during childhood, or history of sunburns, may be the most important behavioral risk factor. Occupational exposure to ultraviolet radiation can also be implicated. The relative risk of SCC is three times as high among people born in areas that receive high amounts of ultraviolet radiation from the sun as among people who move to those areas in adulthood.

Table 93.1 Risk factors for the development of cutaneous squamous cell carcinoma

Exposure to ultraviolet radiation
Exposure to ionizing radiation
Infection with human papillomavirus, especially types 6, 11, 16, and 18
Exposure to chemical carcinogens
Immunosuppression
Genodermatosis
Presence of precursor lesions

Although the relation is not understood, human papillomavirus infection has been associated with SCC. Human papillomavirus types 6 and 11 are frequently found in patients with tumors of the genitalia and type 16 in those with periungual tumors. A link between human papillomavirus and SCC related to epidermodysplasia verruciformis has also been reported.

Chemical agents have historically been a major cause of SCC. Arsenic, used in various medications in the past, can also stimulate carcinogenesis. Arsenic exposure produces invasive tumors and carcinoma in situ on the skin, whether or not the skin is exposed to the sun, as well as arsenical keratoses on the palms and sole. Treatments with radiation therapy such as photochemotherapy (PUVA) can act as an independent carcinogen factor. In addition, patients treated with immunosuppressive drugs resulted to have an increased risk of developing SCC, as compared with the general population, suggesting the hypothesis that also the immune system can play a key role in the development of NMSC (Hoogendijk-van den Akker et al. 2013).

Clinical Presentation

The initial manifestation of SCC is known as actinic keratosis (actinic = sun, keratosis = scaly

spot) (AK). These scaly erythematous spots could be around 5–6 mm in diameter and usually rough with colors ranging from red to brown. AK and SCC occur predominantly in sites with chronic exposure to sunlight such as the face, scalp, neck, and dorsal hand.

Between 1 and 10 % of AK progress into invasive squamous cell carcinoma. Other precancerous conditions that may evolve into SCC include bowenoid papulosis and epidermodysplasia verruciformis. Patients with bowenoid papulosis, which is often associated with human papillomavirus types 16 and 18, present with hyperpigmented papules that have histological features identical to those of Bowen's disease, a type of squamous-cell carcinoma in situ. Epidermodysplasia verruciformis consists of widespread, flat warts that may degenerate into carcinoma in situ or invasive squamous cell carcinoma. The most common forms of SCC in situ are Bowen's disease and erythroplasia of Queyrat. Patients with Bowen's disease present with sharply demarcated, erythematous, velvety, or scaly plaques on sun-exposed areas. Erythroplasia of Queyrat is less common and occurs on the glans penis of uncircumcised men as red, smooth plaques. Invasive SCCs are generally larger, more advanced plaques or nodes, often covered with a thick, irregular horny material, and sometimes with ulceration (Fig. 93.1). Lesions were in general not painful or with no discomfort with the exception of the bleeding

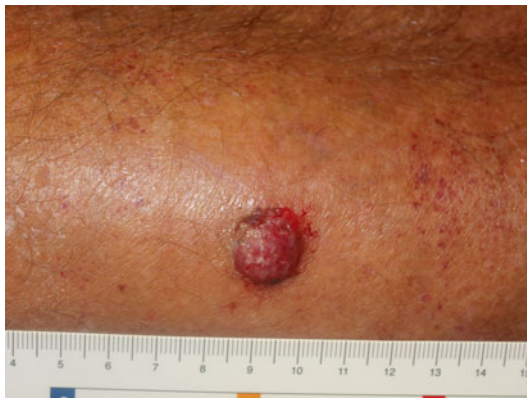

Fig. 93.1 An SCC of the left arm of a patient. The lesion appeared as red node, with irregular horny material and with ulceration

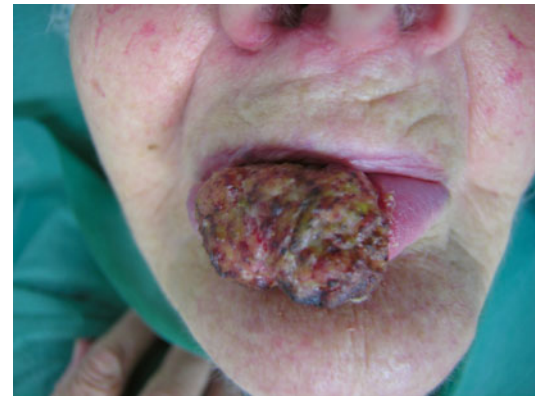

Fig. 93.2 An SCC of labial mucosa that appeared as node and grows fast and soon becomes locally aggressive and disruptive

that can occur in ulcerated lesions. SCC may be locally aggressive (Fig. 93.2), and in rare instances, cutaneous SCC may metastasize to regional lymph nodes or distant sites. The 5-year rate of recurrence of primary cutaneous lesions is 8 %, and the 5-year rate of metastasis is 5 %. Verrucous carcinoma is a less common variant of invasive squamous-cell carcinoma. The indolent, cauliflower-shaped tumors resemble large warts and are locally aggressive but are less likely to metastasize.

Diagnosis

The diagnosis of SCC, although easily made in typical cases, may sometimes be difficult. On this regard, dermatoscopic examination can play a central role to increase the specificity of the diagnosis of such lesions. In fact, the superiority of dermatoscopy over clinical examination has encouraged dermatologists to adopt this device for routine clinical practice, with a progressive spread of dermatoscopy use and to nonpigmented skin tumor and many other kinds of nonpigmented skin lesions including vascular lesions. Zalaudek et al. (2006) defined a specific pattern for the diagnosis of AK called "strawberry" pattern. The strawberry appearance is typified by a reddish pseudonetwork intermingled with hair follicle openings, which are surrounded by whitish halos.

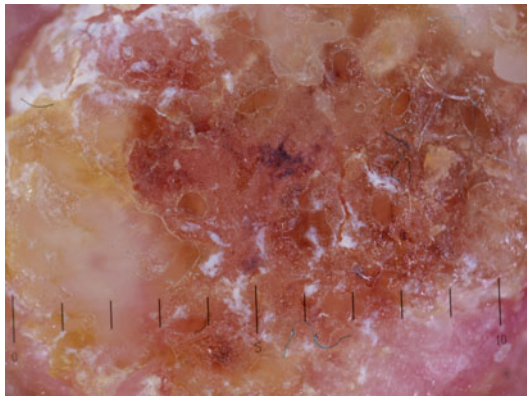

Fig. 93.3 A dermatoscopic image of SCC with a nonspecific pattern, scales, and grouped glomerular blood vessels surrounded by a whitish halo

The dermatoscopic features of SCC are a nonspecific pattern with scales and grouped glomerular blood vessels surrounded by a whitish halo (Fig. 93.3). A scaly surface, brown globules, and glomerular vessels can be seen in the dermatoscopic examination of pigmented Bowen's disease. Pigmented SCC can present a dermatoscopic pattern resembling melanocytic lesions with globules, radial streaks, and homogeneous blue pigmentation and can lead a physician to a wrong diagnosis.

Histological examination is mandatory to confirm the clinical diagnosis.

Histologically SCC consists of irregular masses of epidermal cells that proliferate downward into the dermis.

In well-differentiated carcinomas, tumor cells are pleomorphic/atypical but resembling normal keratinocytes from prickle layer (large, polygonal, with abundant eosinophilic (pink) cytoplasm and central nucleus). Their disposal tends to be similar to that of normal epidermis: immature/basal cells at the periphery, becoming more mature to the center of the tumor masses. Tumor cells transform into keratinized squames and form round nodules with concentric, laminated layers, called "cell nests" or "epithelial/keratinous pearls." The surrounding stroma is reduced and contains inflammatory infiltrate (lymphocytes). Poorly differentiated squamous carcinomas contain more pleomorphic cells and no keratinization. Histological grading of SCC is based on the degree of cellular differentiation. Low-grade tumors are comprised of uniform cells, resembling mature keratinocytes, with intracellular bridge and keratin production. High-grade SCCs are instead characterized by atypical cells, loss of intracellular bridges, and minimal or absent keratin production. Tumors are graded on a scale of 1–4 based on increasing percentage of undifferentiated cells, so-called Broders' Grading System (Table 93.2).

Table 93.2 Broders' grading system for squamous cell carcinoma

Grade	% Undifferentiated cells	Other features
1	<25	Keratinization
2	<50	
3	<75	
4	>75	Atypia, loss of intracellular bridges

Differential Diagnosis

Facial AK is a differential diagnosis of cutaneous melanoma (lentigo maligna) since pigmented facial AK may have a broken-up pseudonetwork. Pseudonetwork can be observed in dermatoscopic examination of certain benign pigmented facial lesions such as AK, ephelide, and junctional nevus.

The SCC must be differentiated from BCC, keratoacanthoma, hypertrophic AK, irritated seborrheic keratosis (SK), and amelanotic malignant melanoma (AMM).

Nonpigmented BCCs are much more common than pigmented BCC. In the dermatoscopic examination, nonpigmented BCCs can be often easily distinguished from any other skin lesion by their asymmetrical arborizing vessels, pink color, and focal ulceration. White regression areas may be seen.

Keratoacanthoma can resemble SCC but it tends to grow more quickly to form an SCC and frequently has a central ulcerated crater (Fig. 93.4). Dermatoscopically white circles, keratin, and blood spots are useful clues to differentiate SCC and keratoacanthoma from other raised nonpigmented skin lesions. The diagnosis of SK is generally clinical; sometimes the differentiation

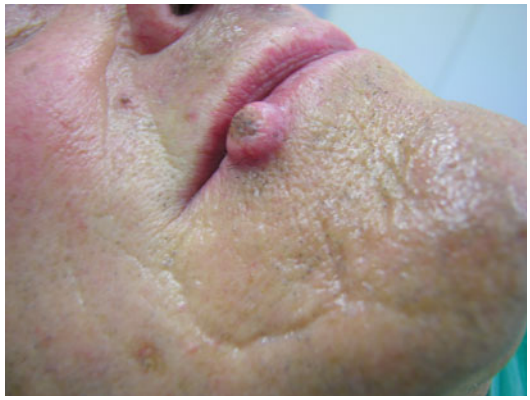

Fig. 93.4 A keratoacanthoma of the lip that can resemble an SCC but tends to grow more quickly to form an SCC and has a central ulcerated crater

between irritated SK and SCC may be difficult in the clinical aspect. Although the classical dermatoscopic criteria of SK that include multiple milia-like cysts and comedo-like openings and additional structures such as hairpin blood vessels can help the diagnostic accuracy.

AMM lesions represent approximately 2–8 % of all melanomas, presenting without or with little pigmentation, respectively. The paucity of pigmentation makes this type of tumor hard to identify, making clinical differential diagnosis difficult. The dermatoscope is a major instrument allowing the evaluation of pigment and above all determining characteristic vascular structures unseen by the naked eye. Such vascular patterns have an important role on the suspicion of melanoma in doubtful nonpigmented lesions. Dermatoscopically AMM can initially show dotted vessels and, as the thickness increases, the vascular polymorphism increases with hairpin and linear-irregular vessels associated with milky-red areas, reticular depigmentation, and chrysalis. Differential diagnosis between pigmented SCC and melanocytic lesions is difficult in some cases.

General Principles of Treatment

The aim of the treatment of SCC can be stated simply as follows: to eliminate the disease, to secure the best functional and cosmetic results, and to avoid relapse. The treatment should take into consideration not only the SCC but also actinic keratosis from whom the SCC has originated. The usual therapies for individual AK/SCC work destructively by surgically removing the lesion. These should always be considered for isolated lesions or early presentations of AKs.

The standard treatment of AK/SCC is excision, followed by histological examination to confirm the diagnosis and to insure that the entire tumor has been removed (Table 93.3, Fig. 93.5).

Brief Overview on the Treatment of Actinic Keratosis

Destructive therapies include liquid nitrogen cryotherapy, curettage with or without electrodessication, and shave excision. The benefits of these techniques are that they are quick, procedurally simple, and easy.

Cryotherapy

Cryotherapy is one of the most commonly utilized techniques, with liquid nitrogen being the most frequently selected cryogen. Applying cryotherapy to the affected area lowers the skin to temperatures that destroy atypical AK cells. This technique is ideal if lesions are scattered or limited in number or for patients who are noncompliant with topical regimes. Cryotherapy is advantageous in that it is generally well tolerated and does not require local anesthetic, but downsides include pain during the procedure and frequent permanent hypopigmentation.

Curettage

Curettage consists of using a curette to mechanically remove atypical cells. A shave excision using a surgical blade is another technique. These may be followed by electrocautery, which will destroy additional atypical cell layers as well as provide hemostasis. These techniques are most appropriate for treating individual AKs, cases where a biopsy is required to rule out SCC, or for hypertrophic AKs that are refractory to other treatments.

Table 93.3 Therapeutic options for actinic keratosis and squamous cell carcinoma

Treatment	Dosage	Advantage	Disadvantage
Therapeutic option for actinic keratosis			
Surgery		Gold standard	You can treat single or a few lesions
		Histological examination is permitted	
Liquid nitrogen cryotherapy, curettage, CO_2 laser treatment		Quick procedure	Multiple lesions can be treated
		Well tolerated	
Diclofenac	Twice daily for 60–90 day	Well tolerated	Less effective treatment
		Can be used in an area up to 25 cm^2	
Imiquimod 5 %	3 times per week for 4 weeks	Good clearance	Marked inflammation and erythema with crusting of the skin
		Good cosmetic appearance after inflammation	May need mild topical steroid to reduce inflammation
PDT		Good cosmetic results	Discomfort treatment for the patients
		Can treat the entire cancer field	Not effective in thick AK
Therapeutic options for SCC			
Surgery		Gold standard	You can treat single or a few lesions
		Histological examination is permitted	
PDT		Good cosmetic results	Discomfort treatment for the patients
		Can treat the entire cancer field	The efficacy is lower in comparison to other diseases
Radiotherapy		Useful in selected cases (elderly patients, head and neck)	
Cryotherapy		Quick procedure	The efficacy is lower in comparison to surgery
		In small SCC or when the surgical treatments are refused/contraindicated	

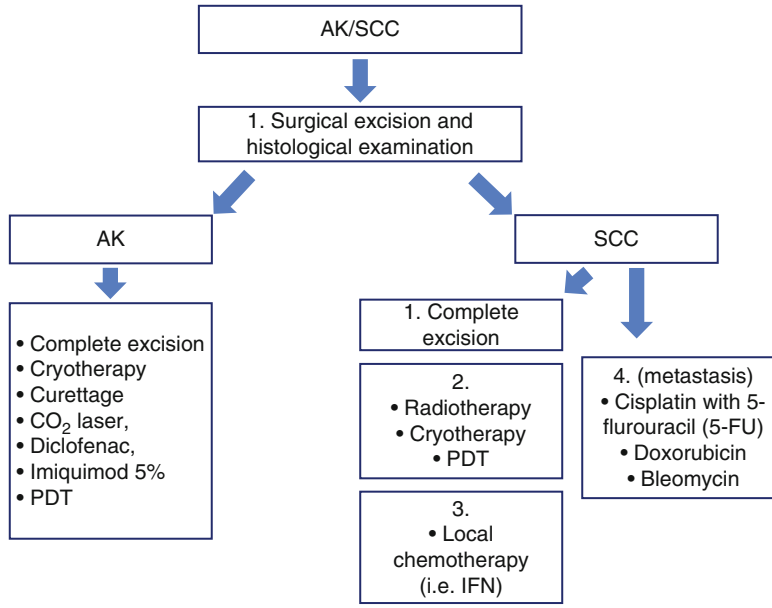

Fig. 93.5 Therapeutic algorithm in AK and SCC

Diclofenac and Imiquimod

For patients with multiple AKs, a different therapeutic approach, known as field therapy, is needed with the goal of "field therapy" for the eradication of both the clinically visible and subclinical AKs within the treatment area. As regards to chemical treatments, diclofenac and imiquimod are the most frequently used in Europe. Diclofenac 3 % gel is a nonsteroidal anti-inflammatory drug that is believed to exert its effects through the inhibition of cyclooxygenase (COX), especially COX-2. Topical 5 % imiquimod cream (Aldara®) is indicated as a treatment for AKs and superficial basal cell carcinomas. It is also used off label for treating Bowen's disease, invasive SCC, lentigo maligna, molluscum contagiosum, keloid scars, and others. Imiquimod acts as a toll-like receptor-7 agonist, which results in modification of the immune response and stimulation of apoptosis, thereby disrupting tumor proliferation.

5-Fluorouracil

The antimetabolite 5-fluorouracil (5-FU) was the first approved topical field therapy. Discovered serendipitously when AKs were noted to become inflamed and subsequently resolved in patients receiving systemic 5-FU as a chemotherapeutic agent, it was eventually designed into an effective topical formulation.

Photodynamic Therapy (PDT) and Other Treatments

Procedural field therapies may be an appropriate option for patients who require minimal downtime, are unlikely to adhere to a topical approach, have AKs resistant to topical therapy, or favor an optimal cosmetic result. Treatment options for procedural field therapy include also photodynamic therapy, manual dermabrasion, laser resurfacing, cryopeeling, and chemical peels. Each of these techniques treats AKs by destroying the superficial layers of the skin through physical or chemical means. Photodynamic therapy (PDT) is a procedural field therapy that utilizes topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate (Metvix®/Metvixia®) to target AKs. These molecules preferentially find their way into the hyperproliferating cells, which lack normal cell to cell adhesion junctions, and are converted intracellularly to protoporphyrin IX (PpIX). This photosensitizer is then exposed to blue or red light, which corresponds to the peaks in the absorption spectrum of PpIX, resulting in a phototoxic reaction that destroys the abnormal cell. PDT is not ideal for treating thicker or deeper AKs and is generally reserved for patients who exhibit an inadequate response to topical field therapy or cryosurgery.

SCC: First Line of Treatment Is Surgical Excision, Followed by Histological Examination

The standard treatment of SCC is excision, followed by histological examination to insure that the entire tumor has been removed. In NMSC with features that predict a high risk of recurrence, such as ulceration, large size, special location, or aggressive histological subtype, special measures may be necessary. Surgery may be conventional or microscopically controlled, the latter procedure referred to as "Mohs' surgery," after its originator. In this procedure, the targeted lesion is excised and the circumferential margins are assessed microscopically for residual tumor. Margins remaining involved undergo repeated excisions, followed by histological assessment, until negative margins are obtained.

Other Treatments Available

When surgical removal is not feasible, alternative treatment options include ionizing radiation, cryotherapy, and photodynamic therapy.

Even if SCC is a radiosensitive tumor, radiotherapy is usually preferred when other techniques cannot be performed for definitive treatment of selected cases (elderly patients, location on head and neck, poorly differentiated histological pattern) and for palliation of inoperable tumors. Cryotherapy may be used in small SCC when other surgical treatments are refused by the patients or contraindicated, particularly in patients with bleedings disorders.

Cutaneous SCC is not as sensitive as basal cell carcinoma to photodynamic therapy with 5-aminolevulinic acid (ALA). The average rate of complete response is around 70 %.

Intratumoral injection of biological control agents (usually interferons) or cytostatic agents, as well as systemic chemotherapy, may be needed in special cases. Chemotherapy and biological therapy with interferon-α (IFN-α) and cis-retinoic acid are active but give limited results (Cranmer et al. 2010).

Metastatic SCC

No standard treatment of metastatic disease has been formulated, although combinations of cisplatin with 5-fluorouracil (5-FU), doxorubicin, or bleomycin have demonstrated some degree of efficacy, achieving complete responses in some cases (Sadek et al. 1990). Clearly, the relative rarity of patients with high-risk, potentially fatal, squamous cell carcinoma of the skin has limited prospective efforts to define ideal management.

Future Treatments

Drugs targeting the epidermal growth factor receptor (EGFR) are currently a significant nonsurgical option for advanced SCC beyond radiotherapy and conventional chemotherapy. The future of anti-EGFR-targeted therapies in the treatment of skin cancer is discussed. Other strategies to potentiate the antitumor activity of cytotoxic agents such as docetaxel or cisplatin are also discussed (Gaffney et al. 2013). Targeted molecular therapies are becoming increasingly widespread and an understanding of the evidence for their use as well as their side effect profile is important in order to offer patients informed and current advice.

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Syphilis

94

Michael A. Waugh

Key Points

- Syphilis is still a frequent sexually transmitted infection (STI), caused by *Treponema pallidum*, with very serious consequences not only for the index patient but sexual partners if the diagnosis is missed.
- There are authoritative guidelines for its treatment.
- The therapeutic guidelines by Centers for Disease Control (CDC) and Prevention for syphilis in adults in the different stages of the infection are followed in this chapter.

Syphilis is still a frequent sexually transmitted infection (STI) with very serious consequences not only for the index patient but sexual partners if the diagnosis is missed.

In Europe the incidence has increased in recent years. It has been realized over the last 50 years that it is common in men who have sex with men (MSM). In the last 30 years in MSM, its coexistence with HIV has been frequently found. When syphilis is diagnosed, HIV and hepatitis B and C should be screened for at the same time in all adults as well as other sexually transmitted infections. In heterosexuals it has become more frequent though unfortunately again often misdiagnosed. It has always been recognized in sex workers and their clients, but it is not infrequently found in "swinger" groups with multiple sexual partners and intravenous drug users.

There are authoritative guidelines for its treatment. Those of Centers for Disease Control (CDC) and Prevention, Atlanta, USA, are followed in this chapter.

Only syphilis in adults will be considered here.

Definition

Syphilis is a systemic disease caused by *Treponema pallidum*. On the basis of clinical findings, the disease has been divided into a series of overlapping stages, which are used to help guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary infection (i.e., ulcer or chancre at the infection site), secondary infection (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and

This chapter is the copy of CDC guidelines. The copied part has been reported between brackets (all the chapter)

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_94, © Springer-Verlag Berlin Heidelberg 2015

lymphadenopathy), neurologic infection (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities, which might occur through the natural history of untreated infection), or tertiary infection (i.e., cardiac or gummatous lesions). Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration. Treatment for both late latent syphilis and tertiary syphilis might require a longer duration of therapy because organisms might be dividing more slowly; however, the validity of this concept has not been assessed.

Diagnosis

Dark-field examinations and tests to detect *T. pallidum* in lesion exudate or tissue are the definitive methods for diagnosing early syphilis (CDC). Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed PCR tests for the detection of *T. pallidum*. A presumptive diagnosis of syphilis is possible with the use of two types of serologic tests: (1) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and RPR) and (2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various EIAs, and chemiluminescence immunoassays). The use of only one type of serologic test is insufficient for diagnosis, because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. False-positive nontreponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions, older age, and injection-drug use (Nandwani and Evans 1995; Association of Public Health Laboratories (APHL) 2009); therefore, persons with a reactive nontreponemal test should receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers may correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method (e.g., VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers. Nontreponemal test titers usually decline after treatment and might become nonreactive with time; however, in some persons, nontreponemal antibodies can persist for a long period of time – a response referred to as the "serofast reaction." Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15–25 % of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years (Romanowski et al. 1991). Treponemal test antibody titers should not be used to assess treatment response.

Some clinical laboratories and blood banks have begun to screen samples using treponemal tests, typically by EIA or chemiluminescence immunoassays (CDC 2008; Pope 2004). This strategy will identify both persons with previous treatment for syphilis and persons with untreated or incompletely treated syphilis. The positive predictive value for syphilis associated with a treponemal screening test result might be lower among populations with a low prevalence of syphilis.

Persons with a positive treponemal screening test should have a standard nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, then the laboratory should perform a different treponemal test (preferably one based on different antigens than the original test) to confirm the results of the initial test. If a second treponemal test is positive, persons with a history of previous treatment will require

no further management unless sexual history suggests likelihood of re-exposure. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection, previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative, further evaluation or treatment is not indicated.

For most HIV-infected persons, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient's response to treatment. However, atypical syphilis serologic test results (i.e., unusually high, unusually low, or fluctuating titers) can occur in HIV-infected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, use of other tests (e.g., biopsy and dark-field microscopy) should be considered.

Clinical signs of neurosyphilis (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities) warrant further investigation and treatment for neurosyphilis. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Cerebrospinal fluid (CSF) laboratory abnormalities are common in persons with early syphilis. The VDRL in cerebrospinal fluid (CSF-VDRL), which is highly specific but insensitive, is the standard serologic test for CSF. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis; however in early syphilis, it can be of unknown prognostic significance (Lukehart et al. 1988). Most other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the laboratory diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count or protein, and a reactive CSF-VDRL with or without clinical manifestations. Among persons with HIV infection, the CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm^3); using a higher cutoff (>20 WBC/mm^3) might improve the specificity of neurosyphilis diagnosis (Marra et al. 2004a). The CSF-VDRL might be nonreactive even when neurosyphilis is present; therefore, additional evaluation using FTA-ABS testing on CSF can be considered. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive; neurosyphilis is highly unlikely with a negative CSF FTA-ABS test (Jaffe et al. 1978).

General Principles of Treatment

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. Selection of the appropriate penicillin preparation is important, because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by some forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for the treatment of syphilis. Reports have indicated that practitioners have inadvertently prescribed combination benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) widely used in the United States. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products to avoid using the inappropriate combination therapy agent for treating syphilis (CDC 2005).

The effectiveness of penicillin for the treatment of syphilis was well established through clinical experience even before the value of randomized controlled clinical trials was recognized. Therefore, nearly all the recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but approximately 50 years of clinical experience.

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin (see section "Management of patients who have a history of penicillin allergy").

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that usually occur within the first 24 h after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction. The Jarisch-Herxheimer reaction occurs most frequently among patients who have early syphilis, presumably because bacterial burdens are higher during these stages. Antipyretics can be used to manage symptoms, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women, but this should not prevent or delay therapy (see section "Syphilis during pregnancy").

Management of Sex Partners

Sexual transmission of *T. pallidum* is thought to occur only when mucocutaneous syphilitic lesions are present. Although such manifestations are uncommon after the first year of infection, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically and treated with a recommended regimen, according to the following recommendations:

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) can be assumed to have early syphilis. For the purpose of determining a treatment regimen, however, serologic titers should not be used to differentiate early from late latent syphilis (see section "Latent syphilis," Treatment).
- Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.

Sexual partners of infected patients should be considered at risk and provided treatment if they have had sexual contact with the patient within 3 months plus the duration of symptoms for patients diagnosed with primary syphilis, 6 months plus duration of symptoms for those with secondary syphilis, and 1 year for patients with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively for more than 50 years to achieve clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no comparative trials have been adequately conducted to guide the selection of an optimal penicillin regimen (i.e., the dose, duration, and preparation). Substantially fewer data are available for non-penicillin regimens.

Recommended Regimen for Adults[a]

Benzathine penicillin G 2.4 million units IM in a single dose

[a]Recommendations for treating syphilis in HIV-infected persons and pregnant women are discussed later in this report (see sections "Syphilis among HIV-infected persons" and "Syphilis in pregnancy")

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis (primary, secondary, and early latent) do not enhance efficacy, regardless of HIV status (Figs. 94.1, 94.2, 94.3, 94.4, 94.5, 94.6, 94.7, 94.8, and 94.9).

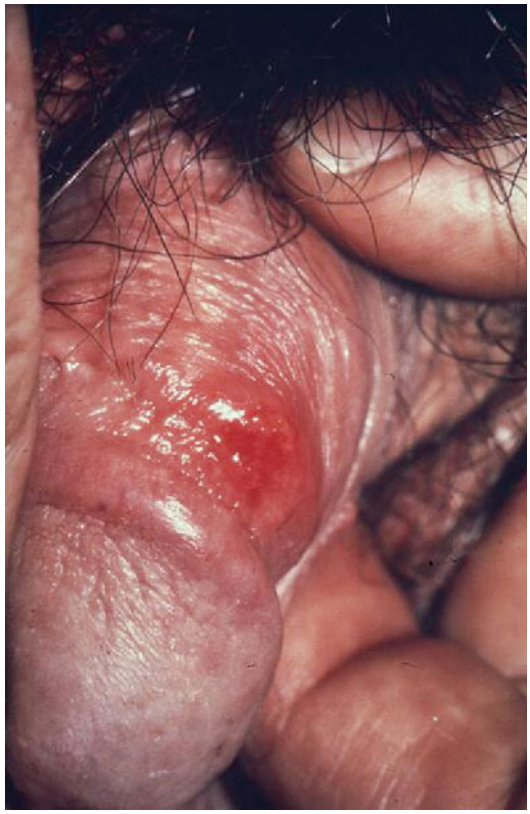

Fig. 94.1 Primary syphilis – chancre male

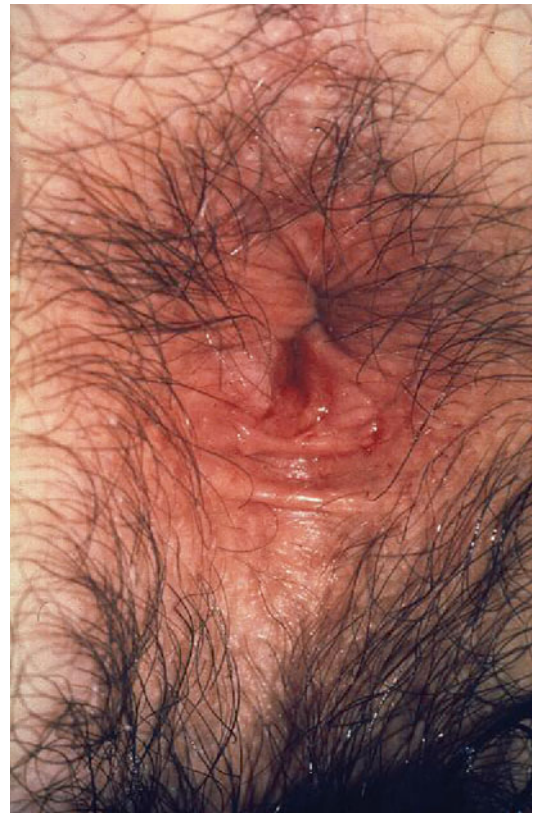

Fig. 94.3 Primary syphilis – chancre anus

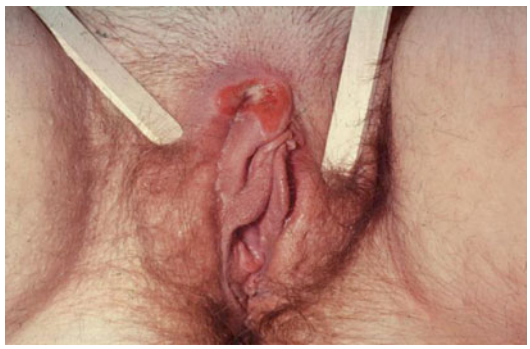

Fig. 94.2 Primary syphilis – chancre female

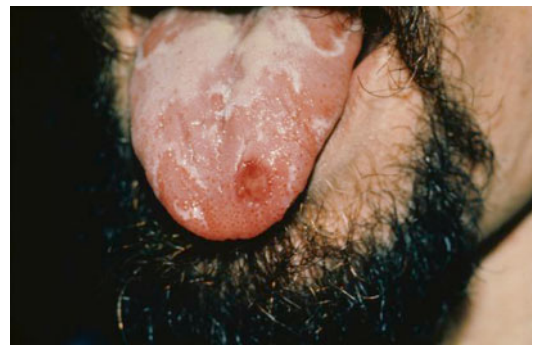

Fig. 94.4 Primary syphilis – chancre tongue

Other Management Considerations

All persons who have syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, persons who have primary syphilis should be retested for HIV after 3 months if the first HIV test result was negative.

Patients who have syphilis and symptoms or signs suggesting neurologic disease (e.g., meningitis and hearing loss) or ophthalmic disease

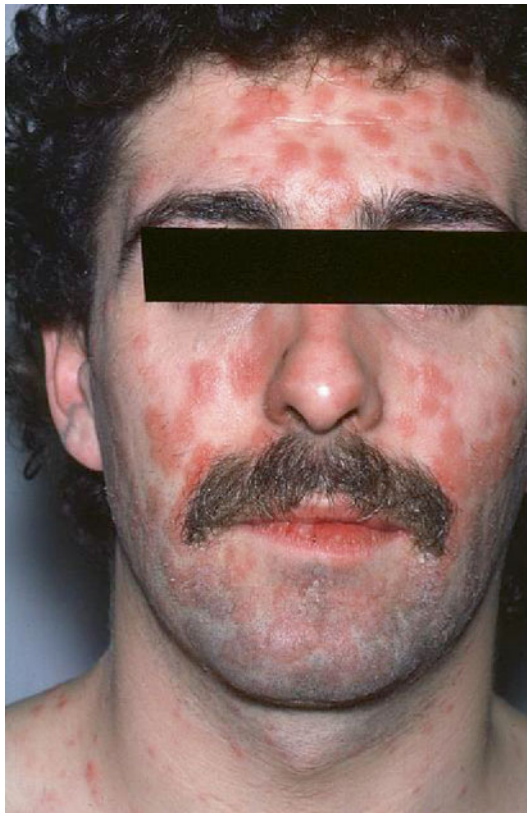

Fig. 94.5 Secondary syphilis – man's face

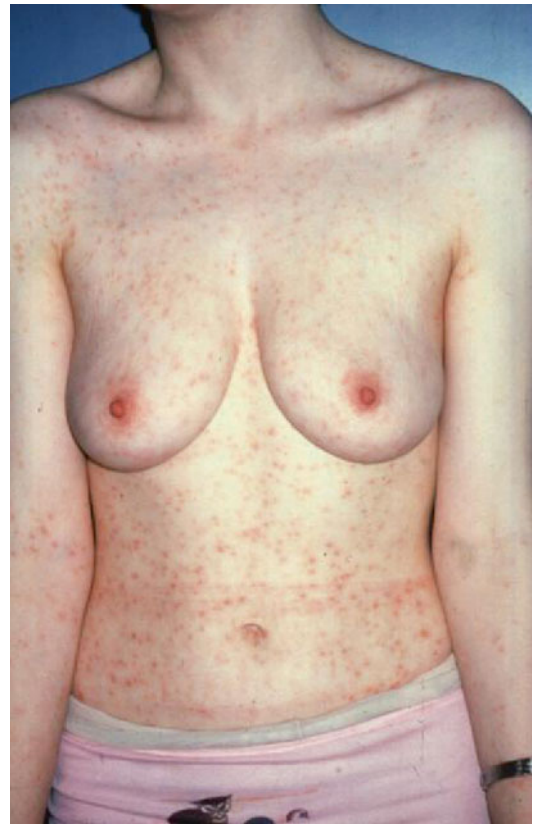

Fig. 94.6 Secondary syphilis – female trunk

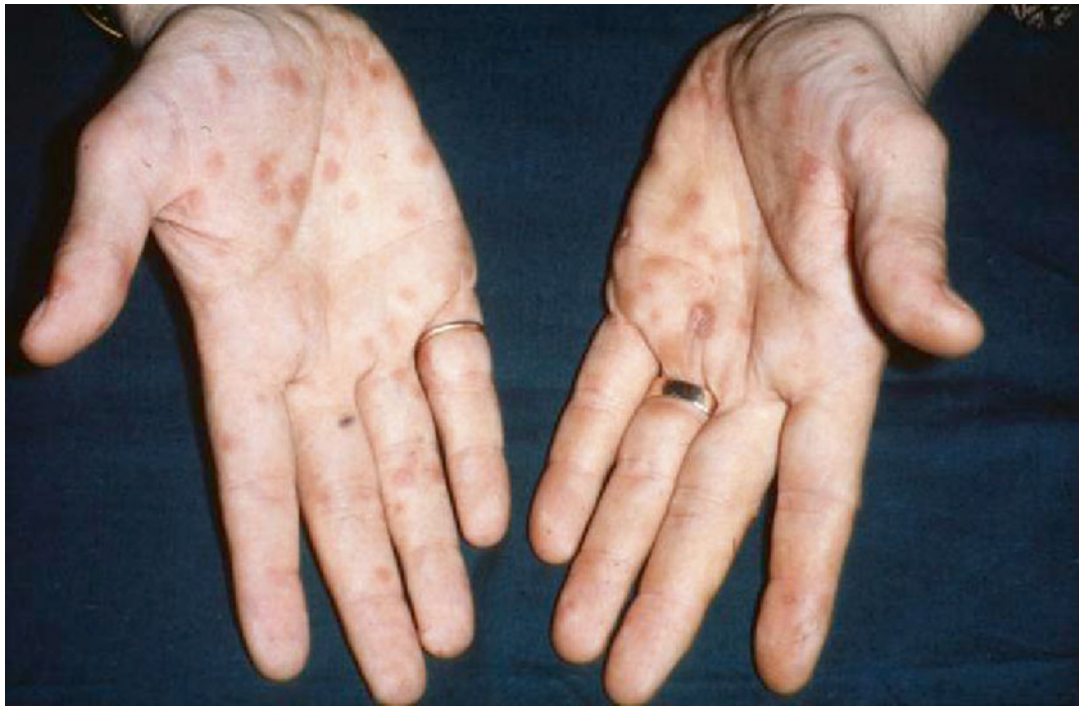

Fig. 94.7 Secondary syphilis – hands

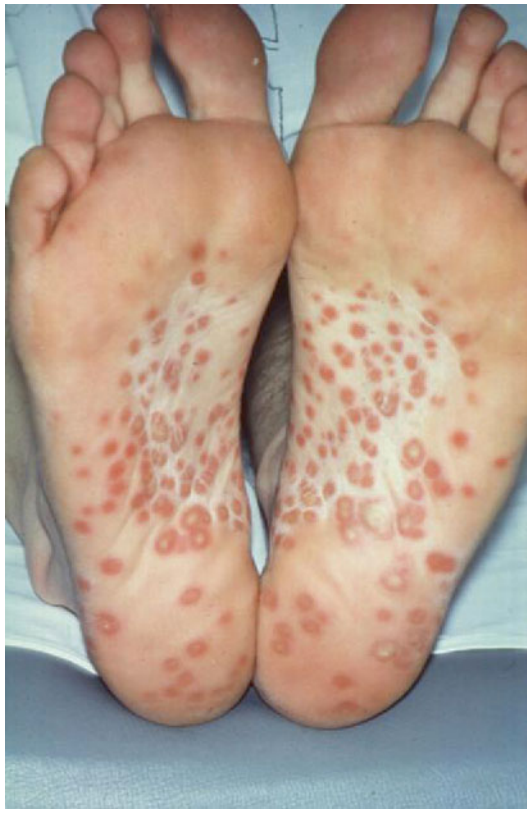

Fig. 94.8 Secondary syphilis – feet

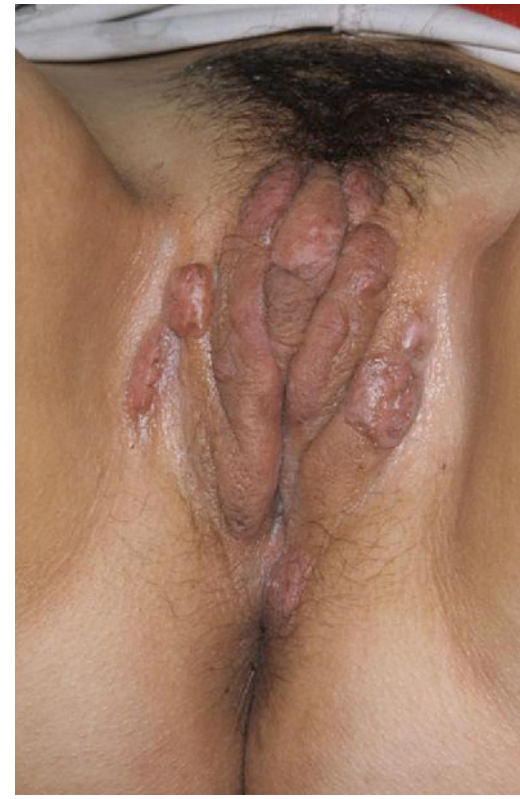

Fig. 94.9 Secondary syphilis – condylomata lata

(e.g., uveitis, iritis, neuroretinitis, and optic neuritis) should have an evaluation that includes CSF analysis, ocular slit-lamp ophthalmologic examination, and otologic examination. Treatment should be guided by the results of this evaluation.

Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis (Lukehart et al. 1988). Therefore, in the absence of clinical neurologic findings, no evidence exists to support variation from the recommended treatment regimen for early syphilis. Symptomatic neurosyphilis develops in only a limited number of persons after treatment with the penicillin regimens recommended for primary and secondary syphilis. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present or treatment failure is documented, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Treatment failure can occur with any regimen. However, assessing response to treatment frequently is difficult, and definitive criteria for cure or failure have not been established. In addition, nontreponemal test titers might decline more slowly for persons who previously have had syphilis (Ghanem et al. 2007). Clinical and serologic evaluation should be performed 6 and 12 months after treatment; more frequent evaluation might be prudent if follow-up is uncertain.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer (i.e.,

compared with the maximum or baseline titer at the time of treatment) probably failed treatment or were reinfected. These patients should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T. pallidum*, a CSF analysis also should be performed.

Although failure of nontreponemal test titers to decline fourfold within 6–12 months after therapy for primary or secondary syphilis might be indicative of treatment failure, clinical trial data have demonstrated that >15 % of patients with early syphilis treated with the recommended therapy will not achieve the two-dilution decline in nontreponemal titer used to define response at 1 year after treatment (Rolfs et al. 1997). Persons whose titers do not decline should be reevaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these patients should receive additional clinical and serologic follow-up. If additional follow-up cannot be ensured, re-treatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in such situations.

For re-treatment, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks are recommended, unless CSF examination indicates that neurosyphilis is present (see section "Neurosyphilis"). In rare instances, serologic titers do not decline despite a negative CSF examination and a repeated course of therapy. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

Data to support the use of alternatives to penicillin in the treatment of early syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic patients who have primary or secondary syphilis. Doxycycline 100 mg orally twice daily for 14 days (Ghanem et al. 2006; Wong et al. 2008) and tetracycline (500 mg four times daily for 14 days) are regimens that have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1 g daily either IM or IV for 10–14 days) is effective for treating early syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined (Hook et al. 1988). Azithromycin as a single 2 g oral dose is effective for treating early syphilis (Riedner et al. 2005; Hook et al. 2002, 2010). However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States (Lukehart et al. 2004; Mitchell et al. 2006; Su et al. 2006) as well as some other countries. As such, the use of azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM or pregnant women. Close follow-up of persons receiving any alternative therapies is essential.

Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform the test adequately (see section "Management of patients who have a history of penicillin allergy").

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see sections "Management of patients who have a history of penicillin allergy" and "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Patients who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis. Patients' conditions can be diagnosed as early latent syphilis if, during the year preceding the evaluation, they had (1) a documented seroconversion or fourfold or greater increase in titer of a nontreponemal test, (2) unequivocal symptoms of primary or secondary syphilis, or (3) a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons whose only possible exposure occurred during the previous 12 months, reactive nontreponemal and treponemal tests are indicative of early latent syphilis. In the absence of these conditions, an asymptomatic person should be considered to have late latent syphilis or syphilis of unknown duration. Nontreponemal serologic titers usually are higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers. All patients with latent syphilis should have careful examination of all accessible mucosal surfaces (i.e., the oral cavity, perianal area, perineum and vagina in women, and underneath the foreskin in uncircumcised men) to evaluate for internal mucosal lesions. All patients who have syphilis should be tested for HIV infection.

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating patients with this stage of disease is to prevent complications. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens.

The following regimens are recommended for penicillin nonallergic patients who have normal CSF examinations (if performed):

Recommended Regimens for Adults[a]

Early latent syphilis

Benzathine penicillin G 2.4 million units IM in a single dose

Late latent syphilis or latent syphilis of unknown duration

Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

[a]Recommendations for treating syphilis in HIV-infected persons and pregnant women are discussed later in this report (see sections "Syphilis among HIV-infected persons" and "Syphilis in pregnancy")

Available data demonstrate no enhanced efficacy of additional doses of penicillin G, amoxicillin, or other antibiotics in early syphilis, regardless of HIV status.

Other Management Considerations

Patients diagnosed with latent syphilis who demonstrate any of the following criteria should have a prompt CSF examination:

- Neurologic (e.g., auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) or ophthalmic signs or symptoms (e.g., iritis and uveitis)
- Evidence of active tertiary syphilis (e.g., aortitis and gumma)
- Serologic treatment failure

If a patient misses a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course of action is unclear. Pharmacologic considerations suggest that an interval of 10–14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis. Pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. A CSF examination should be performed if (1) titers increase fourfold, (2) an initially high titer (≥1:32) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or (3) signs or symptoms attributable to syphilis develop. In such circumstances, even if the CSF examination is negative, re-treatment for latent syphilis should be initiated. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might fail to decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

The effectiveness of alternatives to penicillin in the treatment of latent syphilis has not been well documented. Nonpregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to therapies recommended as alternatives to penicillin for the treatment of primary and secondary syphilis (see section "Primary and secondary syphilis," Treatment). The only acceptable alternatives for the treatment of late latent syphilis or latent syphilis of unknown duration are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), both for 28 days. These therapies should be used only in conjunction with close serologic and clinical follow-up. Based on biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating late latent syphilis or syphilis of unknown duration. However, the optimal dose and duration of ceftriaxone therapy have not been defined, and treatment decisions should be discussed in consultation with a specialist. Some patients who are allergic to penicillin also might be allergic to ceftriaxone; in these circumstances, use of an alternative agent might be required. The efficacy of these alternative regimens in HIV-infected persons has not been well studied.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see sections "Management of patients who have a history of penicillin allergy" and "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Tertiary Syphilis

Tertiary syphilis refers to gumma and cardiovascular syphilis but not to all neurosyphilis. Patients who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen:

Recommended Regimen

Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Other Management Considerations

Patients who have symptomatic late syphilis should be given a CSF examination before therapy is initiated. Some providers treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. These patients should be managed in consultation with an infectious disease specialist.

Follow-Up

Limited information is available concerning clinical response and follow-up of patients who have tertiary syphilis.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

Patients allergic to penicillin should be treated in consultation with an infectious disease specialist.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see sections "Management of patients who have a history of penicillin allergy" and "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Neurosyphilis

Treatment

CNS involvement can occur during any stage of syphilis. However, CSF laboratory abnormalities are common in persons with early syphilis, even in the absence of clinical neurological findings. No evidence exists to support variation from recommended treatment for early syphilis for patients found to have such abnormalities. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis), a CSF examination should be performed.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis and should be managed according to the treatment recommendations for neurosyphilis. Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the recommended regimen for neurosyphilis; those with eye disease should be managed in collaboration with an ophthalmologist. A CSF examination should be performed for all patients with syphilitic eye disease to identify those with abnormalities; patients found to have abnormal CSF test results should be provided follow-up CSF examinations to assess treatment response:

Recommended Regimen

Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion for 10–14 days

If compliance with therapy can be ensured, the following alternative regimen might be considered:

Alternative Regimen

Procaine penicillin 2.4 million units IM once daily

PLUS

Probenecid 500 mg orally four times a day, both for 10–14 days

The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for late syphilis in the absence of neurosyphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations

Other considerations in the management of patients who have neurosyphilis are as follows:

- All persons who have syphilis should be tested for HIV.
- Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven to be beneficial.

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months

until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important (Marra et al. 2004b, 2008). The leukocyte count is a sensitive measure of the effectiveness of therapy. If the cell count has not decreased after 6 months or if the CSF cell count or protein is not normal after 2 years, re-treatment should be considered.

Limited data suggest that in immunocompetent persons and HIV-infected persons on highly active antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters (Marra et al. 2008).

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

Limited data suggest that ceftriaxone 2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for patients with neurosyphilis (Hook et al. 1986; Shann and Wilson 2003). However, the possibility of cross-reactivity between ceftriaxone and penicillin exists. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, if concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, desensitization in consultation with a specialist.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see section "Syphilis during pregnancy").

HIV Infection

See section "Syphilis among HIV-infected persons."

Syphilis Among HIV-Infected Persons

Diagnostic Considerations

Although they are uncommon, unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most reports have involved serologic titers that were higher than expected, but false-negative serologic test results and delayed appearance of seroreactivity also have been reported (Kingston et al. 2005). Regardless, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfected with *T. pallidum* and HIV.

When clinical findings are suggestive of syphilis but serologic tests are nonreactive or their interpretation is unclear, alternative tests (e.g., biopsy of a lesion, dark-field examination, and PCR of lesion material) might be useful for diagnosis. Neurosyphilis should be considered in the differential diagnosis of neurologic disease in HIV-infected persons.

Treatment

Compared with HIV-negative patients, HIV-positive patients who have early syphilis might be at increased risk for neurologic complications (CDC 2007) and might have higher rates of serologic treatment failure with currently recommended regimens. The magnitude of these risks is not defined precisely, but is likely small. No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients (Rolfs et al. 1997). Careful follow-up after therapy is essential.

Primary and Secondary Syphilis Among HIV-Infected Persons

Treatment

Treatment of primary and secondary syphilis among HIV-infected persons is benzathine

penicillin G, 2.4 million units IM in a single dose.

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis do not result in enhanced efficacy, regardless of HIV status (Rolfs et al. 1997).

Other Management Considerations

Most HIV-infected persons respond appropriately to standard benzathine penicillin for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in HIV-infected persons, even in those without neurologic symptoms, although the clinical and prognostic significance of such CSF abnormalities with primary and secondary syphilis is unknown. Several studies have demonstrated that among persons infected with both HIV and syphilis, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤350 cells/mL and/or an RPR titer of ≥1:32 (Marra et al. 2004a; Libois et al. 2007; Ghanem 2009); however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in HIV-infected persons with syphilis (Marra et al. 2008; Ghanem et al. 2008a, b).

Follow-Up

HIV-infected persons should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

HIV-infected persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained fourfold increase in nontreponemal test titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and re-treatment). CSF examination and re-treatment also should be strongly considered for persons whose nontreponemal test titers do not decrease fourfold within 6–12 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM each at weekly intervals for 3 weeks is recommended.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

HIV-infected, penicillin-allergic patients who have primary or secondary syphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see section "Management of patients who have a history of penicillin allergy"). The use of alternatives to penicillin has not been well studied in HIV-infected patients. These therapies should be used only in conjunction with close serologic and clinical follow-up.

Latent Syphilis Among HIV-Infected Persons

Treatment

HIV-infected persons with latent syphilis should be treated according to the stage-specific recommendations for HIV-negative persons:

- Treatment of early latent syphilis among HIV-infected persons is benzathine penicillin G, 2.4 million units IM in a single dose.
- Treatment of late latent syphilis or syphilis of unknown duration among HIV-infected persons is benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks.

Other Management Considerations

All HIV-infected persons with syphilis and neurologic symptoms should undergo immediate CSF examination. Some studies have demonstrated that clinical and CSF abnormalities

consistent with neurosyphilis are most likely in HIV-infected persons who have been diagnosed with syphilis and have a CD4 count of ≤350 cells/ml and/or an RPR titer of ≥1:32 (Marra et al. 2004a; Libois et al. 2007; Ghanem 2009); however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

Follow-Up

Patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. If, at any time, clinical symptoms develop or nontreponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly. If during 12–24 months the nontreponemal titer does not decline fourfold, CSF examination should be strongly considered and treatment administered accordingly.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

The efficacy of alternative nonpenicillin regimens in HIV-infected persons has not been well studied. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see section "Management of patients who have a history of penicillin allergy"). These therapies should be used only in conjunction with close serologic and clinical follow-up. Limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone might be effective (Dowell et al. 1992; Smith et al. 2004). However, the optimal dose and duration of ceftriaxone therapy have not been defined.

Neurosyphilis Among HIV-Infected Persons

Treatment

HIV-infected patients with neurosyphilis should be treated according to the recommendations for HIV-negative patients with neurosyphilis (see section "Neurosyphilis").

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to gauge response after therapy. Limited data suggest that changes in CSF parameters might occur more slowly in HIV-infected patients, especially those with more advanced immunosuppression (Marra et al. 2004b; Ghanem et al. 2008a). If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, re-treatment should be considered.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

HIV-infected, penicillin-allergic patients who have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis. Several small observational studies conducted in HIV-infected patients with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10–14 days might be effective as an alternate agent (Marra et al. 2000; Dowell et al. 1992; Smith et al. 2004).

Syphilis During Pregnancy

All women should be screened serologically for syphilis early in pregnancy. Most states mandate screening at the first prenatal visit for all women (Hollier et al. 2001); antepartum screening by nontreponemal antibody testing is typical, but in some settings, treponemal antibody testing is being used. Pregnant women with reactive treponemal screening tests should have confirmatory testing with nontreponemal tests with titers. In populations in which use of prenatal care is not optimal, RPR test screening and treatment (if the RPR test is reactive) should be performed at the time that pregnancy is confirmed (World Health Organization 2005). For communities and populations in which the prevalence of syphilis is high and for patients at high risk, serologic testing should be performed twice during the third trimester (ideally at 28–32 weeks' gestation) and at delivery. Any woman who delivers a stillborn infant after 20 weeks' gestation should be tested for syphilis. No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy.

Diagnostic Considerations

Seropositive pregnant women should be considered infected unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined. Serofast low antibody titers might not require treatment; however, persistent higher titer antibody tests might indicate reinfection, and treatment might be required.

Treatment

Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection (Alexander et al. 1999). Evidence is insufficient to determine optimal, recommended penicillin regimens (Walker 2001):

Recommended Regimen

Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.

Other Management Considerations

Some evidence suggests that additional therapy can be beneficial for pregnant women in some settings (e.g., a second dose of benzathine penicillin G 2.4 million units IM administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis) (Wendel et al. 2002). When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (i.e., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure (Hollier et al. 2001); such cases should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations.

Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction (Klein et al. 1990). These women should be advised to seek obstetric attention after treatment if they notice any fever, contractions, or decrease in fetal movements. Stillbirth is a rare complication of treatment, but concern for this complication should not delay necessary treatment. All patients who have syphilis should be offered testing for HIV infection.

Follow-Up

Coordinated prenatal care and treatment are vital. Serologic titers should be repeated at 28–32 weeks' gestation and at delivery as recommended for the disease stage. Providers should ensure that the clinical and antibody responses

are appropriate for the patient's stage of disease, although most women will deliver before their serologic response to treatment can be assessed definitively. Inadequate maternal treatment is likely if delivery occurs within 30 days of therapy, if clinical signs of infection are present at delivery, or if the maternal antibody titer at delivery is fourfold higher than the pretreatment titer. Serologic titers can be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high.

Management of Sex Partners

See section General principles, "Management of sex partners."

Special Considerations

Penicillin Allergy

For treatment of syphilis during pregnancy, no proven alternatives to penicillin exist. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Oral stepwise penicillin dose challenge or skin testing might be helpful in identifying women at risk for acute allergic reactions (see section "Management of patients who have a history of penicillin allergy").

Tetracycline and doxycycline usually are not used during pregnancy. Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection nor treats an infected fetus (Walker 2001). Data are insufficient to recommend ceftriaxone for treatment of maternal infection and prevention of congenital syphilis.

HIV Infection

Placental inflammation from congenital infection might increase the risk for perinatal transmission of HIV. All HIV-infected women should be evaluated for syphilis and receive treatment as recommended. Data are insufficient to recommend a specific regimen for HIV-infected pregnant women (see section "Syphilis among HIV-infected patients").

Syphilis in Pregnancy

Pregnant women should be treated with the first line therapy option appropriate for the stage of syphilis and if allergic to penicillin should be desensitized (Janier et al. 2014).

General Principles Management of Sexual Partners

The Guidelines for contact tracing, management of sexual partners and notification of syphilis cases are detailed in 2014 European guideline on the management of syphilis (Janier et al. 2014).

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Systemic Sclerosis

95

Matteo Zanardelli, Zoulikha Zarrab,
and Aldona Pietrzak

Key Points

- Systemic sclerosis is a chronic multisystemic progressive disease that affects the skin and internal organs.
- Raynaud's phenomenon and skin sclerosis are the first signs of the disease.
- Based on the clinical features, the course of the disease and its prognosis can be distinguished in limited, diffuse and overlap systemic sclerosis.
- The therapy should be adjusted according to the severity and progression of the disease.
- Therapy should limit primary vascular damage and subsequently regulate the immune response and the fibrosis. Symptomatic treatments, vasoactive, antifibrotic and immunosuppressive agents, can be taken into consideration in the treatment of the disease.

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Definition and Epidemiology

Systemic sclerosis is a chronic multisystemic progressive disease that affects the skin and internal organs. Generally, Raynaud's phenomenon and vascular changes are the first clinical manifestations followed by sclerotic and fibrotic changes. It is a rare disease: the incidence is 8–12 patients per million population and about 75 % of patients are woman. It has the highest case-specific mortality of any of the autoimmune rheumatic diseases: the 5-year survival is about 50–70 % when pulmonary hypertension is present. It is determined by the involvement of the heart and lung (pulmonary fibrosis, pneumonia) and in some populations of higher frequency of the kidney (uraemia, malignant hypertension).

Basic Concepts of Pathogenesis

Systemic scleroderma is a complex disease, since three systems seem to be involved: the blood vessels, the immune system and the fibroblast. The microvasculature compartment seems to be affected earlier as a first involvement of the diseases. As in other various autoimmune diseases, the pathogenesis can be related to a genetic predisposition and modulated by environmental factors. The disease may be immunologically triggered and is (auto)immune mediated. The altered immune response at skin level is highlighted by the activation of T lymphocytes,

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_95, © Springer-Verlag Berlin Heidelberg 2015

abnormal cytokine production and polyclonal B-cell reactivity. The alteration of the microvasculature environment may dysregulate the release of fibroblast mediators (cytokines and growth factors) leading to progressive fibrosis of skin and internal organs. A significant deposition of collagen type I is released by fibroblasts. Skin changes are caused by abundant accumulation of homogeneous, densely packed collagen fibres, septa penetrating into the subcutaneous tissue, loss of appendages, perivascular lymphocytic infiltrates and thickening of the vessel wall with subsequent devascularisation.

Clinical Presentation

The heterogeneity of systemic sclerosis arises from the range of disease manifestations that vary between patients. Generally, the first symptoms of the disease are Raynaud's phenomenon, skin sclerosis and arthralgias (Figs. 95.1, 95.2, 95.3a, b). Cutaneous sclerosis and the involvement of various internal organs such as gastrointestinal tract, lung, heart, kidney and musculature appear later. Systemic sclerosis is defined by one major criterion (proximal scleroderma) and three minor criteria (among sclerodactyly, digital pitting scars or loss of substance on the distal finger pad and bibasilar pulmonary fibrosis). Based on the clinical features, the course of the disease and its prognosis can be distinguished in:

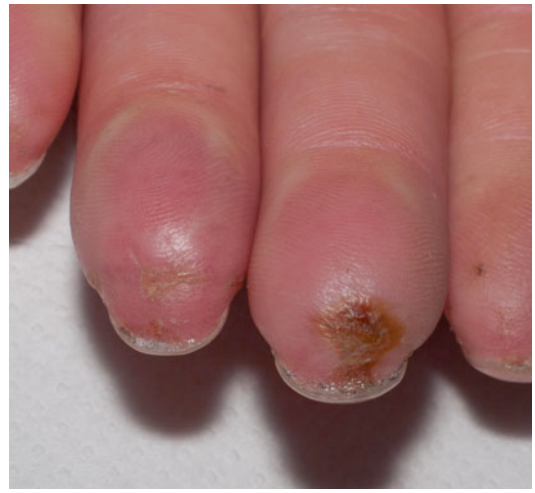

Fig. 95.1 Sclerodactyly and digital pitting scars (With permission of Prof. Grażyna Chodorowska and Prof Dorota Krasowska) (Photo by dr B. Wawrzycki)

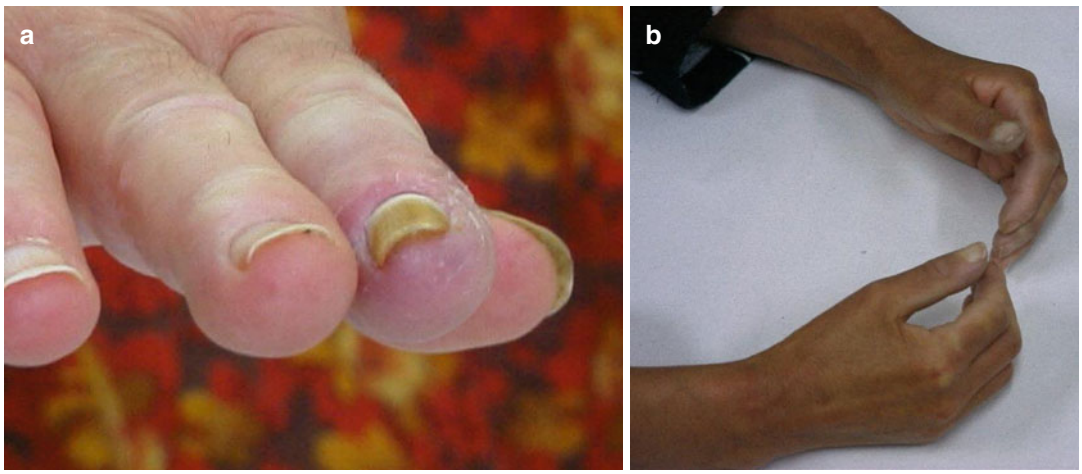

Fig. 95.2 (**a**, **b**) Sclerodactyly (With permission of Prof. Grażyna Chodorowska and Prof Dorota Krasowska)

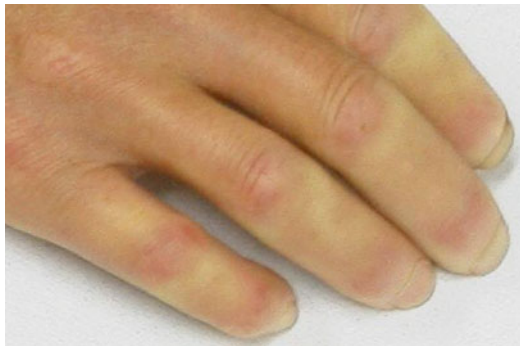

Fig. 95.3 Raynaud's phenomenon

- *Limited scleroderma*: Raynaud's phenomenon for years at presentation. The sclerosis is limited to the hands, feet, face and forearms or absent. It includes the classic CREST (calcinosis cutis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia) syndrome. The incidence of pulmonary hypertension, trigeminal neuralgia, calcinosis and telangiectasia is late. The dilated nail fold capillary loops are dilated.
- *Diffuse scleroderma*: Raynaud's symptoms are visible within 1 year of the onset of skin alterations. The truncal and acral skin are significantly involved. Myocardial dysfunction, diffuse gastrointestinal disease, interstitial lung disease and oliguric renal failure appear earlier and are clearly visible. Systemic lupus erythematosus Sjögren's syndrome and dermatomyositis can be confused with the disease. They are characterized by U1RNP, La, Ro and Pm-Scl antibodies, respectively.
- *Overlap systemic sclerosis*: The features of scleroderma are present together with those of another autoimmune rheumatic disease, as systemic lupus erythematosus, Sjögren's syndrome and dermatomyositis can be confused with the disease. They are characterised by fibrillarin or PM-Scl antibodies. Serologic features of systemic lupus erythematosus, rheumatoid arthritis or Sjögren's disease can be noted.
- Early diagnosis is not always simple. Skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient for the diagnosis. If that is not present, seven additive items apply, with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nail fold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon and disease-related autoantibodies. Antinuclear antibodies are found in 97 % of cases, using HEp-2 cells as substrate.

Centromere antibodies are detectable in 50–70 % of limited variants of the disease as CREST syndrome and antitopoisomerase antibodies (anti-Scl-70) in about 36 % of cases of systemic diffuse scleroderma. The increase of collagen metabolism, due to the activation of fibroblasts, is revealed with high level of β-galactosidase and N-terminal procollagen III propeptide. Early identification of the disease is of great importance from both scientific and clinical points of view. Studies performed in patients at the early stage of the disease might foster research on the processes that play a crucial role in the pathogenesis.

Differential Diagnosis

- Raynaud's phenomenon. Generalised morphea and multiple plaque morphea
- Overlap with systemic lupus erythematosus and dermatomyositis
- Sclerodermiform porphyria cutanea tarda
- Scleromyxoedema: paraproteins, light chains
- Genetic acrogeria
- Haematologic disease as cryoglobulinemia, cold agglutinin disease and hyperviscosity syndrome
- Scleroderma-like lesions, as amyloidosis, scleromyxoedema, mucinosis and lichen sclerosus et atrophicus
- Scleroedema adultorum (Buschke's disease) with acute onset and visible after an infection
- Graft-versus-host disease after transplantation
- Eosinophilic fasciitis
- Chronic graft-versus-host disease

General Principles of Treatment

The therapy should be adjusted according to the severity and progression of the disease. The quantitative measurement of skin score and severity of skin involvement is desirable for follow-up studies. Therapy should limit primary vascular damage and subsequently regulate the immune response and the fibrosis. However, at present, there is no proven antifibrotic agent.

General Recommendations

General recommendations include: avoiding of the changes of temperature, protection from cold, regular physical activity using small balls to avoid contractures of the hands, regular dentistry controls and homeostasis of the oral cavity as long as possible and high diet content of proteins and vitamins. The skin should be protected with clothes and lubrificated with emollients. Nicotine should be avoided. Moreover, psychological guidance, based on interview counselling and autogenous training, is helpful.

Recommended Therapies

Symptomatic Treatment

The cyclooxygenase (COX)-II inhibitors Celebrex), small doses of glucocorticosteroids or nonsteroidal antiphlogistics are used for arthralgia, arthritis and tendon pain.

The reflux oesophagitis can be successfully treated with the proton pump inhibitor omeprazole (20–40 mg/day per os), antacids and H_2 antagonists (cimetidine, ranitidine). Metoclopramide (Paspertin), 3×10 mg/day per os, acts as gastroprokinetic. Small bowel bacterial overgrowth (diarrhoea) can be inhibited by tetracycline, ampicillin and metronidazole using also probiotics. Some sources recommend use of piascledine.

Vasoactive Substances

Vasculopathy is an important feature of systemic sclerosis and involves both the peripheral and visceral vessels. Approximately 50 % of patients with systemic sclerosis suffer from digital ulceration associated with vasculopathy at some point in their disease history. Other complications include critical digital ischaemia, paronychia and finger pulp loss.

Pulmonary arterial hypertension (PAH), developing due to obliterative angiopathy of the pulmonary arteries, is currently the leading cause of scleroderma-related deaths.

- *Calcium channel blockers* are the therapy of choice in Raynaud's phenomenon. Nifedipine 510 mg, three tablets/day, is suggested. Alternatives are nitrendipine, verapamil and nicardipine.
- *Pentoxyphylline*, 0.4–0.8 g/day, acts as a vasodilator and exerts, in addition, immunomodulatory and antifibrotic effects.
- *Prostacyclins* inhibit platelet aggregation and mediate vasodilatation. Intravenous infusions of prostaglandin E_1, e.g. 0.5–2.0 ng/kg per min, are more effective and better tolerated than oral doses of the prostacyclin analogue iloprost (100–300 μg/day). Side effects can be headache, flush and hypotension.
- *Angiotensin-converting enzyme inhibitors*, e.g. captopril (4×12.5 mg/ day) or enalapril (10 mg/day), are useful in patients suffering from hypertension. They represent a considerable advance in preventing or treating acute renal crisis.
- Patients with digital ulcers may benefit from the use of flexible *hydroactive dressings* such as DuoDERM, Sorbsan and antimicrobial creams or hydrogen peroxide solution (1.5–3 %) or silver sulfadiazine cream.
- *Digital sympathectomy and radial microarteriolysis* for a critically ischaemic digit are the last resort for treatment of ischaemic digit.
- *Antagonist of angiotensin II receptor type I* (losartan) exerts clinical benefit in Raynaud's phenomenon after 12 weeks.
- *Clonidine* as an antihypertensive agent (3×0.15–0.3 mg/day p.o.) may be considered.

- *Prazosin* as a receptor blocker (1–4 mg/day p.o.) can be used.
- *Ketanserin* (60–120 mg/day p.o.) as a serotonin antagonist can be considered, but it seems to have low relevance.
- *Fibrinolysis-enhancing* drugs, as dextran, tissue plasminogen activator, urokinase and stanozolol, can be tried.
- *New proposed substances* are endothelin receptor antagonists and phosphodiesterase-5 (PDI-5) inhibitors used for the treatment of PAH and for combination therapy in patients who do not respond to therapy with single agents.
  - Attempts of Viagra

Immunosuppressive Agents

Immunosuppression is considered a cornerstone of therapy of diffuse progressive disease and systemic sclerosis-related interstitial lung disease (SLD). However, the evidence for efficacy of immunosuppressive drugs in treating the disease-related organ involvement is limited.

- *Methotrexate* (MTX) inhibits the intracellular purine and pyrimidine metabolism, amino acid synthesis and polyamine synthesis. Additionally, MTX increases extracellular adenosine concentrations. In vivo MTX shows numerous immunomodulatory effects. It is able to limit the cellular adhesion, the clonal proliferation of T and B cells, the IL-1β production by mononuclear cells and the production of proinflammatory cytokines by activated T cells. If used for skin thickening treatment in the absence of lung disease, MTX with a dose of 15–25 mg once weekly can be exploited for treatment. The use of oral or subcutaneous dosing will be determined based on gastrointestinal tolerance and skin involvement.
- *Ciclosporin A* (1.5–5 mg/kg of body weight per day) is more selectively directed against T cells, IL-2 release and other cytokines. Side effects, as nephrotoxicity, limit its use.
- *Photopheresis* (extracorporeal photochemotherapy) inhibits activated T cells. Long-term treatment, more than 18–36 months, in cycles every 4 weeks, has shown a beneficial effect on disabling symptoms such as fingertip ulcer, hand motility, Raynaud's phenomenon and skin stiffness.
- *Mycophenolate* is available commercially as mycophenolate mofetil (MMF, CellCept) and mycophenolate sodium (MS, Myfortic). After absorption, it is hydrolysed and transformed to the active drug mycophenolic acid. Its use is aimed at the treatment of systemic lupus erythematosus and other autoimmune diseases. Mycophenolic acid reversibly inhibits lymphocyte proliferation, through the block of guanosine monophosphate production, a purine essential for lymphocyte amplification. Mycophenolate can be considered a second-line therapy for treatment of skin thickening in the disease. The maximum dose is 3 g per day in divided doses.
- *Cyclophosphamide* is an alkylating agent used in the treatment of malignancy, vasculitis and lupus nephritis. Its immunomodulatory properties derive from the reduction of B- and T-cell proliferation, through the disruption of DNA integrity. Cyclophosphamide is an important agent to consider for diffuse skin disease if there is concurrent lung disease. If administered intravenously, it should be used at 500 mg/m^2 on the first infusion and then increased to 750 mg/m^2 or higher for subsequent infusions if patient laboratory parameters and side effect profile will allow for it. Oral cyclophosphamide should be administered at a dose of 2 mg/kg/day as tolerated.
- *Azathioprine* is a prodrug and the active form is 6-mercaptopurine (6-MP). 6-MP is a purine structural analogue that reduces de novo synthesis of purines, decreasing cellular proliferation. Azathioprine should be considered as an alternative agent for skin involvement when there is intolerance or unresponsiveness for other agents. The proposed oral doses range from 2 to 3 mg/kg/day.
- *Prednisolone* is considered *by some of the authors* the most effective drug in the early inflammatory stages or episodes of the disease

(with significant immunological activity). At the onset, 40–80 mg/day is tapered off to a maintenance dose (about 10 mg/day). Prednisolone can be combined with other immunosuppressants, in particular with cyclophosphamide (2 mg/kg body weight per day per os).

- *Intravenous immunoglobulin* (IVIG) contains polyclonal IgG antibodies harvested from pooled human plasma. It is proposed for the treatment of a variety of immune diseases. Its mechanism of action is based on the autoantibodies neutralisation, the blocking of the Fc receptors on the surface of B cells and macrophages and the inhibition of inflammatory mediators. Its use lacks robust evidence at this time. If used, it should be administered in a liquid pasteurised form. Five percent concentrated preparation of IVIG should be dosed at 2 g/kg over 2–5 days and administered monthly for up to 6 months.
- *Autologous hematopoietic stem cell transplantation*. Although the results of this study indicate that severe immunosuppression followed by stem cell transplantation is beneficial compared with traditional immunosuppression, further studies involving the greater numbers of patients are needed to establish the role of this treatment strategy
- *Biological therapies*. Several biological therapies have been approved for treating patients with connective tissue diseases such as rheumatoid arthritis or lupus erythematosus disseminates. So far, only few open-label studies have investigated the safety and efficacy of biological therapies in patients with systemic sclerosis. Although it is not a clear demonstration of their efficacy and the studies are limited, the most accredited biological drugs block TGF-β_1, TNF-α and CD-20 pathways.
- *Kinase receptor inhibitors.* Based on experimental and clinical evidence, kinase receptor inhibitors have been proposed as a treatment option in patients with severe SSc. Further studies are needed to clarify the role of imatinib mesylate and other kinase receptor inhibitors, such as dasatinib or nilotinib.
- *Oral administration of bovine type I collagen* (0.1 = −0.5 mg daily) for 12 months reduces the T-cell reactivity to human collagen I, appears to be well tolerated and improves the skin score.

Antifibrotic Substances

- *Penicillin G* (10 million IU/day intravenously within 30 mm for 14 days) acts as prolyl hydroxylase inhibitor with beneficial effects.
- *D-penicillamine* inhibits the cross-link formation of collagen fibrils. In higher doses, side effects such as bone marrow depression, proteinuria, gastrointestinal ulcer, *dysgeusia*, pemphigus, myositis and rash are significant. Recently, it has been shown that high-dose therapy (750–1,000 mg/day) is not superior to low-dose therapy (125 mg every other day) and similar to placebo. Therefore, it can no longer be recommended, the more so as 80 % of the adverse event-related withdrawals occurred in the high-dose patients.
- *Psoralen and ultraviolet A* (PUVA) bath photochemotherapy enhances collagenase activity of fibroblasts and improves skin sclerosis, in particular in generalised morphoea.
- *UVA1* high-dose therapy reduces skin-infiltrating T cells, and it upregulates the expression of matrix metalloproteinase-1 (collage-nase-1). UVA1 phototherapy-treated skin lesions were markedly softened after 9–29 exposures.
- *Minocycline* (50–100 mg/twice daily) is worth trying in early diffuse systemic sclerosis.

Alternatives and Experimental Treatment

- Treatment with *interferon-γ* (3 × 50 μg/week s.c.) is associated with the skin score normalisation and lack of worsening of internal organs. Improvement could not be observed.
- Planned studies with *recombinant human relaxin* were cancelled due to ineffectivity, although in a previous study, 25 mg/kg per day was associated with reduced skin thickening, improved mobility and improved function after 24 weeks.

- *Retinoids*, vitamin D analogue, colchicine, griseofulvin, potassium para-aminobenzoate (Potaba) and cyclophenyl cannot definitely be recommended.

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Acute and Chronic Telogen Effluvium

96

David Hugh Rushton

Key Points

- Hair loss is distressing to many patients.
- In telogen effluvium (TE), once the initiating factor is identified, reassurance is often all that is required. However, the physician should be aware of a possible underlying issue if the increased hair shedding does not resolve.
- At the initial consultation, time must be given to evaluate all possible factors that might have affected the individual up to 4 months prior to the patient becoming aware of an increase in hair shedding.
- Frequently hair loss induces changes in the patient's hair care and grooming routines, which can result in an artificial increase in the observed shedding. Patients should be advised to maintain their normal hair care routine.
- If nutritionally induced hair loss has been identified, either a change in dietary habits or taking the appropriate or stopping the inappropriate supplement should address this problem. The physician also needs to explain the time lag between correcting the imbalance and the patient seeing a reduction in hair loss. In long-standing chronic TE (CTE), many months are required to return the long hair volume to its former status.
- In conditions that result in hair density changes, increased hair shedding is often the first indication of an impending problem and a modified unit area trichogram will aid diagnosis.

Definition and Epidemiology

Hair is considered to be a major component of an individual's general appearance. Throughout history, and in most (although not all) civilisations, scalp hair has been associated with positive signals such as beauty and power. Baldness or hair loss on the other hand has a negative attribute.

The psychological impact of hair loss results in a measurably detrimental change in self-esteem and is associated with images of reduced worth. It is not surprising that both men and women find hair loss a stressful experience even in conditions where a complete recovery can be expected. Yet the distress, even by a temporary loss of hair, profoundly affects an individual's self-confidence and quality of life. This can result in the sufferer seeking help from unscrupulous organisations selling useless, ineffective lotions and potions for large sums of money. Compounding matters, many sufferers will, upon

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_96, © Springer-Verlag Berlin Heidelberg 2015

seeing an increase in hair shedding, change their hair care and grooming habits, thus adversely affecting the aesthetic appearance and inducing an apparent increase in the perceived hair loss. In addition, there may also be a relative increase in sebaceous matter and scaling due to ineffective and inefficient shampooing, which can also exacerbate the loss of hair.

In this chapter we focus on commonly presenting causes leading to acute and chronic telogen effluvium without any change in hair density (parting width unchanged). However, in severe acute or persistent chronic conditions where increased hair shedding is occurring, the possibility of a lag phase issue should be considered. Although increased hair shedding may be present in conditions where there is reduced hair density (Rushton 1993), these will only be briefly discussed. Conditions that involve a delay in the initiation of the new anagen cycle (a lag phase issue) that results in a reduction in the relative number of visible hairs, i.e. reduced hair per cm^2, will not be fully covered. The reader should consult the endocrine literature in such cases for an in-depth guide to the appropriate investigations and treatment options.

Basic Concepts of Pathogenesis

Three hair variables define the aesthetic profile of an individual, (a) the number of hairs per cm^2, (b) hair diameter, and (c) the length of the anagen growth phase and related subsequent release of the telogen hair. In a normal healthy individual in whom there is no underlying scalp scaling malady, these variables exist in a steady state. Only when there is an alteration to one or a combination of these variables is the aesthetic hair prolife changed and hair loss observed.

In telogen effluvium (TE), there is generally no change in the number of hairs per cm^2 nor is there a change in hair diameter; however, an increase in the number of telogen hairs, with a corresponding relative decrease in the number of growing hairs, affects the observed hair when combing and shampooing. Many physicians like to undertake a 'pull test' to confirm hair loss is occurring. This is unnecessary in TE since the patient already knows more hair than normal is falling out. Not only is extracting a large amount of hair from the scalp in a single 'pull' painful, it can cause further distress to an individual already anxious about losing hair. Furthermore, the 'pull test' provides no objective data or useful information about the cause of the hair loss.

If the effluvium is severe or there is a delay in the initiation of the new anagen cycle, there can be a temporary reduction in hair density. In the majority of telogen effluvium cases, no change in hair density occurs. Figure 96.1 illustrates the impact of a decrease in the anagen phase and the resulting relative increase in daily hair shedding for a given total scalp hair density. For example, with a total hair density of 150,000 hairs and an anagen duration of 7 years, the individual would lose 59 hairs per day; however, if the anagen duration was to reduce to 5 years, then the daily hair loss would rise to 82, an increase of 39 %. If the TE lasts only for a few weeks, most individuals would be unaware of any increase in hair shedding, but when shedding is observed, it can set off an adverse sequence of events.

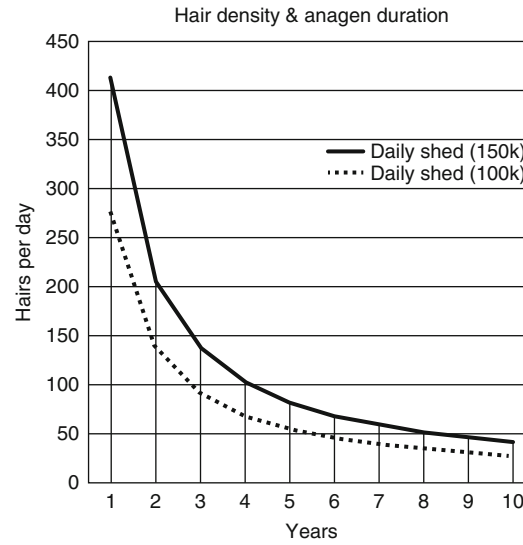

Fig. 96.1 Projected daily hair shedding for an individual with a total hair density of 150,000 or 100,000 hairs with anagen durations from 1 to 10 years

For example, if an individual shampooed every 2 days but as a consequence of seeing an increase in hair shedding they then reduce their shampooing frequency, this would result in an apparent increase in hair lost on subsequent shampoos. This induced change is of course not a true increase but an observed difference in their hair shedding due to the relative change of their hair care routine.

It is frequently quoted that 100 hairs are lost each day; from Fig. 96.1, this corresponds to 4-year anagen duration for a total hair density of 150,000 and approximately 3 years for a total hair density of 100,000. Assuming an average monthly growth rate of 1.2 cm, such individuals would respectively be able to grow their hair to 58 cm or 43 cm in length. Obviously not all of the hair would have grown to these lengths because for 3 months, 9,000 hairs are in telogen, representing respective telogen values of 6 and 9 %. Quoting a general daily hair shedding amount or giving specific percentages for anagen or telogen hair is meaningless. Individuals have their own parameters for these variables and it is the relative change for them, which is the critical factor.

A change in the anagen/telogen (A/T) equilibrium can occur from many events, and it is important to try to identify any alteration to the patient's medical history, hair care routine, scaling maladies, and lifestyle changes. Common events include changes in medication dosages, starting or stopping a medication (oral contraceptive), childbirth (postnatal), fever, illness, miscarriage, menstrual dysfunction, excessive vitamin A intake, weight loss (crash dieting), and surgery involving a general anaesthetic.

Diagnosis

The Initial Consultation

It is of paramount importance to spend time taking a full and complete history of the events that occurred 4 months before the patient became aware of increased hair shedding. Often the cause can be identified and the appropriate reassurance and guidance given. In many cases no further action is required and reassurance alone is sufficient to ease the patient's fear that they will not become bald. It is also important to explain the time delay involved before they will see a reduction in the amount of hair being shed. When TE is linked to a prescription medication, whether an alternative preparation could be prescribed requires careful consideration. A sympathetic understanding is often needed, as many patients are more worried about their hair loss than the underlying medical issue. Simply dismissing the patient's hair loss concerns as unimportant can cause unnecessary distress.

Drug and patient information leaflets frequently list alopecia as a reported side effect but the association is often tenuous; where proven the frequency is relatively rare. However, there are groups of drugs which in all family members cause hair loss (a relative alteration to the anagen/telogen ratio); for example, anticoagulants (heparin, heparinoids, and coumarins) and many cytostatic agents induce an anagen effluvium. Dawber and Van Neste and Van Neste and Rushton publications give a comprehensive list of drugs that can cause hair loss.

When hair loss is a reported side effect, this is often stated as alopecia. However, the very word alopecia to the layperson is often taken to mean they will go bald. Explaining the various types of alopecia requires skill to allay any unfounded fears of the patient becoming bald. It should also be remembered that the published data proving drug-induced hair loss is somewhat limited. Demonstrating cause and effect is particularly difficult in medication-induced TE. Establishing a positive causative link usually requires rechallenging the patient with the drug once the hair loss has abated, but patients are often unwilling to restart a medication they believe caused their hair loss.

The recently identified role of the exogen phase in hair shedding could explain synchronised hair moults in animals and the non-synchronised hair shedding in humans. How the hair is released in exogen is still unknown but

some medications appear to induce a premature telogen effluvium by activating the exogen pathways. It is not unusual to discover a patient observing increased hair shedding within 4 weeks of starting a prescribed medication. The hair morphology of the shed hair is that of a telogen bulb indicating the premature release of the telogen hair. Examination of the shed hairs distinguishes the hair from an anagen effluvium, as would occur with chemotherapy, from a true telogen effluvium. Whether an altered exogen phase continues to operate during drug therapy is the subject of ongoing research.

Since TE only becomes evident if the disturbance to the anagen/telogen balance lasts long enough to induce an observed increase in hair shedding, it is important to recognise that the underlying cause may not be immediately obvious and should alert the physician to consider undertaking some biochemical investigations. This situation is usually encountered if the cause(s) does not self-correct and the hair shedding has been present for 6 months or more; in this situation chronic telogen effluvium is the diagnosis.

Fig. 96.2 Hair samples presented at consultation by a patient complaining of unexplained chronic telogen effluvium over a 7-year period. Her mother obtained the sample on the right at the age of 18 years, a family tradition in her culture (the hair in females is traditionally left uncut from birth until their 18th birthday). The *left* sample was cut when aged 27 due to the distress of persistent unexplained increased hair shedding for the previous 5 years; the hair had not been cut since her 18th birthday and weighs 30 % less than the *right* sample

Chronic Telogen Effluvium

Chronic telogen effluvium (CTE) occurs where there is a relative decrease in the proportion of growing hair (anagen) and an increase in telogen hair, which has persisted for at least 6 months. This results in a reduction in the long hair volume (less hair to clip up or tie back in the ponytail; Fig. 96.2) and a frequent complaint seen in dermatological clinics. In addition, compared with the normal hair growth situation (Fig. *96.3*), there is a relative increase in the incoming new hair (Fig. *96.4*).

In the absence of an obvious cause for persistent increased hair shedding, biochemical investigations frequently reveal no apparent problem. This situation is compounded by current laboratory practice where the lower female reference ranges for some haematological variables (haemoglobin [Hb], red blood cell count [RBC], and serum ferritin) were derived from arbitrarily assigned parameters. Unfortunately these studies contained a significant number of iron-deficient females. The significance of this can be seen when a male presenting with a Hb of 125 g/L (12.5 g/dL) would be considered anaemic and investigated, yet such a value in the female is deemed normal with no further action considered; this situation also applies for RBC and serum ferritin. Given that in non-human mammals there is no sex difference for Hb or RBC concentrations (veterinarians do not evaluate ferritin), I would recommend employing the lower male reference ranges for Hb, RBC, and serum ferritin until the appropriate studies in proven iron-replete women

Fig. 96.3 The normal presentation of scalp hair from an individual being studied during the establishment of normal parameters for hair variables in females (Rushton D.H. Chemical and morphological properties of scalp hair in normal and abnormal states.1988, PhD Thesis; Welsh School of Pharmacy, University of Wales)

Fig. 96.4 Typical presentation of chronic telogen effluvium (CTE) in a 28-year-old female patient complaining of unexplained increased hair shedding for over 2 years. Note the abnormal number of short hair compared with the presentation found in a normal 28-year-old female (Fig. 96.3)

have been undertaken. With regard to the currently cited parameters for other micronutrients and various vitamins, conflicting reference range values are widespread and objective evidence supporting specific parameters is lacking.

The role of nutrition in hair growth is well established in severe malnutrition, anaemia, and anorexia nervosa. However in the absence of an underlying pathology, nutritional effects are poorly understood. Investigating chronic telogen effluvium in apparently healthy individuals and, in particular women, requires a different approach. Employing reference ranges constructed to define the limits of illness must be interrupted in relation to the fact that most individuals complaining of CTE are apparently healthy. Consequently, optimising blood variables for the non-essential tissues often requires higher concentrations than those used to define illness.

Studies have shown that CTE arises from a nutritional imbalance and iron deficiency appears to be the most frequent cause. While 34 % of premenopausal females have CTE, it is well recognised that while there is widespread iron deficiency in menstruating females, many do not experience increased hair loss. The recently identified iron-regulating hormone hepcidin is involved in hair follicle iron metabolism and haemochromatosis where there is variable penetrance; a similar situation might operate in CTE.

Data from 200 apparently healthy women complaining of CTE showed depleted iron stores (as assessed by serum ferritin) as the main finding. Sixty-five per cent failed to achieve the lower reference level for males (40 ng/ml), while 95 % had a serum ferritin level below (70 ng/ml), the 99 % confidence limit for iron staining in the bone marrow; the accepted 'gold standard' for being iron replete. Total iron binding capacity (TIBC) values not only reflect the iron transport status; they also indicate protein insufficiency. TIBC levels in the lower half of the reference range, indicating an adequate iron status, were found in women with low serum ferritins. These findings suggest that a large number of women with CTE might also have a suboptimal intake of first-class proteins. Normally, TIBC increases in response to iron deficiency with concentrations above or in the upper half of the reference range. Furthermore, 28.5 % of this group had a raised serum folic acid level suggesting excessive vitamin supplementation, which was probably taken to treat their excessive hair shedding.

Despite the accumulating publications linking unexplained chronic telogen effluvium and low serum ferritin concentrations in women, some dermatologists still believe there is no association at all or that the link is tenuous. These views, based on five subjects with no objective follow-up hair data or serum ferritin values or with

confounding and contradicting issues, were subsequently criticised. Despite these shortcomings, both are still widely cited. It is noteworthy that the homozygous 'Mask' mouse (a hepcidin knockout mutant that inhibits iron absorption) fed on a normal mouse diet develops a gradual loss of body but not facial hair leading to almost complete trunk nudity within 4 weeks. In addition, they become iron deficient and anaemic and the females are infertile. However following iron supplementation to their normal diet, all symptoms completely resolve.

Excessive intake of vitamin A causes hair loss, as can vitamin A deficiency. Low serum zinc (Zn) is frequently cited to cause hair loss, but with the exception of acrodermatitis enteropathica, there is little evidence to support this widespread belief. However both low vitamin A and Zn have been linked to increased skin exfoliation and scaling, which if present on the scalp can induce hair loss. Recently low vitamin D concentrations <20 nmol/L (8 ng/ml; 2.5 nmol/L, equals 1 ng/ml) have been associated with increased hair shedding, but further work is needed to confirm the role of low vitamin D concentrations and hair loss.

Acute and Chronic Telogen Effluvium in Patients with Impending or Exhibiting Reduced Hair Density

The possibility of increased hair shedding in patients with reduced hair density, particularly in women, needs to be considered. While the previous sections detailed how to investigate acute and chronic telogen effluvium without a change in hair density, sometimes telogen effluvium occurs initially in patients in whom reduced hair density will become a future problem; in these cases a hormonal imbalance should be considered. In those presenting with reduced hair density, the possibility of coexisting factors, as described above, should be considered.

When the clinical history is unhelpful in identifying a possible cause for reduced hair density, how do you proceed? Understanding tissue sensitivity is an important concept in the absence of any gross pathology (hyperandrogenism; acne and/or hirsutism); you have to consider tissue sensitivity in a patient with a normal androgen status. This situation is challenging in a busy clinical environment since such patients require additional time to identify a potential problem. In these cases such patients would benefit from undergoing a hair analysis. The ideal test is the modified unit area trichogram, which evaluates two variables that are diagnostic for male and female pattern hair loss that is actively progressing and is much more sensitive than a 'pull test' or a scalp biopsy. In the modified unit area trichogram, a sample of at least 50 hairs is required. The individual hairs are epilated in the direction of hair growth from the area under investigation and then placed onto a microscope slide with double-sided tape. The percentages of telogen ≤30 mm in length and vellus hair (hair ≤40 μm in diameter ≤30 mm in length) are determined. If the per cent of telogen hair ≤30 mm is above 6.1 % in males or 7.2 % in females (Rushton et al. 1990) or the per cent of vellus hair is >10.2 in males or >13.0 in females, then an active androgenic drive must be considered. When both variables are elevated, treatment should not be delayed.

In males, finasteride 1 mg (Propecia) a 5α-reductase inhibitor has proven effective in around 40 % of men by preventing the conversion of testosterone to dihydrotestosterone (DHT) via the 5α-reductase pathway. Dutasteride, a type I and type II 5α-reductase inhibitor, has yet to undergo formal evaluation for use in male pattern hair loss. While minoxidil does not appear to affect the 5α-reductase pathway, it can prolong the anagen phase, thereby limiting the number of transitions into telogen and delaying the progression of male pattern hair loss.

Figure 96.5 lists the treatment options for hair loss in women with respect to likely outcomes, but help in enabling the patient to achieve an acceptable aesthetic appearance often requires addressing the hair care as well as the medical needs.

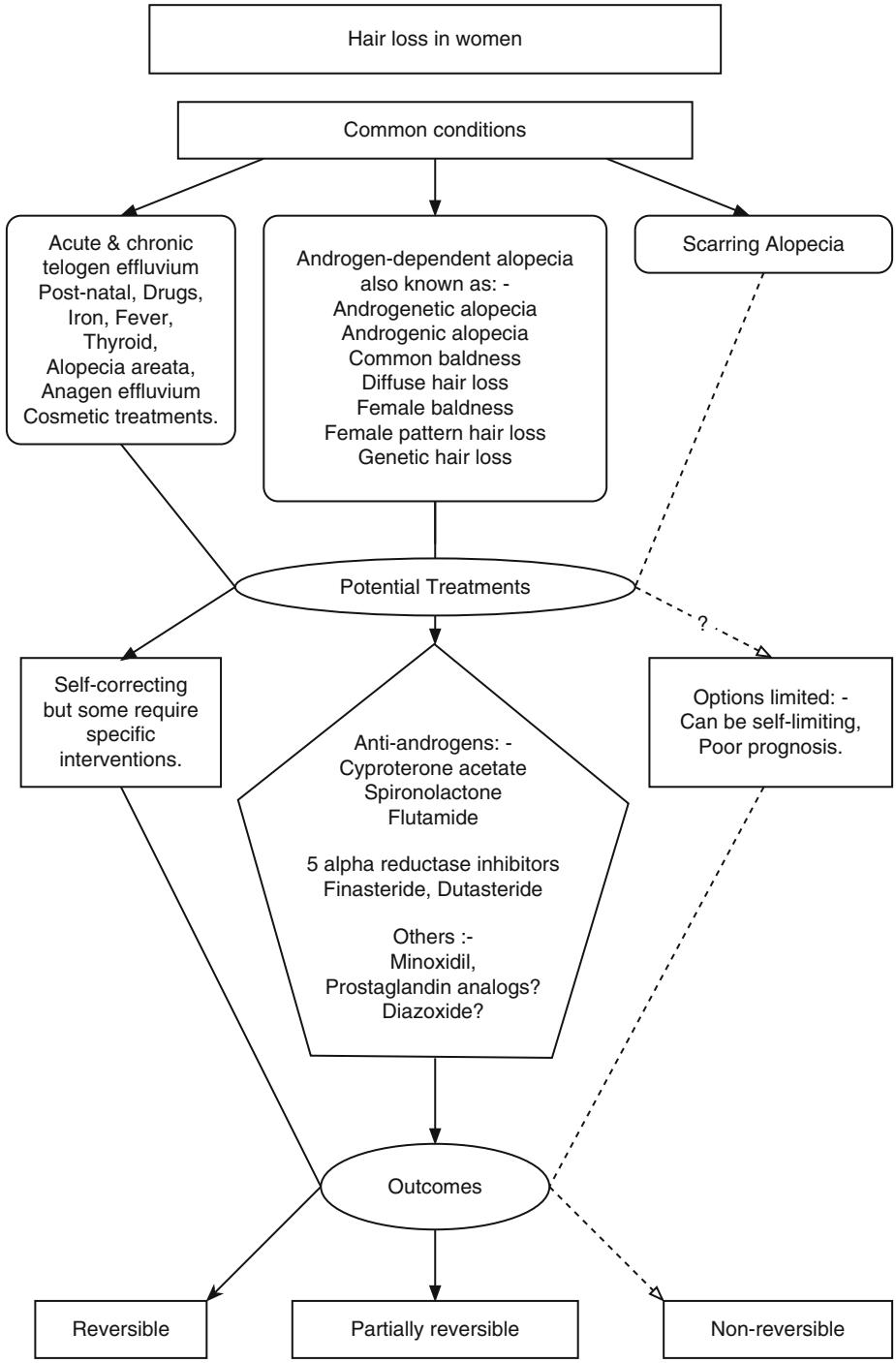

Fig. 96.5 Flow chart for common hair loss conditions in women

Telogen effluvium, at a glance

Hair loss is distressing to many patients and simply dismissing their concerns is both irresponsible and unethical. Too often the patient is dismissed because hair loss is non-life threatening.

In TE once the initiating factor is identified, reassurance is often all that is required. However, the physician should be aware of a possible underlying issue if the increased hair shedding does not abate.

At the initial consultation, time must be given to evaluate all possible factors that might have affected the individual up to 4 months prior to the patient becoming aware of an increase in hair shedding.

Frequently hair loss induces changes in the patient's hair care and grooming routines, which can result in an artificial increase in the observed shedding. Patients should be advised to maintain their normal hair care routine.

If nutritionally induced hair loss has been identified, either a change in dietary habits or taking the appropriate or stopping the inappropriate supplement should address this problem. The physician also needs to explain the time lag between correcting the imbalance and the patient seeing a reduction in hair loss. In long-standing CTE, many months are required to return the long hair volume to its former status.

In conditions that result in hair density changes, increased hair shedding is often the first indication of an impending problem. Undertaking a modified unit area trichogram will identify an active androgen-mediated condition.

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Tinea Versicolor (Pityriasis Versicolor)

97

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Key Points

- Tinea versicolor (TV), also known as pityriasis versicolor, is a superficial fungal infection of the skin, caused by lipophilic fungi of the genus *Malassezia*, and it is characterized by fine scaly patches and macules.
- Clinical varieties: hypochromic and hyperchromic. The course for both the varieties is chronic.
- The treatment of TV is based on antifungal therapy. Topical therapy is recommended for limited cases. In case of extensive or recurrent cases, systemic treatments can be considered. Long-term management has to be performed to avoid relapses.

Definition and Epidemiology

Tinea versicolor (TV), also known as pityriasis versicolor, is a superficial fungal infection of the skin. Normally it is caused by lipophilic fungi of the genus *Malassezia*. The fungal species inducing TV are *M. globosa*, *M. sympodialis*, and *M. furfur*. Clinical signs are very clear since different fungi species develop filaments and induce the peculiar stratum corneum damage, characterized by depigmentation and inflammation. TV is one of the commonest skin diseases with a wide geographical range. This infection may occur in healthy individuals and in immunocompromised patients, although it is not a marker of human immunodeficiency virus (HIV) infection.

Basic Concepts of Pathogenesis

Malassezia yeast belongs to a group of fungi that are normally commensals on human and animal skin. They metabolized fatty compounds in sebum and most of the species are lipophilic. The presence of yeast and hyphae in the skin of patients with TV was first described by Eichested in 1864. In 1873, Rivolta suggested that yeast was also present in dandruff. The genus *Malassezia* was described in 1889 and *Malassezia furfur* was the name given to the organism seen in pityriasis versicolor (PV). Sabouraud considered that there was a distinct difference between the yeast that caused pityriasis versicolor and those on scaly

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_97,

scalps, named *Pityrosporum or Malassezia*. In 1961 first, and other studies later, demonstrated the connection between *M. furfur* in scales of TV and the yeast, *P. orbiculare*, grown in laboratory culture. The apparent conflict between the two different names of the genera, *Malassezia* and *Pityrosporum*, has been resolved with the molecular genetic techniques applied to taxonomy. The genetic markers of the yeast, seen in scalp scales, were shown to be identical to the organisms seen in the pityriasis versicolor on the skin. The molecular genetic techniques highlighted more species than originally suspected. Today we recognize seven main species – *M. furfur*, *M. sympoidalis*, *M. pachydermatis*, *M. globosa*, *M. obtusa*, *M. sloffiae*, and *M. restricta* – and less common species as *M. dermatitis*, *M. nana*, and *M. yamatoensis. M. furfur* and *M. globosa* are involved in TV, where there is a transformation of the yeast phase into the mycelial phase. Mycelium invades the keratinocytes of the stratum corneum and induces skin depigmentation by tyrosinase activity inhibition.

Some circumstances favor TV development:

- High sebum production.
- Humidity: this explains the prevalence in warm climates and the increase in situation of hyperhidrosis and occlusive clothes.
- Familial/individual factors have also been reported.
- Immunological factors may be involved in the pathogenesis, but these are almost unknown. Investigations show that the host does not show a cell-mediated immune deficiency to *Malassezia* mycelial antigens. Patients are instead often sensitized by *Malassezia* (IgG response).

Clinical Presentation

Two clinical varieties are reported: hypochromic and hyperchromic variants.

Hypochromic or hypopigmented TV is characterized by hypochromic patches or macules covered with fine scales, initially with irregular borders that progressively converge to form large patches. Their size varies from a few millimeters to several centimeters. This form usually occurs in dark-skinned individuals.

The hyperchromic or hyperpigmented variety consists of light brown patches with scales on the surface. Especially in the axillary region, the groin, and the submammary folds, mixed clinical presentations may be found. In fact the name "versicolor" is due to the numerous variations in the color of the macules, from brown to pink or to white.

TV does not affect the palms, soles, and mucosae. The legs and foot are usually not affected. Lesions involving the face can be present in adults and in children. Scales can be removed easily with the fingernail.

Both clinical varieties are often asymptomatic. Sometimes pruritus may be present but rarely disturbs the patient. The visible nonaesthetic lesions are instead more disturbing for patients. Without treatment, TV usually has a chronic evolution. The lesions grow in number. Sun exposure deepens the color of the lesions. After treatment, recurrences are very frequent, and consecutive treatments are often necessary.

Diagnosis

The diagnosis is usually made clinically. It is often easy because of the characteristic macules and the distribution of lesions. The variable clinical features of TV and the existence of other skin disorders with similar findings make it preferable to be confirmed with mycological direct microscopic examination (potassium hydroxide preparation; KOH). Both hyphae and yeast cells are evident in a pattern that is often described as "spaghetti and meatballs." Moreover, in a third of cases, examination with Wood's lamp reveals yellow to yellow-green fluorescence. Direct microscopy may be easy by the use of scotch tape. The adhesive rubber is pressed against the skin and mounted on a slide. It is a reliable and easy method to assess the value of treatment. Culture or pathological examinations are usually not necessary for the diagnosis. With the periodic acid-Schiff (PAS) staining, fungal elements are detected in the stratum corneum.

Differential Diagnosis

The differential diagnosis of TV includes several common and uncommon skin disorders. The KOH preparation is a simple and well-established method to confirm the diagnosis. The skin diseases that have to be differentially diagnosed from PV are the following:

- Pityriasis alba: it presents with hypopigmented macules and small patches on the face and rarely on the upper extremities. Fine scales may be visible. The disorder is common in children with an atopic history.
- Pityriasis rosea: it consists of erythematous macules and small patches in a "Christmas tree-like" distribution on the trunk. They exhibit a collaret of scales. A large patch usually precedes the widespread eruption. In dark-skinned individuals, hyperpigmentation can be clearly visible.
- Confluent and reticulated papillomatosis of Gougerot and Carteaud: this uncommon cutaneous disorder usually appears in young adults. It is characterized by hyperpigmented, scaly patches with a reticulated appearance involving the neck, the chest, and the upper back.
- Vitiligo: it is a common disease characterized by totally "ab initio" depigmented macules and patches. In contrast, TV exhibits hypopigmented skin lesions.
- Erythrasma: it can present erythematous or hyperpigmented patches in the axillae or groin. It is included in the differential diagnosis with TV involving the intertrigo. Lesions of erythrasma exhibit coral red fluorescence upon illumination with Wood's lamp.
- Secondary syphilis: patients may present with erythematous to brown macules, papules, or small plaques in a generalized distribution. Lesions are also often present on the palms and soles.
- Mycosis fungoides: it is characterized by hypo- or hyperpigmented erythematous patches on the skin, with a predilection for the trunk and extremities. The hypopigmented variant of the disorder occurs most commonly in individuals with dark skin.
- Seborrheic dermatitis: it is usually more erythematous than pityriasis versicolor and typically has thicker scales. The involvement of seborrheic areas, as the scalps, eyebrows, and nasolabial folds, allows us to identify the correct diagnosis.

General Principles of Treatment

The general therapeutic guideline for TV consists of topical and oral treatment. For children only topical treatments are recommended. After the treatment, depigmentation usually persists for several months: sun exposure is necessary for repigmentation. Recurrent episodes are common because is a commensal of skin flora. Especially if the patient lives in a warm and humid area, medical cleaners one or two times a week to avoid relapse should be prescribed.

Topical Treatment

Several topical treatments are available for the treatment of TV as:

- Propylene glycol, 50 % in water twice daily for 2–4 weeks.
- Zinc pyrithione shampoo, once a day for 2–4 weeks.
- Selenium sulfide, 2.5 % suspension, three times a week. It must be applied for 15 min on the skin before being washed off.
- Cyclopiroxilamine, once–twice a day for 2 weeks.
- Terbinafine, cream of solution 1 %, once a day for 2–4 weeks. Terbinafine can be combined with propylene glycol in topical products, as spray. The spray remains active for several hours after application (highly lipophilic and keratophilic).
- Imidazole derivatives, as miconazole, isoconazole, tioconazole, voriconazole, ketoconazole, bifonazole, sulconazole, clotrimazole, and econazole. One application per day for weeks is usually sufficient.

These antifungal drugs may be preferred by the patient in non-cream forms, such as a gel and a spray, when available.

Some therapeutic strategies involve the use of topical treatments for a short period or for a

short contact. For example, a short treatment of 3 consecutive days with 1 % bifonazole cream seems to be efficient. Moreover with the application of ketoconazole (emulsion 2 %) on the skin surface (including hair and face) for 5 min, after 1 month, 84 % of the patients have a negative scotch test, and after 1 year, 80 % have no recurrence.

Prophylactic Treatment

Relapses in TV are very common. Thus it is important that the time of the therapeutic management should be considered carefully. First it is necessary to suppress predisposing factors, especially excessive sun exposure, use of oily tanning lotions, and excessive sweating.

Prophylactic pyrithione zinc-based soap or selenium sulfate-based soap can be useful in the long-term management. They can be used once–twice a week for many months. Some patients have recurrences in summer, when the climate is warm and the perspiration is favored. We suggest the use of these soaps as an adjuvant therapy also during the pharmacological treatment, as well as after treatment or in the period of the year critical for the relapse.

Application of ketoconazole emulsion before summer can be useful for asymptomatic patients with previous relapses.

Systemic Treatments

When topical treatments fail, oral treatment may be considered and exploited. When patients have frequent relapses, the therapeutic response and the compliance may be better with the oral medications.

The therapeutic regimens of the different treatments are the following:

- Itraconazole: tablets (pills) 200 mg/day for 5–10 days.
- Fluconazole: pills 300 mg (one single dose). The penetration and absorption after ingestion of fluconazole in the skin is rapid.
- Ketoconazole: pills 200 mg/day for 7–15 days. Liver function tests may be necessary.

The newer azoles (itraconazole and fluconazole) show a safe profile. There are no published pediatric studies comparing the efficacy of itraconazole versus fluconazole for the treatment of TV. Studies in adults suggest that the initial cure rates with both drugs are comparable. There is some evidence from adult studies that relapses are less frequent with fluconazole treatment.

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Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)

98

Grace Obeid, Laurence Valeyrie-Allanore, and Pierre Wolkenstein

Abbreviations

BSA	Body surface area
EMM	Erythema multiforme major
GVHD	Graft-versus-host disease
IVIg	Intravenous immunoglobulin
SJS	Stevens-Johnson syndrome
SSSS	Staphylococcal scalded skin syndrome
TEN	Toxic epidermal necrolysis
VAS	Visual analog scale

Key Points

- Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN) are two variants of the same acute, rare, life-threatening, severe drug reaction characterized by extensive necrosis and sloughing of the epidermis, erosions of the mucous membranes, and severe constitutional symptoms.
- SJS and TEN are usually drug induced with antibacterial sulfonamides, anticonvulsant agents, oxicam NSAIDs, and allopurinol being the most frequently causative agents.
- Pathogenesis is complicated but implicates the activation of CD_8^+ cells and liberation of granulysin along with other toxins.
- Early withdrawal of the culprit drug(s) and supportive therapy remain the cornerstone of SJS/TEN treatment and aim to prevent irreversible sequelae.
- Specific treatments have been investigated, and some of them, mainly cyclosporine, seem to be promising for SJS/TEN patients.

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Definition and Epidemiology

Toxic epidermal necrolysis (TEN) is a rare, life-threatening, usually drug-induced, mucocutaneous disease characterized by extensive necrosis of the epidermis and widespread sloughing of the skin and mucosal surfaces. TEN and Stevens-Johnson syndrome (SJS) are considered to be two variants of the same pathological process differing only by the degree of skin involvement with an involved body surface area (BSA) of <10 % in SJS and >30 % in TEN. The incidence of TEN is evaluated to 0.4–1.2 cases per million person-years. TEN occurs in all age groups but is more frequent in women, the elderly, and HIV-infected patients. According to the published data, the mortality rate in TEN varies from 25 to

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_98, © Springer-Verlag Berlin Heidelberg 2015

Table 98.1 SCORTEN

Prognostic factors	Points
Age >40 years	1
Heart rate >120 bpm	1
Cancer/malignant hemopathy	1
BSA >10 %	1
Urea blood level >10 mmol/l	1
Bicarbonate blood level >20 mmol/l	1
Glucose blood level >14 mmol/l	1

Total score	Mortality rate (%)
0–1	3.2
2	12.1
3	35.8
4	58.3
>5	90

Table 98.2 List of the most frequently involved drugs in SJS/TEN

Nevirapine
Lamotrigine
Carbamazepine
Phenytoin
Phenobarbital
Co-trimoxazole and other antiinfective sulfonamides
Sulfasalazine
Allopurinol
Oxicam nonsteroidal anti-inflammatory drugs
Aminopenicillins
Cephalosporins
Quinolones

30 % (Harr and French 2010; Mockenhaupt et al. 2008). A prognosis score entitled SCORTEN (see Table 98.1) was proposed in 2000 for SJS/TEN (Bastuji-Garin et al. 2000) and was found to be an efficient tool to predict mortality rate in this group of patients. SCORTEN is a 7-point score with each point corresponding to a variable and a mortality rate varying from 3.2 % for a score of 0–1 point to 90 % for a score ≥5 points. SCORTEN should be performed on day 1 and repeated on day 3 post-admission (Chang et al. 2011). Surviving patients maintain an increased risk of morbidity with a 5-year survival rate of 65 %.

Basic Concepts of Pathogenesis

TEN is considered to be a hypersensitivity reaction to a drug in at least 70 % of cases (Sassolas et al. 2010). It typically occurs between day 7 and day 21 after exposure to the culprit drug but can be delayed (until 8 weeks after the exposure) in some cases or precipitated in case of repeated exposure. In 1995, Roujeau et al. described an increased risk of TEN with a number of drugs including sulfonamides, aromatic anticonvulsants, allopurinol, oxicam NSAIDs, aminopenicillins, cephalosporins, and quinolones. More recently, the European Severe Cutaneous Adverse Reaction (EuroSCAR) study identified mainly the same drugs and added marketed drugs to finally list nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, co-trimoxazole and other antiinfective sulfonamides, sulfasalazine, allopurinol, and oxicam nonsteroidal anti-inflammatory agents as being high-risk medications (Mockenhaupt et al. 2008) (see Table 98.2).

Sassolas et al. (2010) developed an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis (ALDEN). This tool takes into consideration six parameters with a score of −1 to 10 for each. In a particular TEN case, a given drug is considered as very probably the causative agent if the score is [≥6], probably the causative agent if the score is [4–5], possibly the causative agent if the score is [2–3], unlikely the causative agent if the score is [0–1], and very unlikely the causative agent if the score is [<0] (see Table 98.3).

Even though drug hypersensitivity is, by far, the most frequent etiology, not all TEN cases are drug induced. Other causative factors have been identified such as *Mycoplasma pneumoniae* infection, contrast agents, vaccination, cytomegalovirus reactivation, and other viral diseases including Coxsackie virus.

Physical factors including ultraviolet light and x-rays may trigger drug-induced SJS/TEN, and the sites of exposure are typically the most affected by the disease.

Idiopathic SJS/TEN is defined by cases where no causative factor can be identified.

Table 98.3 ALDEN score

Description of the parameter	Score
Period between the drug intake and onset of reaction (index day)	
5–28 days	3
29–56 days	2
1–4 days	1
>56 days	−1
Drug started on index day	−3
With previous history of adverse reaction, 1–4 days	3
With previous history of adverse reaction, 5–56 days	1
Presence of drug in the body on index day	
Stopped on the index day or within 5 times the elimination half-life before the index day	0
Stopped at a time point before the index day by <5 times the elimination half-life	−1
Stopped at a time point before the index day by >5 times the elimination half-life	−3
Previous history of adverse reaction	
SJS/TEN from same drug	4
SJS/TEN from similar drug	2
Other reactions from similar drug	1
No history of exposure to the drug	0
Previous use without any reaction	−2
Continued drug use beyond index day	
Stopped or unknown	0
Continued	−2
Drug notoriety from previous results of the SCAR study	
High risk	3
Lower risk	2
Under surveillance	1
All other drugs, including newly released drugs	0
No evidence of association	−1
Other possible etiologic alternatives	
Infectious agents	−1
If the patient is taking multiple drugs and at least has a score >3, subtract 1 point from each of the other drugs	−1

The pathological mechanism underlying SJS/TEN is only partially elucidated despite many advances that have been made during the past years in this field.

Among the demonstrated facts regarding the SJS/TEN pathogenesis, it has been shown that this hypersensitivity reaction is mainly a T-cell-mediated disease with predominating $CD8^+$ lymphocytes in blister fluid and in perivascular superficial dermis with an evidence of epidermal exocytosis. $CD8^+$ cells play a major role in keratinocyte apoptosis induction but are also assisted by $CD4^+$ cells (are mainly represented $CD4^+$ cells with strong expression of CD40 ligand) and various cells of the innate immune system including $CD3^-CD56^+$ NK cells, dendritic cells, mast cells, $CD14^+CD16^+$ monocytes, granulocytes, and NK/T cells. $CD8^+$ cells are considered to be the major inducers of apoptosis along with natural killer (NK) cells. The complex interaction between all of the above-listed cell types leads ultimately to the release of tumor necrosis factor-alpha (TNF-α), nitric oxide (NO), interleukin 8 (IL-8), and cell adhesion molecules causing the massive epidermal damage despite the relatively limited number of immunological cells in TEN lesions.

The remaining still unresolved question is the exact mechanism leading to T-cell stimulation by a particular drug in TEN. Two major theories are being discussed and studied recently: The first suggests that the drug directly binds to specific major histocompatibility complex (MHC) I allotype and T-cell receptor (TCR) leading to a T-cell response (Pichler et al. 2011). This concept has been demonstrated in patients with known hypersensitivity reactions to sulfamethoxazole (SMX) (Castrejon et al. 2010). The second theory claims that the drug or its metabolites act as haptens and render keratinocytes antigenic, therefore stimulating T cells via antigen presenting cells (APCs). This second concept was demonstrated in both abacavir- and SMX-induced TEN (Chessman et al. 2008; Castrejon et al. 2010).

Regardless of the initial mechanism, $CD8^+$ cell (among others) activation results in apoptosis of the keratinocytes via the exocytosis of mainly granzyme B/perforin and granulysin. This latter was shown to be the major cytotoxic agent, increasing early during the course of the disease and exhibiting its cytotoxicity in a dose-dependent fashion, with significantly higher levels of granulysin in blister fluid and in blood when compared to co-secreted substances including granzyme B, perforin, and soluble Fas ligand (FasL). Furthermore, a positive correlation was detected between granulysin levels and the body

surface area involved (Chung et al. 2008). However, this molecule does not seem to be specific to SJS/TEN and may be observed in other bullous diseases such as generalized fixed drug eruption (Schlapbach et al. 2011).

Soluble Fas ligand (FasL), nitric oxide (NO), and tumor necrosis factor-α (TNF-α) also contribute to keratinocyte apoptosis. Important to note is that, despite its cytotoxic potential, TNF-α activates on the other hand the antiapoptotic nuclear factor-kappaB (NF-κB) pathway allowing a protective role in TEN and making its inhibition inefficient and even dangerous.

Finally, we should emphasize on the demonstrated genetic predisposition of certain populations and ethnic groups to drug hypersensitivity reactions (manifesting as SJS/TEN) with the use of specific drugs. In fact, a strong association was found between patients with SJS/TEN induced by aromatic antiepileptic agents, including carbamazepine, phenytoin, oxcarbazepine, and lamotrigine and human leukocyte antigen (HLA)-B*1502 in Han Chinese, Thai, Malaysian, and South Indian populations (Man et al. 2007; Locharernkul et al. 2008), but not in Japanese, Korean, or European populations (Lonjou et al. 2006). Similarly, a strong association was reported between HLA-B*5801 and allopurinol-induced SJS/Lyell patients in Han Chinese and in the European descent (Lonjou et al. 2008). In Europeans, abacavir-induced SJS/Lyell is associated with HLA-B*5701 (Mallal et al. 2002) and carbamazepine-induced SJS/Lyell with A*3101 (McCormack et al. 2011). This genetic predisposition seems to be specific to both the ethnicity and the drug but is still unable to explain the onset of the disease.

Clinical Presentation

TEN begins most frequently with a prodromal phase of nonspecific signs and symptoms including fever, malaise, headache, rhinitis, cough, anorexia, pharyngitis, chest pain, vomiting, diarrhea, myalgias, and arthralgias lasting for several days. Often, antibiotics and anti-inflammatory treatments are given during this phase of the disease and may create a confusing factor while searching for the culprit drug.

Painful inflammation and ulceration of the mucosal surfaces (involving at least two mucosal sites) occur in 90 % of cases and may precede cutaneous manifestations. By the end of the prodromal phase, it starts and manifests as pain upon swallowing, photophobia, burning eyes, and painful micturition. Oral mucosae are involved in 71–100 % of cases, ocular mucosae in 50–78 %, anogenital mucosae in 40–63 %, and the three mucosal sites in 34–50 % of patients.

Skin eruption appears as a morbilliform rash with symmetrical lesions distributed initially over the face, neck, chin, proximal extremities, and upper trunk. The rash then extends to the rest of the body. Individual lesions are typically irregularly shaped, erythematous, dusky-red, purpuric macules that coalesce progressively (Fig. 98.1). Otherwise, they may consist of atypical targetoid macules, and the coalescence of necrotic lesions leads to diffuse erythema with a skin that becomes tender to touch and lateral pressure producing detachment of the epidermis from the dermis, known as the Nikolsky sign. Skin lesions then evolve to flaccid blisters that break easily leading ultimately to denudation of the epidermis in sheets resembling wet cigar paper revealing large areas of exposed dermis (Fig. 98.2).

The percentage of skin detachment determines a classification into three categories: SJS <10 %

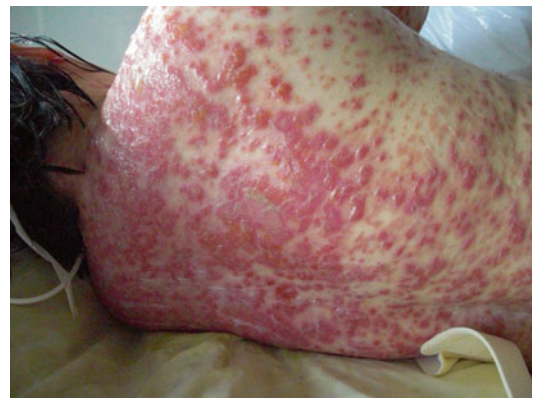

Fig. 98.1 Skin eruption with extensive blisters and erosions

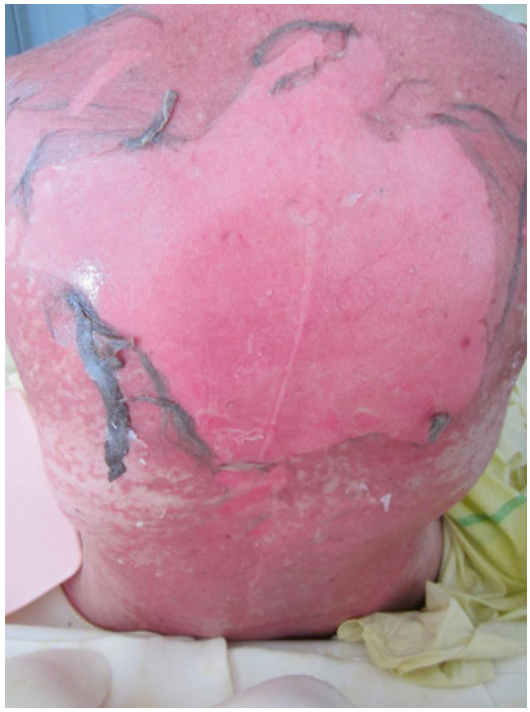

Fig. 98.2 Toxic epidermal necrosis. Denudation of the epidermis in sheets involving mainly the trunk

of body surface area (BSA), SJS/TEN overlap between 10 and 30 %, and TEN >30 % of BSA.

In severe cases of TEN, internal organs may be affected by the disease, most frequently the respiratory tract with sloughing of the respiratory tract mucosa in some cases and the gastrointestinal tract with symptoms including diarrhea, abdominal pain, esophageal and gastrointestinal bleeding, excretion of necrotic intestinal epithelium, etc.

Diagnosis

A case of TEN is diagnosed based on clinical and histologic features.

Following a prodromal phase that lasts for up to 2 weeks, clinical manifestations (described above) of TEN begin. A "progression phase" characterized by erythema and sloughing of the epidermis extending to a certain level of body surface area (BSA) along with mucous involvement is followed by a "plateau phase" where systemic complications are the most likely to occur. A progressive clinical improvement signals the "regression phase" with lightening of the erythema and drying of the removed epidermis. Reepidermization then takes place at a variable rate.

Histologic features include full-thickness epidermal necrosis, subepidermal split, and a scant lymphocytic infiltrate at the dermoepidermal junction. Recently, a retrospective review of clinical records and biopsy specimens showed that full-thickness epidermal necrosis is associated with mortality but is not an independent predictive factor for hospital death (Valeyrie-Allanore et al. 2013).

Recently, certain serum markers for the early detection of TEN have been studied but remain controversial. They include granulysin levels and serum high-mobility group protein B1 (HMGB1) levels. The latter seems however to increase in other bullous diseases and therefore is not specific to SJS/TEN cases (Pichler et al. 2011).

Differential Diagnosis

Many dermatological diseases may mimic TEN especially during the early stages and before the establishment of the full clinical picture. The differential diagnosis of TEN includes, among many others:

- *Generalized bullous fixed drug eruption*: Even though constitutional symptoms are seldom present and mucous membranes are less frequently involved in generalized bullous fixed drug eruption compared to TEN, distinction may be difficult between the two conditions especially that histological findings are comparable. The milder course of the disease, the absence of sequelae, and the rapid recovery of patients affected by generalized bullous fixed drug eruption are important distinguishing features.
- *Staphylococcal scalded skin syndrome* (SSSS): In SSSS, epidermolysis at the subcorneal level is caused by exotoxins released by *Staphylococcus aureus* and may be clinically mistaken with TEN. However, SSSS spares the mucous membranes and affects more

frequently the pediatric population. In doubtful cases, a skin biopsy revealing the superficial blistering level confirms the diagnosis.

- *Erythema multiforme major* (EMM): Distinction between EMM with mucous membrane involvement has been differentiated from SJS/TEN based on clinical presentation and etiological factors (infectious agents rather than medications).
- *Drug-induced linear IgA dermatosis*: This disease presents as annularly disposed bullous lesions with or without mucous involvement. Direct immunofluorescence studies reveal linear deposits of IgA at the basement membrane and help therefore to rectify the diagnosis.
- Severe acute *graft*-versus-*host disease* (GVHD): Acute GVHD that occurs in the bone marrow and in allogenic hematopoietic stem cell transplant patients may be a bullous disease affecting both the skin and the mucous membranes. Stage IV GVHD with histological full-thickness epidermal necrosis may be difficult to differentiate from TEN. Diarrhea and alterations in liver function tests are other features of GVHD.

General Principles of Treatment

As soon as a case of TEN is suspected, management of the disease should respect the following steps:

(a) Confirmation of the diagnosis (see above)
(b) Evaluation of the severity and the prognosis of the disease (see above)
(c) Identification and early withdrawal of the culprit drug(s)
(d) Early initiation of the supportive therapy in a specialized unit and discussion of a systemic treatment

Identification and Early Withdrawal of the Culprit Drug

A thorough medication history is mandatory in order to determine the drug that is the most likely responsible for the severe drug eruption. All the medications or applied substances used for the last 2 months should be listed with the date of introduction and, if applicable, the date of withdrawal for each of them, along with the date of onset of both the mucocutaneous and prodromal symptoms. Typically, the aforementioned algorithm "ALDEN" is used to identify the causative drug in daily practice. Once the potential offending drugs are identified, they should be withdrawn as soon as possible for it was shown that the early withdrawal of the culprit drugs is associated with an increased survival rate.

Supportive Treatment

TEN patients should be transferred into a dermatological intensive care unit or a burn center when the SCORTEN (which should be evaluated accurately on admission) exceeds 1 and to a medical intensive care unit when the pathological process extends to the pulmonary mucosae with PO_2 level <80 mmHg, mainly for a symptomatic treatment associated or not to a specific treatment, depending on each case.

Supportive care includes:

- Evaluation of the patient's general condition (vital signs, state of consciousness, SaO_2, PO_2, etc.).
- Evaluation of the extent of necrolysis using the rule of nines.
- Urgent fluid and electrolyte replacement in order to compensate electrolyte imbalance and fluid loss throughout the skin due to edema and cutaneous sloughing. Peripheral venous access must preferably be outside the affected skin area.

The amount of required fluids depends on the sloughing skin surface and equals two-thirds to three-fourths the amount that would be necessary in a burn case affecting the same skin surface. A formula that could be helpful during the acute phase is the following:

"1.5 ml × % of peeling or potentially peeling skin × kg/day"

A diuresis of 50–80 ml/h should be targeted during this phase using a normal saline solution and adjusted depending on the daily blood tests:

- Regulation of glucose blood levels.
- Hypercaloric and hyperprotidic enteral nutrition through a nasogastric tube, starting at 1,500 ml/day with gradual increase in daily nutrient intake.
- Prophylactic anticoagulation therapy in order to prevent deep venous thrombosis.
- Pain management with initiation of morphine therapy when pain exceeds a score of 4 on a 10-point visual analog scale (VAS).
- Maintaining an environmental temperature of approximately 28 °C.
- Bacterial and fungal cultures of the skin, blood, and urine at least twice weekly. Antibiotics should not be initiated unless an infection is documented.

Wound Care

Cutaneous Care

Wound care should be performed many times daily using petroleum jelly ointment, and the skin should be manipulated carefully. Nonadhesive dressings are the most adequate for TEN cases, and hydrocellular dressings such as "Coloplast" are classically used. More recently, "Biobrane" which is a temporary biosynthetic skin dressing and umbilical cord mesenchymal stem cell transplantation have been shown to improve clinical outcome (Boorboor et al. 2008). A daily bath using diluted chlorhexidine (1/5,000e–1/10,000e) should be done, if tolerated by the patient.

Mucous Membrane Care

Oral mucosae are subject to adhesion formation and should consequently be taken care of on a daily basis using gargles such as bicarbonate and chlorhexidine mouthwash.

Emollients such as petroleum jelly should be applied extensively on external genital organs. Ophthalmological exam and care are mandatory in all TEN patients. The use of antibiotic eyedrops, vitamin A, and antiseptic agents every 2 h during the acute phase, along with adhesions lysis, helps in preventing irreversible sequelae. When the corneal damage is more pronounced, amniotic membrane transplantation and scleral contact lens may be used to optimize visual acuity and minimize corneal damage.

Systemic Treatment

To date, symptomatic support and nursing care measures remain the cornerstone in the treatment of SJS/TEN in the absence of a consensual gold-standard treatment that would shorten the natural course of the disease or halts its progression. A number of immunomodulating molecules have, however, been tested on small series of patients suffering from SJS/TEN with variable, mostly unsatisfactory, outcomes. They include:

Systemic Corticosteroids

Systemic corticosteroids have been used for a long time in the treatment of SJS/TEN, but this approach is still subject to debate because of contradictory outcomes in terms of reduction in mortality rate in this group of patients. Furthermore, a higher risk of infectious complications and a longer hospital stay have been described in corticosteroid-treated patients (Kardaun and Jonkman 2007). Systemic corticosteroids seem to be beneficial in TEN German patients but not in TEN French patients. Other persisting domains of uncertainty are the modality of treatment delivery (pulse therapy or nonpulsed therapy), the most convenient time to introduce the treatment in the course of the disease, the right posology to use, and the dosage-tempering scheme to adopt before completely discontinuing the treatment.

Systemic corticosteroids have also been used in combination with other treatments (such as IVIg and anti-TNF-α) for TEN patients and with encouraging results, but there is still no established consensus clearly indicating their introduction in patients suffering from TEN.

Thalidomide

Even though thalidomide exhibits an anti-TNF-α activity and should theoretically improve TEN, a prospective trial of thalidomide in TEN was interrupted before its end because of increased

mortality in the treated group. This is explained by the fact that TNF-α, besides its role in the disease induction, also activates the antiapoptotic nuclear factor-kappaB (NF-κB) pathway allowing a protective role in TEN. Surprisingly, a few case reports of TEN successfully treated with anti-TNF-α have been published afterward in the literature (Kreft et al. 2010).

Intravenous Immunoglobulin (IVIg)

Through binding Fas ligand, IVIg are able to inhibit Fas-mediated cell death and have therefore been used in the treatment of TEN. A decrease in disease progression rate was noted in the original study for doses ranging from 0.2 to 0.75 g/kg body weight per day for four consecutive days (Morici et al. 2000). In spite of the initial encouraging results, no mortality benefit was found in more recent studies (Bachot et al. 2003). Lately, a meta-analysis showed that although high-dose IVIg improved mortality and that treated children had a good prognosis, the evidence still does not support a clinical benefit of IVIg (Huang et al. 2012).

Furthermore, IVIg treatment may result in nephrotoxicity leading to renal failure and must therefore be manipulated with caution in patients with impaired kidney function.

This therapeutic strategy is no longer used in the daily practice in our severe cutaneous reaction center.

Plasmapheresis or Hemodialysis

Both techniques aim to remove the causative agent, its metabolites, or proinflammatory cytokines from the circulation in an attempt to discontinue the evolution of the disease. This therapeutic means has been classically proposed in cases that were refractory to supportive therapy and other systemic treatments, with dramatic improvement in most of the patients. More studies need to be done so as to bring enough proof to the use of plasmapheresis and hemodialysis in TEN cases.

Cyclosporine

Cyclosporine is a calcineurin inhibitor that blocks the function of T cells. Cyclosporine has recently been used with success in the treatment of SJS/TEN in a phase II open trial done on 29 patients using 3 mg/kg/day for 10 days, tapered over a month (Valeyrie-Allanore et al. 2010). Cyclosporine could be efficient in blocking the disease progression. Further studies are required, however, to validate the efficacy of cyclosporine in TEN patients.

A number of other treatment options have been attempted in a small number of SJS/TEN patients with encouraging outcomes. They include granulocyte colony-stimulating factor (GCSF) and N-acetylcysteine (NAC).

Complications and Sequelae

Beyond the early acute phase of the disease, late complications and sequelae may occur and involve both the skin and the mucous membranes. On the cutaneous level, dyspigmentation is one of the most frequently encountered sequelae manifesting either as hypo- or hyperpigmentation persisting for months or years. Eruptive melanocytic nevi, along with pruritus, have also been described following TEN cases. Skin appendages' damage can eventually result in onycholysis, onychodystrophy, loss of fingernails, and hair thinning. Ocular sequelae remain the most common complication of TEN and occur in up to 75 % of cases. Early ophthalmologic care aims to reduce the incidence of ocular sequelae ranging from eye dryness and sandy sensation to corneal scarring and blindness. Other ocular complications include symblepharon, trichiasis, photophobia, subconjunctival fibrosis, entropion, ectropion, and sicca syndrome. The lips and oral cavity should be taken into consideration when treating a patient with TEN in order to avoid many of the complications occurring at this level such as xerostomia, reduced salivary flow and pH, periodontal disease, gingival inflammation, and oral discomfort. The abovementioned complications are usually reversible but can lead to synechiae formation. On the other hand, pulmonary, gastrointestinal, and genitourinary tract involvement may result in permanent esophageal, bronchial, vaginal, urethral, and anal strictures

requiring surgical correction. Dyspareunia has been reported as another complication in female patients and erosive balanitis, urethral erosions, and phimosis in male affected individuals. A multidisciplinary team including a dermatologist, an ophthalmologist, a psychiatrist, a gynecologist, and an odontologist must follow up the patient for at least 1 year following the severe drug reaction.

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Gonococcal Urethritis

99

Christina Stefanaki

Key Points

- Gonococcal urethritis is caused by *Neisseria gonorrhoeae*.
- *N. gonorrhoeae* is transmitted through sexual contact and vertically.
- Gonorrhea remains a major public health problem.
- Gonorrhea manifests in men as acute anterior urethritis with dysuria and profuse and purulent discharge.
- Diagnosis of gonococcal infection is based on the identification of the microorganism in secretions from infected sites using Gram stain, culture, and/or molecular biology techniques. No test offers 100 % sensitivity and specificity.
- *Neisseria gonorrhoeae* has developed resistance to multiple classes of antibiotics, and recently, resistance and even clinical failures to ceftriaxone and cefixime have been confirmed.
- According to the European guidelines for the diagnosis and treatment of gonorrhea in adults, uncomplicated gonococcal urethritis should be treated with ceftriaxone 500 mg intramuscularly (IM) as a single dose together with azithromycin 2 g as a single oral dose.
- Sexual partners in the preceding 60 days should be treated as well.
- A test of cure is recommended in all cases.
- Treatment failures and resistant strains should be reported to health authorities.

Definition and Epidemiology

By definition, urethritis is characterized by urethral inflammation that can result from infectious and noninfectious conditions and symptoms and, if present, include discharge of mucopurulent or purulent material, dysuria, or urethral pruritus. Gonococcal urethritis is caused by *Neisseria gonorrhoeae*.

Basic Concepts of Pathogenesis

Neisseria gonorrhoeae is a Gram-negative aerobic coccus-shaped bacterium typically found in pairs, usually visualized intracellularly in polymorphonuclear leukocytes. The bacterium is capable of attaching to columnar epithelial cells via pili or fimbrae, and the most common sites of attachment are the mucosal cells of male and

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_99, © Springer-Verlag Berlin Heidelberg 2015

female urogenital tracts. PilC and Opa are outer membrane proteins that aid the attachment of the microorganism, and then intracellular invasion is mediated by adhesins and sphingomyelinase. After endocytosis, the bacterium replicates and proliferates locally, producing inflammation. Gonococcus, by producing a variety of peptides and lipids, is capable of causing tissue destruction. The bacterium escapes the host defense mechanisms by intracellular replication and by the production, by certain strains, of immunoglobulin A proteases that cleave the heavy chain of the immunoglobulin. Gonococcus is very susceptible to environmental shifts outside the cells, such as temperature changes, ultraviolet light, and drying, and is easily killed under those conditions.

Neisseria gonorrhoeae is restricted only to humans and is transmitted through sexual contact (vaginal, anal/or oral) and vertically from mother to child at parturition.

The incubation period ranges from 2 to 8 days, with most infections being symptomatic within 15 days.

Epidemiology

Gonorrhea remains a major public health problem. In 2008, the World Health Organization (WHO) estimated 106 million cases among adults worldwide (3.4 million in the WHO European region). In the European Union (EU), gonorrhea was the second most commonly reported bacterial sexually transmitted infection (STI) after chlamydia in 2010. However, the incidence is underestimated because of suboptimal diagnostics, case reporting, and surveillance. In the United States, gonorrhea is the second most commonly reported notifiable infection, with >300,000 cases reported during 2011. As men are becoming symptomatic, the infection is reported three times more frequently in men than women. Young age (15–29 years), sexual orientation (men having sex with men are considered more vulnerable), and ethnic minority are considered risk factors for gonorrhea.

Clinical Presentation

Gonorrhea has a broad spectrum of clinical manifestations in both men and women ranging from asymptomatic and symptomatic localized infections to disseminated infections. Generally the primary infection tends to involve mucous membranes consisting of columnar epithelium, and the sites more commonly involved are the urethra, cervix, rectum, pharynx, and conjunctiva.

Typically gonorrhea manifests in men as acute anterior urethritis with dysuria and profuse and purulent discharge. About one quarter of infected men present with less pronounced symptoms, with a mucopurulent discharge similar to non-gonococcal etiologies evident only after urethral manipulation. Even without treatment, symptoms subside after a period of 6 months. Only about 10 % of the infected men remain asymptomatic.

Complications include inflammation of Cowper and Tyson glands, epididymitis, prostatitis, and orchitis. Unilateral testicular pain and swelling indicates epididymitis or orchitis.

Clinical manifestations of gonorrhea and complications are summarized in Table 99.1.

Diagnosis

Diagnosis of gonococcal infection is based on the identification of the microorganism in secretions from infected sites (urethra, endocervix, posterior pharynx, anus) using Gram stain, culture, and/or molecular biology techniques. No test offers 100 % sensitivity and specificity (Table 99.2).

For gonococcal urethritis Gram stain is positive in more than 95 % of symptomatic men. However, it can give false-negative results in asymptomatic infection. In Gram-stained smears, gonococci are visualized as Gram-negative diplococci within neutrophils.

The gold standard for the diagnosis of gonococcal urethritis is culture and should be performed in all cases. Thayer-Martin (antibiotic containing selective media) or selective New York media are used for culture. Culture, accompanied

Table 99.1 Clinical manifestations of gonorrhea and complications

Gonococcal infection		
Men	Women	Children
Asymptomatic (10 %)	Asymptomatic (50 %)	Ophthalmia neonatorum
Urethritis	Cervicitis	Vulvovaginitis
Proctitis	Proctitis	*Complications* Blindness Disseminated infection
Pharyngitis	Pharyngitis	
Gonococcal ophthalmia	Gonococcal ophthalmia	
Complications Prostatitis Epididymitis Orchitis Disseminated infection	*Complications* Bartholinitis Salpingitis PID Perihepatitis (Fitz-Hugh-Curtis syndrome) Ectopic pregnancy Infertility Disseminated infection	

Proctitis: asymptomatic in 50 %, common in those who practice anal intercourse or by autoinoculation in women, manifests with rectal mucopurulent discharge, pain at defecation, constipation, and tenesmus
Pharyngitis: usually asymptomatic, symptoms range from pharyngeal erythema and cervical lymphadenopathy to ulceration with pseudomembrane formation
Cervicitis: vaginal discharge, dysuria, intermenstrual bleeding, menorrhagia
Bartholinitis: acute swelling of the Bartholin's gland with swelling of the labial fold and purulent discharge upon pressure
PID (*pelvic inflammatory disease*): lower abdominal pain, vaginal bleeding, dyspareunia, adnexal or cervical motion tenderness, fever
Gonococcal ophthalmia and ophthalmia neonatorum: due to self inoculation or unusual sexual practices, purulent conjunctivitis, can rapidly progress to keratitis and corneal opacities and blindness
Perihepatitis (*Fitz-Hugh-Curtis syndrome*): rare, PID is accompanied by right upper quadrant pain due to inflammation of the adjacent peritoneum
Disseminated infection: rare, usually in women during menstruation and neonates (0.5–1 % of patients). Classic triad of migratory polyarthritis, tenosynovitis, and skin rash consisting of hemorrhagic pustules. May result in endocarditis and meningitis

Table 99.2 Diagnosis of gonococcal infections

	Gram stain	Culture	NAATS
Urethra	++	+++	+++
Cervix	+	++	+++
Pharynx[a]	–	+	+++
Anus[a]	+	+	+++
Urine[a]	–	–	++

Indications of different methods according to the site of infection
[a]Confirmation of positive culture for *N. gonorrhoeae* by a molecular method is mandatory in extragenital sites

by the antimicrobial susceptibility tests, allows the identification of resistant gonococci to common antibiotics and the better surveillance of the infection. The sensitivity of culture is high for genital samples providing that specimen collection, transport, storage, and isolation procedures are optimized.

Molecular techniques such as nucleic acid hybridization tests and nucleic acid amplification tests (NAATS) are widely used for the diagnosis of gonococcus. NAATS, particularly PCR, are highly sensitive and specific and superior to culture for diagnosis of gonococcal urethritis. If non-culture techniques are used for diagnosis, regional monitoring of gonococcal antimicrobial susceptibility is needed.

All persons found to have gonorrhea also should be tested for other STDs, including chlamydia, syphilis and HIV.

Differential Diagnosis

Gonococcal urethritis should be differentiated from other causes of urethral discharge like *Chlamydia trachomatis* and *Trichomonas vaginalis*.

General Principles of Treatment

Effective treatment is a cornerstone of gonorrhea control efforts, but treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies. *Neisseria gonorrhoeae* has developed resistance to multiple classes of antibiotics including penicillins, tetracyclines, macrolides, and fluoroquinolones. During the 1990s and 2000s, fluoroquinolone resistance in *N. gonorrhoeae* emerged in the United States, becoming prevalent in Hawaii and California and among men who have sex with men (MSM) before spreading throughout the United States. In 2007, because of emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States, CDC no longer recommended fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining recommended antimicrobial class. Previous data indicated that ceftriaxone as a single intramuscular injection of 250 mg provided high and sustained bactericidal levels in the blood and was highly efficacious at all anatomic sites of infection. On the other hand, a single oral dose of cefixime 400 mg did not provide bactericidal levels as high nor as sustained as an intramuscular 250 mg dose of ceftriaxone and demonstrated limited efficacy for treatment of pharyngeal gonorrhea (Tables 99.3, 99.4, 99.5 and 99.6).

The minimum inhibitory concentration (MIC), the lowest antimicrobial concentration that inhibits visible bacterial growth in the laboratory, is used to assess antimicrobial susceptibility. Increasing MICs can predict the emergence of resistance. During recent years a steady rise in minimum inhibitory concentrations (MICs), resistance, and even clinical failures to ceftriaxone and cefixime have now been confirmed. Since 2000, treatment failures with the use of third-generation cephalosporins have been reported in Japan. In Europe there were reports of treatment failures with cefixime standard treatment in England and Norway in 2010. In 2011, the first *N. gonorrhoeae* strain with decreased susceptibility to cefixime and subsequent treatment failure was reported in Austria. The first case of genital infection of highly cefixime- and ceftriaxone-resistant *N. gonorrhoeae* in Europe was reported in France, and a suspected ceftriaxone-resistant strain was reported in Spain, and subsequently ceftriaxone treatment failure of pharyngeal gonorrhea was reported in Sweden. The results from the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) have shown that susceptibility to cefixime and ceftriaxone is decreasing in Europe. In this emergent situation of gonorrhea becoming untreatable, WHO has published the global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*, the European Centre for Disease Prevention and Control (ECDC) has published the response plan to control and manage the threat of multidrug-resistant gonorrhea in Europe, and the Centers for Disease Control and Prevention (CDC) have also taken action for the United States.

Already in 2010 CDC's sexually transmitted diseases (STDs) treatment guideline combination therapy was recommended for gonorrhea with a cephalosporin (ceftriaxone 250 mg intramuscularly or cefixime 400 mg orally) plus either azithromycin orally or doxycycline orally, even if nucleic acid amplification testing (NAAT) for *C. trachomatis* was negative at the time of treatment. Those guidelines recommended combination antimicrobial therapy to combat the infection and to avoid the development of multidrug resistance, rather than adopting the administration of an increased dose of cephalosporins. According to limited data, combination antimicrobial therapy with extended-spectrum cephalosporins and azithromycin seems to show synergy in vitro and in vivo. Unfortunately, published data are very limited on the treatment of multidrug-resistant gonorrhea, and treatment recommendations are based on early clinical efficacy trials, pharmacokinetic/pharmacodynamic considerations, in vitro antimicrobial susceptibility surveillance data, case reports of antimicrobial resistance, and anticipated trends in antimicrobial resistance.

According to the European guidelines for the diagnosis and treatment of gonorrhea in adults,

Table 99.3 First-line treatments for different manifestations of gonorrhea according to the European guidelines

First-line treatment for gonorrhea					
Urethritis, proctitis, cervicitis	Pharyngeal infection	Conjunctivitis (adults)	Disseminated infection	PID	Epididymitis, orchitis
Ceftriaxone 500 mg IM single dose + Azithromycin 2 g single oral dose	Ceftriaxone 500 mg IM single dose + Azithromycin 2 g single oral dose	The eye should be irrigated with sterile saline solution once. Ceftriaxone 500 mg IM as a single dose for 3 days	Ceftriaxone 1 g IM or IV every 24 h for 7 days	Ceftriaxone 500 mg IM as a single dose + Doxycycline 100 mg oral dose twice daily + Metronidazole 400 mg oral dose twice daily for 14 days	Ceftriaxone 500 mg IM single dose + Doxycycline 100 mg oral dose twice daily for 10–14 days

Table 99.4 Second-line treatments for different manifestations of gonorrhea according to the European guidelines (see text)

Urethritis, proctitis, cervicitis	Pharyngeal infection	Conjunctivitis (adults)	Disseminated infection	Epididymitis, orchitis
1. Cefixime 400 mg oral single dose + azithromycin 2 g single oral dose	1. Ceftriaxone 500 mg IM single dose	1. Spectinomycin 2 g IM single dose daily for 3 days	Spectinomycin 2 g IM every 12 h	Ciprofloxacin 500 mg single oral dose[a] + Doxycycline 100 mg oral dose twice daily for 10–14 days
2. Ceftriaxone 500 mg IM single dose	2. Ciprofloxacin 500 mg single oral dose[a]	2. Azithromycin 2 g oral single dose + doxycycline 100 mg oral dose twice daily 1 week + Ciprofloxacin 250 mg oral dose daily for 3 days[a]		
3. Spectinomycin 2 g IM single dose + azithromycin 2 g single oral dose	3. Ofloxacin 400 mg single oral dose[a]			
	4. Azithromycin 2 g single oral dose[a]			

[a]Fluoroquinolone or azithromycin resistance are excluded by appropriate laboratory susceptibility testing

uncomplicated gonococcal urethritis should be treated with ceftriaxone 500 mg intramuscularly (IM) as a single dose together with azithromycin 2 g as a single oral dose. Azithromycin tablets may be taken with or without food, but gastrointestinal side effects can be less if taken after food. If ceftriaxone 500 mg for IM injection is not available, the IM suspension can be mixed as follows: 3.5 ml of 10 mg/ml lidocaine without adrenalin is suspended into a 1 g vial of ceftriaxone and mixed; 2 ml of the mixture is drawn and injected IM. On the other hand for the treatment of uncomplicated urogenital gonorrhea, CDC recommends combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin, particularly in

Table 99.5 Penicillin allergy

Spectinomycin 2 g IM as a single dose + Azithromycin 2 g oral single dose
Alternative regimen
Ciprofloxacin 500 mg oral as a single dose or ofloxacin 400 mg oral as a single dose or azithromycin 2 g as a single oral dose[a]

[a]Only if fluoroquinolone or azithromycin resistance are excluded by appropriate laboratory susceptibility testing

Table 99.6 Pregnancy and breastfeeding[a,b]

Recommended treatment
Ceftriaxone 500 mg IM single dose
Alternative regimen
Spectinomycin 2 g IM single dose

[a]The safety of azithromycin in pregnancy has not been confirmed, but clinical experience indicates that it may be safely used. It should only be used under medical supervision if the expected benefit to the mother is thought to be greater than the possible risk to the fetus. Azithromycin passes into breast milk and is not recommended whilst breastfeeding

[b]Pregnant and breastfeeding women should not be treated with fluoroquinolone or tetracycline antimicrobials

strains with elevated cefixime MICs. Moreover, ceftriaxone and azithromycin seem to show synergy both in vitro and in vivo.

When ceftriaxone cannot be used for treatment of urogenital or rectal gonorrhea, two alternative options are available: cefixime 400 mg orally plus azithromycin 2 g orally, if ceftriaxone is not available or administration of injectable antimicrobials is not possible or refused by the patient, or spectinomycin 2 g IM as a single dose together with azithromycin 2 g orally in a single dose, if ceftriaxone cannot be given because of severe allergy or in case of resistance to extended-spectrum cephalosporins. CDC gives also the option of azithromycin 2 g orally in a single dose.

Cefixime 400 mg p.o. is no longer recommended as a first-line treatment of gonorrhea, and it is only an alternative option in cases when ceftriaxone cannot be administered. It should never be given without azithromycin 2 g p.o., because continued resistance to cefixime might hasten the development of resistance to ceftriaxone, the last antimicrobial that is known to be highly effective in a single dose for treatment of gonorrhea. Maintaining effectiveness of ceftriaxone for as long as possible is critical.

Several other injectable cephalosporins like ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenecid 1 g p.o. and cefotaxime 500 mg IM have shown effectiveness against gonorrhea except pharyngeal infection; however, they offer no advantage over ceftriaxone, and they are not recommended. Other cephalosporins given orally, like cefpodoxime 400 mg or cefuroxime axetil 1 g, are not effective for pharyngeal infection, raise the same concerns for resistance as cefixime and should not be used.

Spectinomycin an effective alternative option for treatment of gonorrhea unfortunately is not available in many countries. It has poor efficacy against pharyngeal infection.

Azithromycin 1 g is not recommended as treatment failures have been documented, and there are concerns about possible rapid emergence of antimicrobial resistance. Those concerns are not that great with the 2 g dose which is preferred. However, treatment with azithromycin 2 g should be limited only in cases when antimicrobial susceptibility is already known or when there is known allergy to cephalosporins. Already high level azithromycin resistance and treatment failures have been observed in Europe.

Fluoroquinolones once a first-line treatment for gonorrhea are no longer recommended because of widespread worldwide resistance. Only when ceftriaxone cannot be administered and the antimicrobial sensitivity is already known, ciprofloxacin 500 mg p.o. or ofloxacin 400 mg p.o. as a single dose may be given.

Azithromycin 2 g which is included in standard treatment for gonorrhea is the preferred treatment for *C. trachomatis*, and it is well known that coinfection with *C. trachomatis* is common. If treatment for gonorrhea does not include azithromycin, doxycycline 100 mg oral dose twice daily for 7 days should be given unless coinfection has been excluded with NAAT testing.

Treatment of Sexual Partners and Follow-Up

For all patients with gonorrhea, every effort should be made to ensure that the patients' sex partners from the preceding 60 days are evaluated and treated for *N. gonorrhoeae* with a recommended regimen. Patients should abstain from sexual contact for 7 days after the recommended regimen until they and their partners are completely cured.

Patients should be assessed after treatment to ensure resolution of symptoms, compliance with therapy, and partner's notification and treatment. It is important to exclude reinfection, particularly in cases of treatment failure, as the alternative could be resistance to standard treatment.

A test of cure is recommended in all cases to identify persisting infection and emerging resistance, particularly in cases of pharyngeal infection, which is substantially harder to treat than genital and anorectal infections. In symptomatic patients, test of cure is performed with culture 3–7 days after completion of therapy, which permits antimicrobial sensitivity testing, and can be supplemented a week later with a NAAT for increased sensitivity if culture is negative. In asymptomatic patients, test of cure can be performed with a NAAT 2 weeks after completion of treatment. If the NAAT is positive, every effort should be made to perform a confirmatory culture and antibiotic susceptibility testing before further treatment is given.

Treatment Failure

If infection persists after the follow-up test of cure, reinfection by an untreated partner should be excluded first. If reinfection is unlikely, treatment should be guided by antimicrobial susceptibility tests. Ideally, as much clinical and laboratory data as possible should be collected and reported on treatment failures. If antimicrobial susceptibility testing is impossible to obtain or if *extended-spectrum cephalosporin resistance identified* according to European guidelines for treatment of gonorrhea, the following combination therapy could be tried:

- Ceftriaxone 1 g IM as a single dose *together with* azithromycin 2 g oral single dose
- 2 g azithromycin single oral dose + gentamicin 240 mg single IM dose

According to WHO two other regimens could be tried: 2 g azithromycin single oral dose + spectinomycin 2 g single IM dose OR either gentamicin 240 mg IM or spectinomycin 2 g IM.

The combination of azithromycin and gentamicin is currently under clinical study and may be valuable if infection persists after treatment with ceftriaxone. For many years gentamicin (together with doxycycline) has been successfully used in Malawi, Africa, and high in vitro susceptibility in Europe has been proven. However, a recent meta-analysis found that single-dose gentamicin 240 mg IM treatment resulted in a pooled cure rate of 91.5 %, failing to meet the current criteria of ≥95 % effectiveness for recommended treatment for gonorrhea. Further trials are needed to confirm the efficacy of this treatment regimen.

Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations.

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Urethritis: Nongonococcal

100

Irene Stefanaki

Key Points

- Nongonococcal urethritis (NGU) represents the commonest form of urethritis in developed countries.
- There is a wide range of responsible microorganisms, with *Chlamydia trachomatis* identified more frequently. However, in almost half of cases, no specific pathogen is detected.
- Patients with symptoms or objective signs should undergo testing with a Gram-stained urethral swab or first-pass urine specimen.
- Males with confirmed or suspected urethritis should be tested for *N. gonorrhoeae* and *C. trachomatis*.
- Patients with NGU should be offered a therapeutic regimen effective against *C. trachomatis*.
- Patient follow-up and proper management of sexual contacts are essential to ensure therapeutic success.

Definition and Epidemiology

It is a urethral inflammation not caused by *Neisseria gonorrhoeae*.

It is the commonest form of urethritis in Europe, the USA, Canada, and Australia. Although the related symptoms and signs are usually mild or absent and therapeutic regimens easy to follow, it has the potential of serious sequelae on the reproductive system of males and their female partners if the condition remains undiagnosed and untreated.

Basic Concepts of Pathogenesis

Urethritis may be due to infectious agents (bacterial, viral, fungal), noninfectious conditions (e.g., mechanical or chemical trauma, urethral strictures, and foreign bodies), or both. In infectious nongonococcal urethritis (NGU), the commonest pathogen is *Chlamydia trachomatis* accounting for 15–40 % of cases with a predilection for younger ages, followed by *Mycoplasma genitalium* (see Table 100.1). Other microorganisms including *Trichomonas vaginalis* (rates depending on its prevalence in the community, uncommon in men who have sex with men (MSM)), HSV, HPV, adenovirus, *Candida* sp., *N. meningitidis*, *Haemophilus* sp., *Moraxella catarrhalis*, *Streptococcus* sp., urinary tract infections, and enteric bacteria (in cases of insertive anal intercourse) are more uncommon, whereas in approximately 50 % of cases, no pathogen can be

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_100, © Springer-Verlag Berlin Heidelberg 2015

Table 100.1 Infectious agents in NGU

Pathogen	Detection rates (%)
Chlamydia trachomatis	15–40
Mycoplasma genitalium	10–25
Trichomonas vaginalis	1–20
HPV, *Candida* sp., *N. meningitidis*, *Haemophilus* sp., *Moraxella catarrhalis*, *Streptococcus* sp.	<10 %
Urinary tract infections	<10 %
HSV	<5 %
Adenovirus	<5 %
Enteric flora	<5 %
Ureaplasma urealyticum	Controversial

detected. *Ureaplasma urealyticum* colonizes the urethra in 30–40 % of healthy sexually active young males, but it has also been implicated in the pathogenesis of NGU.

It is speculated that the etiology of asymptomatic NGU may differ from symptomatic NGU, because detection rates of *C. trachomatis* and *M. genitalium* are lower in asymptomatic patients.

Clinical Presentation

NGU may be asymptomatic or cause mild to moderate urethral irritation, pruritus, dysuria, and minimal urethral discharge which is often noticed in the morning or after urethral massage.

Complications of NGU include epididymitis/orchitis which, if left untreated, can eventually lead to male infertility and Reiter's syndrome. In the case of chlamydial and probably *M. genitalium* NGU, female partners who are not referred for screening and therapy could potentially develop pelvic inflammatory disease (PID) with subsequent possible infertility or extrauterine pregnancy.

Physical Examination

The aim of physical examination is to check for the presence of urethral discharge, detect any observable concomitant sexually transmitted diseases (STDs), diagnose other conditions that could imitate NGU, and search for possible complications. Therefore, it should include:

- Inspection of the urethra for obvious discharge
- Inspection of the genitalia (including the perianal area) for any signs of other STDs (e.g., syphilis, condylomata acuminata, herpes simplex)
- Palpation of the urethra for possible strictures, abscesses, or foreign bodies
- Palpation of the testes and spermatic cord for signs suggestive of orchitis/epididymitis

Diagnosis

1. *Confirmation of urethritis*. Urethritis can be confirmed either with the sign of urethral discharge on physical examination or with the following laboratory tests revealing WBCs in the anterior urethra:
   (i) A Gram-stained urethral smear containing ≥5 WBCs per high-power microscopic field.
   (ii) A centrifuged and Gram-stained first-pass urine (FPU) specimen demonstrating ≥10 WBCs per high-power microscopic field.

   In the case of observable urethral discharge, urethral smear is preferable to FPU since it will assist to exclude gonococcal urethritis and probably demonstrate other pathogens (*T. vaginalis*, *Candida* sp.). Leukocyte esterase test on FPU and methylene blue-stained urethral smear have also been used but have lower sensitivity.

   All patients with confirmed or suspected urethritis should be tested for *N. gonorrhoeae* and *C. trachomatis*.
2. *Exclusion of gonococcal urethritis. N. gonorrhoeae* can be ruled out by the absence of polymorphonuclear leukocytes with intracellular Gram-negative diplococci in a Gram-stained urethral specimen and by diagnostic tests specific for gonococcal infection (culture of urethral smear, nucleic acid hybridization tests, or single nucleic acid amplification tests (NAATs)).

3. *Detection of causative microorganism*. Patients with NGU should be tested for *C. trachomatis*, since it is an STD reportable to health authorities; furthermore, its diagnosis could enforce compliance to treatment, partner notification, and proper management, as well as provide an opportunity for health education. Available tests for *C. trachomatis* in urethral swab specimens include NAATs, nucleic acid hybridization tests, enzyme-linked immunosorbent assay tests (ELISA), direct immunofluorescence, and cell culture, with NAATs having the higher sensitivity (90–95 %). In the case of overt urethral discharge, microscopic examination of a urethral specimen could detect *Candida* sp. (KOH preparation) and *T. vaginalis* (wet preparation). *M. genitalium* can be detected by NAAT, although in clinical practice this is not performed routinely.

Differential Diagnosis

NGU should be differentiated from the following conditions:

- By definition NGU has to be distinguished from gonococcal urethritis. Clinically, gonococcal urethritis is characterized by a more abrupt initiation of abundant purulent urethral discharge that causes considerable discomfort; diagnosis of *N. gonorrhoeae* is confirmed by Gram stain microscopy of urethral smear and specific testing as previously described.
- Chronic or acute prostatitis can manifest as pelvic pain, urethral discomfort, and premature ejaculation.
- Upper urinary tract infection is sometimes accompanied by minimal urethral discharge.
- Noninfectious causes of urethritis include mechanical or chemical trauma corresponding to individual sexual practices, urethral strictures and fissures, abscesses, or foreign bodies. Males with venereophobia often manipulate their penis to check for signs of disease, resulting in self-induced urethral irritation.

General Principles of Treatment

If laboratory-based diagnosis is not available, symptomatic patients should be treated for both gonorrhea and chlamydia. If NGU has been confirmed by Gram-stain microscopy, therapy should be initiated as soon as possible, even before the results of specific tests for *N. gonorrhoeae* and *C. trachomatis* are available.

According to 2009 European guideline on the management of male NGU and 2010 CDC STD treatment guidelines, recommended regimens include either azithromycin at a single dose of 1 g or doxycycline 100 mg orally twice a day for 7 days. Both drugs are highly effective against *C. trachomatis*. Azithromycin has the additional advantage of a single dose, with subsequent better compliance. In the case of urethritis caused by *M. genitalium*, azithromycin seems to be more beneficial compared to doxycycline, although treatment failures can be observed with both drugs. Azithromycin and doxycycline are generally effective against other NGU pathogens, with the exception of *T. vaginalis* that responds to metronidazole or tinidazole. Alternatively, patients can receive erythromycin, ofloxacin, or levofloxacin. Recommended and alternative therapeutic schemes are reviewed in Table 100.2.

All of the above therapeutic schemes appear to be efficacious. Randomized clinical studies comparing the cure rates of each regimen are difficult to perform, since the causal microorganism is often not identified.

Patients should refrain from sexual contacts for 1 week (7 days after treatment with azithromycin or during the 7 days of therapy with doxycycline), provided that by that time they are asymptomatic and their partners have also been treated.

Patients with NGU should be monitored for other STDs (including syphilis and HIV). As in all cases of STD counseling, patients should be informed about the 3 month "window" period that precedes serologic detection of these diseases in order to have a repeat test 3 months after the first screening.

Patients with concomitant HIV infection should be managed in the same way as HIV-negative patients. Pathogens causing urethritis facilitate the transmission of HIV.

Follow-Up

An initial follow-up contact with the patient to ensure that symptoms have subsided, and that the patient and his partners have completed therapy without having unprotected intercourse during the period defined by the provider, is advised 3 weeks after completing therapy. If all of the above conditions are fulfilled, a test of cure is not necessary; otherwise, the patient should be reassessed and re-treated. This follow-up visit is also useful in reviewing the results of the screening test and dealing with other STDs that may have been diagnosed. Earlier assessment is not suggested, because urethral discharge and associated symptoms can persist for sometime after NGU therapy, although the infectious cause has been eradicated.

For patients with documented chlamydial urethritis, a further follow-up visit after 3–6 months is advisable in order to repeat testing for *C. trachomatis*, since reinfection during the first 6 months following treatment is not unusual in this group.

Partner Referral

All sexual partners of males with NGU should be assessed and treated, even in the absence of specific diagnosis of a pathogen. The exact preceding period for defining partners at risk is not established, but it should involve at least 2 months prior to diagnosis, or even longer according to the individual history of sexual contacts. Patients and their partners should be informed that symptoms and signs may be absent or mild –especially in the cases of cervical, anal, or pharyngeal infection – and that failure to treat partners could result in reinfection of the person initially treated, as well as in possible complications for all involved sexual contacts. Management of partners should follow the same guidelines previously mentioned.

Pregnant partners of males with NGU cannot receive doxycycline, ofloxacin, or levofloxacin. However, azithromycin is considered safe and effective and can be administered at the standard single dose of 1 g orally. Alternatively, pregnant women can receive amoxicillin 500 mg orally three times a day for 7 days or erythromycin as described in Table 100.2, although gastrointestinal side effects related to erythromycin could result in noncompliance with the latter. A test of cure 3 weeks after completion of therapy is recommended for all pregnant women with documented chlamydial infection to ensure cure.

Persistent and Recurrent NGU

Approximately 10–20 % of patients continue to have symptoms or physical signs 1–3 months after completion of therapy for NGU. If compliance to initial therapy and proper partner management are ensured, these patients are considered to have persistent/recurrent NGU.

Etiology of persistent NGU is not clear but could be attributed to:

- Failure of the recommended schemes (especially doxycycline) to eradicate *M. genitalium*. Therapy with moxifloxacin 400 mg daily for 7 days has proved effective, but there have been reports of severe hepatotoxicity and Stevens–Johnson syndrome. Some authors propose more extended regimens with azithromycin to avoid resistance of *M. genitalium*.
- Resistance of *U. urealyticum* to doxycycline.
- Cases of NGU caused by *T. vaginalis* require therapy with metronidazole or tinidazole.

First- and second-line treatments for persistent/recurrent NGU are summarized in Table 100.3.

Treatment with metronidazole or tinidazole is only advised when *T. vaginalis* is suspected as the responsible organism (e.g., in areas with high prevalence of *T. vaginalis* or when detected by

Table 100.2 Treatment regimens for NGU

	Drug	Dosage	Frequency	Duration	Route of admission	Source of guidelines
Recommended therapies	Azithromycin	1 g	×1	Single dose	po	IUSTI/WHO 2009 European STD guidelines, CDC 2010 STD guidelines
	Doxycycline	100 mg	BID	7 days	po	IUSTI/WHO 2009 European STD guidelines, CDC 2010 STD guidelines
Alternative therapies	Erythromycin base	500 mg	BID	7 days	po	IUSTI/WHO 2009 European STD guidelines
	Erythromycin base	500 mg	QID	7 days	po	CDC 2010 STD guidelines
	Erythromycin ethylsuccinate	800 mg	QID	7 days	po	CDC 2010 STD guidelines
	Ofloxacin	200 mg	BID	7 days	po	IUSTI/WHO 2009 European STD guidelines
	Ofloxacin	400 mg	qd	7 days	po	IUSTI/WHO 2009 European STD guidelines
	Ofloxacin	300 mg	BID	7 days	po	CDC 2010 STD guidelines
	Levofloxacin	500 mg	qd	7 days	po	CDC 2010 STD guidelines

po orally, *BID* twice a day, *QID* four times a day, *qd* once daily

Table 100.3 Therapeutic regimens for persistent/recurrent NGU

	Drug	Therapeutic scheme	Source of guidelines
First-line treatments	Azithromycin	500 mg stat then 250 mg daily for the next 4 days	IUSTI/WHO 2009 European STD guidelines
	PLUS		
	Metronidazole[a]	400–500 mg BID for 5 days	
	Erythromycin	500 mg QID for 3 weeks	IUSTI/WHO 2009 European STD guidelines
	PLUS		
	Metronidazole[a]	400–500 mg BID for 5 days	
	Metronidazole	2 g stat in a single dose	CDC 2010 STD guidelines
	OR		
	Tinidazole	2 g stat in a single dose	
	PLUS		
	Azithromycin[b]	1 g stat in a single dose	
Second-line treatments	Moxifloxacin	400 mg once daily for 7–10 days	IUSTI/WHO 2009 European STD guidelines
	PLUS		
	Metronidazole[a]	400–500 mg BID for 5 days	

BID twice a day, *QID* four times a day
[a]In areas where *T. vaginalis* is prevalent
[b]If not used for initial episode

microscopy, culture, or an NAAT on urethral specimen or urine).

Re-treatment of sexual partners who had received appropriate therapy during the initial diagnosis is not needed. However, in cases of NGU attributable to *M. genitalium*, possible failure of initial therapy should be taken into account.

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Urticaria

101

Frances Lawlor and Anne Kobza Black

Key Points

- The hallmark lesion in urticaria is the weal.
- Urticaria can be acute (<6 weeks) or chronic. Chronic urticaria may be spontaneous or inducible (physical) and may last years.
- Taking a history and examining the patient are extremely important as is an explanation about the condition and its treatment.
- Treatment is given to suppress symptoms if possible.
- Treatment is with minimally sedating antihistamines in an "updosing" regimen. Antihistamines are taken regularly as "prophylaxis" to keep the disease controlled. Systemic steroids are not recommended.
- Second- and third-line drugs may be prescribed, being added to the existing regimen.

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Definition and Epidemiology

Urticaria appears on the skin as multiple short-lived erythematous, macular, annular and wealing lesions which usually itch. Each lesion lasts less than 24 h. The lesions change continually, and weals vary in size from tiny (1–2 mm) to very large (several centimetres). Angioedema, a deeper form of urticaria, presents as swellings of the eyes, lips, ears and other areas. It involves subcutaneous or submucosal tissues. These swellings may last between 24 and 72 h, are often not itchy and also leave normal skin. Angioedema may occur alone (pure angioedema) or concurrently with the urticaria.

A physical urticaria is one which occurs in response to a specific physical stimulus. The physical stimuli which produce lesions are divided into mechanical trauma (friction and pressure), change in temperature (cold and heat), light and water. Physical urticarias often occur in association with spontaneous urticaria and with each other. Recently it has been proposed that urticarias provoked by exercise, heat and emotion (cholinergic urticaria), by water (aquagenic urticaria) and contact urticaria are reclassified as urticaria cause unknown.

Any urticaria which remits in up to 6 weeks after onset is acute urticaria. Urticaria lasting longer than 6 weeks is defined chronic urticaria.

There are no data relating specifically to the incidence of acute urticaria in the population. Chronic urticaria comprises 70 % of all urticaria patients seen

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_101, © Springer-Verlag Berlin Heidelberg 2015

at dermatology clinics. Women are affected twice as frequently as men. Twenty percent of patients seen in urticaria clinics have physical urticarias.

Basic Concepts of Pathogenesis

Acute Urticaria

The most dramatic urticaria, acute allergic urticaria is an IgE-mediated allergic reaction which may be associated with systemic anaphylaxis. Many of these patients are atopic subjects. Systemic anaphylaxis is a rare but serious manifestation. A minor IgE-mediated reaction may present solely as urticaria without systemic symptoms. This response may be provoked by insect stings, drugs, blood products, latex and by various foods, for example, fish, milk, nuts, beans, shellfish, eggs, potatoes, celery, parsley or spices. Acute urticaria may also be associated with viral or bacterial infections, ingestion of medication such as antibiotics or non-steroidal anti-inflammatory drugs or with the onset of thyroid disease, but frequently no cause or association is found. Aspirin is the sole cause of urticaria in some people and worsens the disease in 50 % of patients. The mechanism is non-immunological, but the precise mechanism has not been defined. Other non-steroidal anti-inflammatory medication may behave in the same way. Codeine and morphine release histamine from mast cells.

Angiotensin converting enzyme inhibitors may cause severe angioedema and should be stopped if possible in patients with urticaria and angioedema. In occasional cases pseudoallergens including dyes (e.g. tartrazine, sunset yellow and red and blue dyes) and preservatives (e.g. benzoic acid, salicylates and ascorbic acid) have been reported to cause acute urticaria.

Chronic Urticaria

In the absence of a physical provoking factor, *no underlying allergic or medical cause is found in most cases*. In patients presenting with pure angioedema, it is necessary to consider hereditary angioedema (HAE). Type 1 HAE affects 85 % of sufferers. There is a quantitative deficiency of C1 esterase inhibitor (C1INH). This deficiency is autosomal dominantly inherited due to a mutation on the C1INH inhibitor gene on chromosome 11. Type 2 HAE affecting 15 % of the sufferers shows a functional defect of C1INH. Type 3 HAE has been recognised recently. This is less clearly categorised and very rare. It is familial, occurs in women, is considered oestrogen dependent, and some families show a mutation in the gene encoding for factor 12. An acquired form of HAE has occurred in lymphoproliferative disease, for example, B-cell lymphoma as well as systemic lupus erythematosus and both rectal adenocarcinoma and thyroid carcinoma.

It is suggested that the term *chronic spontaneous urticaria* be used instead of chronic idiopathic urticaria because some subtypes of chronic urticaria have been delineated.

Pathogenesis

Up to 40 % of CU patients express mast cell-activating factors which appear to be directed against the high-affinity IgE receptor (FcεRI) and against IgE. The subclasses are usually IgG1 and IgG3, which bind complement, and participation of complement in enhancing histamine release is probable in some patients. This points to an *autoreactive* (autoimmune) aetiology. The suggestion of an autoimmune aetiology of the disease in these patients is supported by association with thyroid autoimmunity, another autoimmune disease, a strong association with HLA-DRB1 (DR4) and by the response to treatments designed to remove, reduce or neutralise autoantibodies.

There is no easy or commercially available test to detect the autoantibodies directed against high-affinity IgE receptor (FcεRI) and IgE. A screening test is the use of the autologous serum skin test, to detect a weal-inducing factor in the serum of patients with active chronic urticaria, and further identification is the measurement of differential histamine release from normal basophils of low and high IgE occupancy. Some units use a blood test, the basophil histamine release

assay as the measure of autoimmune aetiology. It is now commercially available at RefLabs ApS, Copenhagen, Denmark.

A further subgroup may be associated with infection either viral or bacterial.

In Europe, *Helicobacter pylori*, hepatitis B and C and possibly Streptococcus A and dental infections can occasionally cause chronic urticaria. Parasite infections may cause urticaria outside Europe.

Another subgroup contains those patients who suffer pseudoallergic reactions to dyes and preservatives in foods. These reactions are non-allergic, dose dependent and usually delayed.

Clinical Presentation

The clinical characteristics of the lesions have been described above. It is generally not appreciated how severely the condition affects the quality of life because of the itching, occasional pain and the disfigurement and unpredictability of the lesions. Patients who attended a hospital urticaria clinic had a similar quality of life in many aspects as those waiting for a triple coronary bypass.

Although 50 % of patients with urticaria had been cleared in 6 months to a year, up to 25 % of those with urticaria with or without angioedema still had lesions 20 years later. The clinical course in any patient is impossible to predict, although there is often a gradual tendency towards improvement. Some patients have intermittent episodes, and most develop exacerbations during infections.

Diagnosis

The diagnosis is clinical as patients may not have visible lesion when assessed:

- The *initial interview* with the patient will give nearly all available useful information.
- If there are no specific indicators in the history, *the only routine investigation* suggested is a full blood count, erythrocyte sedimentation rate and urine analysis.
- If the history is suggestive of *physical urticaria*, challenge tests should be performed if possible to confirm the diagnosis. Clinical examination should include testing for symptomatic dermographism. Routine tests for immediate food *allergy* (e.g. *prick* tests) *are not indicated*, but may be performed to investigate a suspected food allergen in the history. If patients strongly suspect a *dietary factor*, *a p*lacebo-co*ntrolled challenge testing* to food additives may be carried out, and a positive result confirmed by re-challenge, or a low pseudoallergen diet can be tried for 4–6 weeks to access response. If *C1INH inhibitor deficiency* is suspected, *the plasma level of C4* is the screening test for hereditary angioedema. Treatment of HAE is not covered.
- A *skin biopsy* is necessary to demonstrate a suspected *urticarial vasculitis* or may be helpful to confirm delayed pressure urticaria.

Differential Diagnosis

The main differential diagnosis of urticaria is *urticarial vasculitis*. Here weals last 3–7 days and are burning, painful or itchy, purpuric, urticarial and very occasionally bullous. Bruised-looking angioedema is suggestive of urticarial vasculitis which is often poorly responsive to antihistamines. An autoimmune disorder such as lupus erythematosus should be considered in patients with confirmed urticarial vasculitis.

Other *differential diagnoses* include acute inflammatory skin conditions in the early phase, such as acute contact dermatitis, erythema multiforme and prebullous eruptions. In the early stages of inflammatory diseases when the swellings may fluctuate, conditions such as acute contact dermatitis and collagen vascular diseases including lupus erythematosus and dermatomyositis and granulomatous cheilitis may be confused with angioedema.

General Principles of Treatment

Patient Education

1. *Where this is no obvious cause of urticaria from the history and clinical examination, it is important for the patient to understand that the condition is not allergic in origin*, except in certain acute cases. "Ordinary" (spontaneous) urticaria is not associated with any underlying diseases, not fatal, not malignant, not contagious and not curable. However, there is usually a tendency to improvement, it can be emphasised at the onset of urticaria, and most will remit spontaneously within weeks. Once chronic, having lasted for more than 6 weeks, in 50 % of patients the disease will remit within 1 year. However, no promises can be made as in some it will last years.
2. *Patients should understand that an exhaustive series of tests will not be helpful*.
3. *Patients should be requested to avoid the drugs which exacerbate urticaria* including ACE inhibitors and non-steroidal anti-inflammatory drugs especially aspirin and histamine liberators such as codeine, but paracetamol is usually tolerated.
4. *Low pseudoallergen diets can be tried for a defined period in those patients who suggest a pseudoallergen-related problem and who wish to adhere to them*. Otherwise diets should only exclude substances proven to be a problem.
5. *Keeping* cool, cool baths and soothing topical applications, e.g. Calamine cream or 1 % menthol in a moisturising base, and minimising alcohol are helpful in some people.

Overview of Drug Treatment

1. *The treatment of urticaria is with minimally sedating H1 antihistamines. The condition can usually be controlled with H_1 antihistamines taken in adequate dosage*.

   The aim of drug treatment for urticaria with antihistamines is to decrease the itch and the number and size of duration of the weals. It may not be possible to completely control the condition without an unacceptable level of side effects.
2. *Since each individual patient responds uniquely, it may be necessary to change antihistamines and use doses higher than those recommended by the manufacturers, "off label" prescribing*.

   Current advice is to use one minimally sedating antihistamine in upto fourfold dosage, i.e. four tablets/day. The increased dose may be more potent due to an anti-inflammatory effect. This is described as "updosing". Dosage can be increased at approximately 2 week intervals. A combination of antihistamines of a different chemical group such as loratadine 10 mg in the morning and cetirizine 10 mg in the evening is not recommended but appears to be useful in practice. If the patient does not respond to updosing, it is suggested that a second-line treatment is added.

   Antihistamines are well absorbed when taken orally, and absorption is not related to the ingestion of food (except for fexofenadine where grapefruit juice reduces serum levels). The timing of tablet taking is important and should be related both to the time of day when the urticaria is at its worst and to the half-life of the drug or its active metabolite. The half-life is longer in the elderly, so the drug may accumulate, and the half-life is shorter in children who tolerate higher doses. It is necessary to be aware of renal impairment and liver impairment as different antihistamines are metabolised in different ways. Tablets should be taken regularly, and patients should understand that it can take time to reach steady blood levels after every dose increase.

   The currently available minimally sedating antihistamines are safe from the cardiac point of view, although in those with heart disease, bilastine, mizolastine and rupatadine can affect the ECG. One should also be aware generally of congenital QT prolongation and concomitant use of tricyclic antidepressants, some antipsychotics, antiarrhythmic drugs and electrolyte imbalance especially with the above three listed antihistamines. One must

be aware, when using certain antihistamines, the accumulation of the drugs by inhibition of degradation by cytochrome P450 by drugs metabolised by the same pathway. Loratadine, desloratadine and rupatadine and mizolastine are metabolised in this way. So one must be aware of possible interactions with azoles and macrolide antibiotics and careful in liver disease when using these drugs.

3. *There has been a change in recommendations with regard to prescribing in pregnancy*. Although most women try to avoid taking drugs in the first 3 months of pregnancy, H1 antihistamines are not teratogenic in humans and have not caused any problems in practice to date, and it is now suggested that taking minimally sedating antihistamines cetirizine and loratadine in pregnancy is safe, as is chlorpheniramine. However, if possible they should be stopped about 1 week before delivery to avoid any effects on the neonate. Antihistamines are excreted in small amounts in breast milk, and so breastfeeding may be a problem. Any antihistamine has the potential to worsen urticaria. The mechanism is not known, but it is suggested that this may be due to a direct toxic effect on the mast cell membrane.

   Only if the above first-line treatment fails should one consider second-line and then third-line treatment.

   Minimally sedating antihistamines are therefore first-line drug treatment for urticaria. This group of drugs includes cetirizine, levocetirizine, fexofenadine hydrochloride, loratadine, desloratadine, acrivastine (very short-acting), mizolastine, bilastine, ebastine and rupatadine. These drugs are H1 receptor inverse agonists shifting the H1 receptor into an inactive state. Generally they do not cause significant drowsiness, psychomotor impairment or anticholinergic side effects, although updosing with cetirizine is capable of inducing drowsiness. However, there is individual variation, and patients should be warned of these rare possibilities, and also excess alcohol should be avoided. Generally all these antihistamines are as effective as each other in clinical trials.

   It should be emphasised to the patient that the antihistamine is not a cure but is best taken regularly as a prophylactic until the urticaria resolves.

4. Antihistamines available (see also antihistamines chapter):
   (a) *Cetirizine* is derived from hydroxyzine. The manufacturers' recommended dose is 10 mg over 24 h. It is excreted by the kidneys and may cause problems in the elderly where lower doses should be given. The drug rarely causes drowsiness but does more frequently if the dosage prescribed is from 20 to 40 mg/day.
   (b) *Levocetirizine* is a metabolite of cetirizine.
   (c) *Loratadine* is an effective antihistamine with no significant sedation.
   (d) *Desloratadine* is a metabolite of loratadine.
   (e) *Mizolastine* is also an effective antihistamine; manufacturers recommend a dose of 10 mg per day. Prolongation of the QT interval has occurred in occasional patients, so the dose should not be increased.
   (f) *Acrivastine* is not usually potent enough alone to control urticaria. The manufacturers' recommended dose is 8 mg three times a day. It is helpful if a rapid response to treatment is sought and as an adjunct to treatment with other antihistamines as it has a fast onset and a short duration of action.
   (g) *Ebastine* at a dose of 10 mg daily is an effective antihistamine with no significant sedation or side effects or interactions with other medications.
   (h) *Rupatadine* is effective and interacts as described previously (see Chaps. 1 and 2).
   (i) *Fexofenadine hydrochloride* is an active metabolite of terfenadine without cardiotoxic effects. To date, few adverse effects and no drowsiness have been reported.
5. *Classical antihistamines*:

   If necessary and if sedation might be helpful, a sedating antihistamine could be

used especially for nighttime sedation. The group includes *chlorpheniramine maleate*, *hydroxyzine hydrochloride and diphenhydramine hydrochloride*. *Doxepin*, a tricyclic antidepressant with a powerful antihistaminic activity, can control urticaria when used on its own but may be better for night sedation of the anxious patient. With the exception of hydroxyzine, these drugs tend to be less effective than the second-generation antihistamines.

6. *Second-line treatment*: *If the patient is symptomatic after 4 weeks*, *it is suggested that the antihistamine be changed and/or a trial of a leukotriene antagonist* (*e.g. montelukast 10 mg*) *instituted for a month to see if there is a response*.
7. *Third-line treatment*: *Drugs added to the existing antihistamine regimen* include H2 antihistamine, cyclosporin, dapsone, methotrexate, mycophenolate mofetil and omalizumab.
   (a) *H2 Receptor Antagonists*
   The results of trials combining H_1 and H_2 receptor antagonists are conflicting, but though some show a significant improvement compared to either medication alone, in practice the combination is disappointing and does not usually produce a clinically significant improvement. The most recent European Guidelines suggest them as third-line treatment.
   (b) Cyclosporin
   Cyclosporin is effective in many patients. A response may be noticed after 2 weeks. The dosage is between 3 and 5 mg/kg/day.
   Baseline antihistamines must be continued and the usual blood tests and blood pressure estimations performed.
   (c) *Dapsone*
   Dapsone may be helpful when control is not achieved with full dosage of antihistamine. After an FBC and a G6PD level estimation, it seems wise to start with a low dose and increase until control is achieved, as tolerated.
   (d) *Omalizumab*
   Omalizumab is an effective treatment in many patients. It is expensive and regimens continue to evolve. The drug is injected monthly usually in a dose of 150 mg or 300 mg. It seems that some patients go into remission after one to three treatments, but most who improve relapse at this stage if the drug is stopped. It should be reserved for those with a severe limitation in both quality of life and whose urticarial activity score is high and who have not responded or are not suitable for other third-line therapies.
   (e) *Methotrexate*
   Methotrexate, used in the same way and with the same checks as psoriasis, is an effective treatment.
   Onset of action is slow, but good control can be achieved.
   (f) *Mycophenolate Mofetil*
   Mycophenolate mofetil can be effective, used in the same dosage and with the same checks as in Bullous pemphigoid. It has a slow onset of action.
8. *Other Treatments Used*
   (a) *Ultraviolet B and PUVA* have been effective in some patients.
   (b) *Intravenous immunoglobulin and plasmapheresis* have been used in those severely affected. Although there are some controlled studies which demonstrate that the addition of medication with in vitro mast cell-stabilising properties, such as ketotifen, nifedipine and theophylline, to antihistamines leads to improved control of urticaria, these are not mainstream treatments.
   (c) *Systemic steroids should not be used* for the treatment of urticaria except in exacerbations and for 3–7 days, in a dose of up to 30 mg /day. They are not always effective, and the side effects are unacceptable in the long term.
   Longer-term therapy may be occasionally necessary for severe urticarial vasculitis and delayed pressure urticaria not

responding to other therapy but should only be used at lower dosage in the long term.

Treatment of Angioedema

Acquired ordinary angioedema should be treated in the *same way as urticaria* with a dosage of H_1 antihistamine which suppresses the disease. If angioedema occurs in the mouth and causes systemic problems, e.g. dyspnoea, dysphagia, wheezing or syncope, *epinephrine* (*adrenaline*) (0.5 mg–1.0 ml of 1:1,000 mg/ml solution intramuscular or subcutaneous injection) should be used. Adrenaline is available for self-administration by patients as a mini-jet (0.5 ml) or as an adrenaline EpiPen (0.3 ml for an adult or 0.15 ml for paediatric use). Patients should be taught how to self-administer and when to administer. Patients with a history of severe oropharyngeal and laryngeal angioedema or anaphylaxis should have two in-date ones available for emergency use, as a repeat dose should be administered after 10 min if the initial response is not satisfactory.

Treatments for the Physical Urticarias

Symptomatic Dermographism

This usually responds well to treatment with H_1 antihistamines; ultraviolet B therapy at suberythrogenic doses two to three times/week for 8 weeks minimum may provide additional improvement.

Delayed Pressure Urticaria

This nearly always occurs in conjunction with chronic urticaria, but the pressure urticaria may be the major problem. Baseline treatment is with H_1 antihistamines and pressure on the skin minimised as far as possible. Large doses of antihistamine may have an effect on pressure-induced weals. In very severe disease, a short course of prednisolone (30 mg daily) can be given, but side effects are unacceptable if long-term use is contemplated. Many drugs have been used in this disabling disease including *intravenous immunoglobulin, montelukast*, *cyclosporin*, *dapsone*, *mycophenolate mofetil*, *etanercept*, *chloroquine and omalizumab*, but response to therapy continues to be uncertain.

Cholinergic Urticaria

Cholinergic urticaria responds partially to antihistamines.

Danazol (200–800 mg) or *stanozolol* (2.5–10 mg daily) may be used in resistant disease, with occasional effect. Drugs which have been used include beta blockers and omalizumab. A small group improved when desensitised to their own sweat. Some patients can control their problem by inducing tolerance.

Cold Urticaria, Localised Heat Urticaria, and Vibratory Angioedema

In these conditions *H_1 antagonists* are usually effective. Induction of tolerance by repeated graduated exposure to the physical precipitant may be helpful but is cumbersome to perform and needs to be maintained.

It is important to warn patients with cold urticaria against cold water bathing due to the risks associated with systemic histamine release and potential drowning. Etanercept given for other medical reasons has been a successful treatment, as have omalizumab and anakinra.

Severe localised heat urticaria has responded to omalizumab.

Solar Urticaria

This condition is difficult to treat. Staying inside during the bright part of the day and UV film on the windows help. Regular application of a *high-factor sunblock* active against UVB and UVA may help. *Antihistamines* should be used as first-line drug treatment. *Ultraviolet light* in small increments has produced tolerance.

If the above measures are not helping, intravenous immunoglobulin and cyclosporin have been used.

Aquagenic Urticaria

This rare physical urticaria usually responds to conventional *H_1 antihistamines*.

Proposed Treatment Algorithm in Urticaria

- *Take a full clinical history*:
  - Remove any identifiable cause, e.g. foods in IgE-mediated reactions and physical factors.
- *Discuss the diagnosis with the patients*:
  - General advice – explanation and information
  - Advise avoidance of aggravating factors:
    - NSAIDS, ACE inhibitors, codeine and morphine.
    - Minimise heat, stress and alcohol.
    - Avoid pseudoallergens in diet if proven to be a problem.
- *Treatment of urticaria*:
  - Emphasise that treatment must be taken regularly.
    - Second-generation, nonsedating antihistamines are the first-line treatment (normal dose).
  - Updose ×2, every 2 weeks if the symptoms persist.
    - Updose (×4) second-generation antihistamines or change antihistamine/add leukotriene antagonist (if the symptoms persist).
    - Add second- and/or third-line treatment as necessary.
  - Cyclosporin/methotrexate/mycophenolate mofetil/omalizumab.
  - All drugs are added to the updosed antihistamine regimen.
  - IVIG, plasmapheresis, danazol (Dapsone), UVB and PUVA have also been used.

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Varicella

102

Theognosia Vergou

Key Points

- Varicella is transmitted mainly by airborne droplets or less commonly by direct contact with the vesicular fluid from skin lesions. Varicella is highly contagious (80–90 % transmissibility rates between family members).
- After the prodromal symptoms, the skin eruption appears, with the hallmark pathognomonic sign of varicella being the clinical presentation of lesions at different stages of development at the same time, in any part of the body.
- Varicella in pregnant women needs attention. The highest risk for the embryo is between the 7th and the 20th week of pregnancy.
- In adults and immunocompromised patients, primary varicella pneumonia is a very important complication, with mortality rates 10–30 %.

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Definition and Epidemiology

Varicella, commonly referred to as chickenpox, is a highly transmissible infection caused by varicella-zoster virus (VZV), a DNA virus of the herpes group, transmitted by direct contact with infective individuals. Varicella is the primary infection of this highly contagious virus, while herpes zoster is the result of viral reactivation. Although varicella commonly occurs as a benign disease of childhood, it may be associated with life-threatening complications when it affects adults, pregnant women, newborns or immunocompromised patients. It mainly affects children below the age of 10 years old and shows peaks in winter and spring.

Basic Concepts of Pathogenesis

Varicella-zoster virus (VZV) is the causative agent of two diseases, varicella (chickenpox) and zoster (shingles). After an acute varicella infection is cleared, VZV establishes latency in the ganglia from which it can emerge later in life to give rise to a secondary infection, zoster. In contrast to varicella, which is disseminated, zoster, occurring in partially immune hosts, is usually limited to the dermatomes innervated by the ganglia in which reactivation occurs.

In Europe, 90 % of children get infected with VZV before 12 years of age, and around 95 % of adults are immune to VZV.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_102, © Springer-Verlag Berlin Heidelberg 2015

Varicella is transmitted mainly by airborne droplets or less commonly by direct contact with the vesicular fluid from skin lesions. Varicella is highly contagious (80–90 % transmissibility rates between family members). Primary viraemia results after viral replication to the regional lymph nodes (2–4 days). The virus is removed by cells of the reticuloendothelial system, which represent the major site of viral replication. Fourteen to sixteen days after the exposure to the virus, skin lesions are present. Secondary viraemia follows, with replication of the virus to the liver, the spleen and other organs. After temporary immunity following varicella infection, VZV reactivation (with the clinical form of herpes zoster) may occur, due to the decline of cell-mediated immunity (CMI), as a consequence of ageing or other immune-suppressing processes.

Clinical Presentation

The incubation period ranges from 11 to 20 days. After this period, the prodromal symptoms include fever, malaise, headache and myalgia. The skin eruption usually starts from the scalp and the face with later centripetal distribution to the trunk. The eruption may extend to the proximal part of upper extremities and thighs. The initial skin lesions are erythematous macules that very rapidly evolve to papules and then to vesicles surrounded by an erythematous halo ("dewdrops on a rose petal"). Vesicles evolve later to pustules and finally to crusts that disappear in 7–10 days without residual scarring. The hallmark pathognomonic sign of varicella is the clinical presentation of lesions at different stages of development at the same time, in any part of the body (Figs. 102.1 and 102.2). The lesions may be very pruritic. Secondary bacterial infections are one of the most common complications and may result to characteristic scars due to scratching.

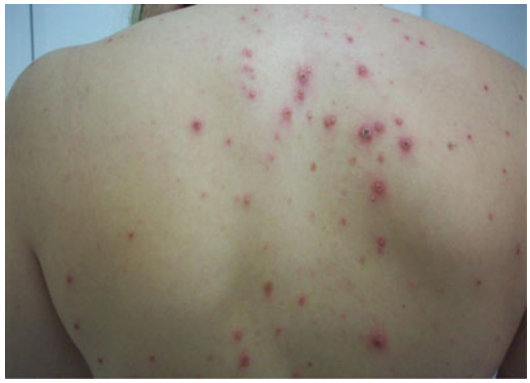
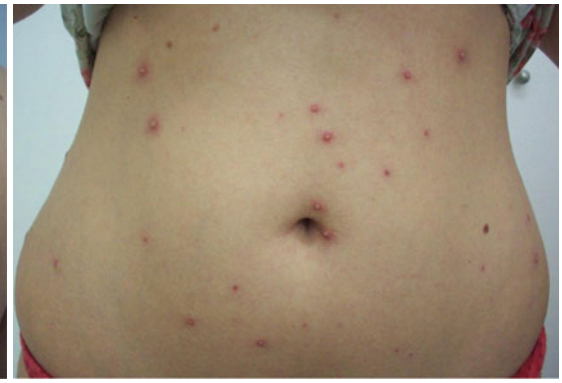
In most cases, severe complications are described in adults, pregnant women, newborns and immunosuppressed patients. In adults and immunocompromised patients, primary varicella pneumonia is a very important complication, with mortality rates 10–30 %. Neurological complications include encephalitis, acute cerebellar ataxia, Reye syndrome, etc., are rare and are usually seen in immunocompromised patients. Haemorrhagic type of varicella is rare, with skin lesions filled with haemorrhagic content. The patient suffers from high fever and severe malaise. Other rare complications are optic neuritis or keratitis, myocarditis, arthritis, pancreatitis, hepatitis, vasculitis and orchitis.

Varicella in pregnancy is a situation in which the physician needs to be vigilant. It carries a 2 % risk of embryopathy. The reported incidence of gestational varicella is 1–7 per 10,000 pregnancies. Regarding the mother, an increased risk for disseminated varicella or primary varicella pneumonia exists. Intrauterine infection may take place, due to the viraemia of the mother. The highest risk for the embryo is between the 7th and the 20th week of pregnancy. If maternal varicella happens in the first two trimesters of pregnancy, this may cause congenital varicella syndrome, which is characterised by skeletal hypoplasia and abnormalities, neurological and ocular defects, low birth weight and skin scars. If the mother is infected in late pregnancy, this may result to premature delivery or stillbirth. In the case of maternal infection 5 days before or 2 days after the delivery, then the newborn will have varicella between the fifth and the tenth day of birth, due to the fact that there was no time for the embryo to get sufficient maternal antibodies. Perinatal varicella is associated with 20 % mortality rates.

Differential Diagnosis

Differential diagnosis has to be done between other generalised vesicular eruptions, such as:

- Dermatitis herpetiformis
- Disseminated herpes simplex (HSV typically has more localised lesions at the site of primary infection)
- Eczema herpeticum
- Vesicular viral exanthems (Coxsackie, ECHO)
- Pityriasis lichenoides et varioliformis acuta (PLEVA is a chronic inflammatory disorder)
- Rickettsialpox (the initial lesion is the site of the mite bite)
- Drug eruptions

Figs. 102.1 and 102.2 The characteristic pathognomonic sign of varicella is the presentation of lesions at different stages of development at the same time (papules, vesicles, pustules)

- Contact dermatitis
- Insect bites or scabies
- Bullous impetigo

Diagnosis

In most cases varicella diagnosis is made mainly by clinical examination and history. A Tzanck smear will show characteristic multinucleated epithelial giant cells, but it cannot rule out an HSV infection. The same also applies for skin biopsy. Viral culture is the most specific test, but not the most sensitive. Serology shows retrospective diagnosis of varicella, with the presence of IgM antibodies and a fourfold increase in the IgG antibodies. During the second to third week of infection, both antibodies reach their peak, with IgM declining quickly and IgG staying at low levels for life. Other diagnostic tools are immunofluorescence and PCR.

General Principles of Treatment

Symptomatic therapy for varicella includes antihistamines and emollients for pruritus and antipyretics for fever. It is sufficient for children with a normal immune system. Topical antibiotics may be needed for secondary bacterial infections, or even systemic antibiotics, if there is a widespread bacterial infection. Compresses or rinses with saline for skin, perineal and mouth lesions are helpful.

Acyclovir is indicated in immunocompromised adults and children. It is not recommended routinely for the treatment of uncomplicated varicella in otherwise healthy children. It is generally indicated for the treatment of otherwise healthy adults, due to the very increased risk of varicella complications and disseminated disease. The initiation of treatment has to take place within 24–72 h after the onset of cutaneous eruption. The oral dose for adults is 800 mg, five times daily for 7 days, and the dose for children is 20 mg/kg (higher dose is 800 mg), four times daily for 5 days. Another approved therapeutic form for children is as follows: in children <2 years old, 200 mg, four times daily; 2–5 years old, 400 mg, four times daily; and >6 years old, 800 mg, four times daily for 5 days. In immunocompromised adults or in adults with severe complications, acyclovir is administered intravenously, 10 mg/kg (500 mg/m^2), every 8 h for 7–10 days, and the same dose also applies for children. The oral dose for adults for valaciclovir is 1 g, three times daily, for 7 days, and the dose for famciclovir is 500 mg, three times daily, for 7 days. Both drugs have an indication only for the treatment of herpes zoster and have also been used for varicella in adults.

Passive immunisation is achieved with varicella-zoster immunoglobulin (VZIG). It is important for the administration to take place within 3 days of exposure, and the protective effect lasts for 3 weeks. It is indicated, at a dose of 125 U/kg, in immunocompromised patients that did not have varicella in

the past and that are exposed in an environment with varicella. It can also be administered in pregnant women with serious exposure to varicella, and there are reports in the literature that it could lower the risk for congenital varicella syndrome. Neonates of pregnant women that had clinical symptoms of varicella 5 days before or 2 days after delivery have to be protected with VZIG as soon as possible. Even though there are no controlled clinical trials for intravenous acyclovir in this case, experts recommend it, at a dose of 15–30 mg/kg/day. VZIG is also indicated for the passive immunisation of immunocompromised children after an important exposure to varicella or herpes zoster.

In the case of a possible exposure to varicella in a pregnant woman with unknown immune status, serum testing should be performed. If the serum results are negative or unavailable within 96 h from exposure, VZIG should be administered. Women with significant varicella infection in pregnancy should be treated with oral antiviral agents (e.g. acyclovir 800 mg, five times daily). In cases of progression to varicella pneumonitis, maternal admission to hospital should be seriously considered. Intravenous acyclovir can be considered for severe complications in pregnancy (oral forms have poor bioavailability). The dose is usually 10–15 mg/kg or 500 mg/m^2 IV, every 8 h, for 5–10 days, for varicella pneumonitis, and it should be started within 24–72 h of the onset of rash.

Active immunisation with live attenuated VZV vaccine is available in several countries outside Europe (Australia, Canada, Costa Rica, Ecuador, Israel, New Zealand, Oman, Panama, Qatar, Saudi Arabia, South Korea, Taiwan, the United Arab Emirates, Uruguay and the USA), as well as some European countries (Germany, Greece, Latvia, Luxembourg) and regions (7 out of 21 in Italy, 2 out of 17 in Spain) have introduced routine varicella vaccination after 1995.

Initially a single-dose vaccine was performed in children aged 11–14 months. Additionally, catch-up vaccinations for all susceptible children and adolescents were recommended, with two doses in children over 13 years of age. In many countries, after 2006, a combined measles-mumps-rubella-varicella (MMR-V) vaccine is available, licensed with a two-dose schedule (the second dose at the age of 4–6 years old).

Epidemiologic data have shown that paediatric varicella cases decreased by 67 % and paediatric hospitalisations by 43 % after the implementation of the vaccine. There are also reports from studies showing that due to the vaccination programmes against varicella, there is an important decrease in the incidence of herpes zoster. This has been explained based on the fact that the acquired active immunisation with the vaccine protects ten times more than the natural immunisation after a varicella infection during the childhood. Some single-country modelling studies have shown the opposite results, thus an increase in herpes zoster incidence. The most recent data from a model-based evaluation from three European countries supports the idea that, after varicella immunisation, an increase of herpes zoster incidence is not a certain fact and it rather depends on the presence or absence of factors promoting a strong boosting intensity and which might or might not be heavily affected by changes in varicella circulation due to mass immunisation. These findings might explain the opposed empirical evidences observed about the increases of herpes zoster in sites where mass varicella vaccination is ongoing.

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Vascular Birthmarks: Vascular Malformations and Haemangiomas

103

Fabio Arcangeli and Davide Brunelli

Key Points

- Vascular malformations and haemangiomas are among the most common dermatological conditions that can be observed in infancy, and the dermatologist is often involved in the first diagnosis or acts as an important consultant when planning therapeutic and follow-up strategies. Precise knowledge of the natural history of these pathologies and the general implications arising from them is essential to be able to direct parents toward making an informed therapeutic choice.
- Today vascular anomalies are described according to the ISSVA (International Society for the Study of Vascular Anomalies) classification drawn up at the 1996 workshop in Rome. Haemangiomas can be considered benign tumours characterised by an abnormal proliferation of capillary vessels. Their history shows rapid growth in the first months of life, followed by a slow involution in subsequent years. Capillary malformations, in contrast, are characterised by the presence of permanently abnormally dilated capillaries. These do not regress spontaneously but grow in proportion to the somatic development of the individual. Both conditions can have different degrees of severity, and they also involve the visceral organs in the context of complex syndromal patterns.

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Vascular Malformations

Definition

Within the group of vascular malformations (Table 103.1), the capillary malformations (CM), more commonly known as port wine stains, are the most frequently occurring and have the highest epidemiological profile. They are characterised by the presence of capillary anomalies at the level of the papillary and reticular regions of the dermis: the vessels are permanently dilated, giving rise to the typical skin colouration that can vary from pale red to deep purple. They are present at birth in 0.3 % of newborns with an equal distribution between the two sexes.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_103, © Springer-Verlag Berlin Heidelberg 2015

Table 103.1 Updated ISSVA classification of vascular anomalies

Vascular tumours	Vascular malformations
Infantile haemangiomas	*Slow-flow vascular malformations*
Congenital haemangiomas: rapidly involuting congenital	Capillary malformation (CM)
Haemangioma (RICH); noninvoluting congenital haemangioma (NICH)	Port wine stain Telangiectasia
Tufted angioma (with or without Kasabach-Merritt syndrome)	Angiokeratoma
Kaposiform haemangioendothelioma (with or without Kasabach-Merritt syndrome)	Venous malformation (VM)
	Common sporadic VM
Spindle cell haemangioendothelioma	Bean syndrome
Other, rare haemangioendotheliomas	Familial cutaneous and mucosal venous
Epithelioid	Malformation (VMCM)
Composite	Glomuvenous malformation (GVM)
Retiform	(Glomangioma)
Polymorphous	Maffucci syndrome
Dabska tumour	Lymphatic malformation (LM)
Lymphangioendotheliomatosis	*Fast-flow vascular malformations*
etc.	Arterial malformation (AM)
Dermatologic-acquired vascular tumours	Arteriovenous fistula (AVF)
Pyogenic granuloma	Arteriovenous malformation (AVM)
Targetoid haemangioma	*Complex combined vascular malformations*
Glomeruloid haemangioma	CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM
Microvenular haemangioma	
etc.	

C capillary, *V* venous, *AV* arteriovenous, *M* malformations

Basic Concepts of Pathogenesis

There is not yet a generally accepted explanation for this phenomenon. Among the most accredited theories is the one put forward by Waner and Suen in 1999, who postulated that the existence of a relative or absolute lack of autonomic and sensory innervation was the basis for this pathology. The lack of adequate innervation would cause alteration in the vasoregulatory mechanisms resulting in permanent vessel dilation and increased blood flow in the affected areas. A recent discovery of undoubted interest is that of a somatic mutation of the GNAQ gene on the 9q21 chromosome that would seem to confirm the universally accepted but never proven hypothesis of the presence of a somatic mutation being the basis of both capillary malformation and its associated syndromes.

Clinical Presentation

The extent of the CM can vary from a few millimetres to over 50 % of the body surface, affecting almost any somatic region, although port wine stains occur most frequently on the head and neck (Fig. 103.1). When they occur on the face, over 50 % of the CMs affect only one of the three cutaneous areas corresponding to the sensory branches of the trigeminal nerve. Clinical diagnosis is normally straightforward with a skin biopsy only rarely necessary for confirmation. CMs do not regress but grow according to the somatic development of the individual, and over the years, the surface becomes darker and subject to such phenomena as thickening and nodular hypertrophy (cobbling). In adulthood these phenomena may cause significant clinical conditions, with the increased disfigurement leading to

Table 103.2 Principal syndromes associated with the presence of capillary malformations

Name	Clinical features		
Sturge-Weber	Craniofacial CM (periorbital and temporal area)	Ophthalmic lesions (choroid haemangiomas) and homolateral leptomeninges (vascular anomalies, calcification)	Neurological (epilepsy, sometimes mental retardation) and ocular (glaucoma) symptoms
Parkes Weber	CM involving a lower limb	Arteriovenous microfistulas	Hypertrophy of the skeleton and soft tissues
Klippel-Trenaunay	CM involving a lower limb	Complex venous malformation	Gigantism of the limb

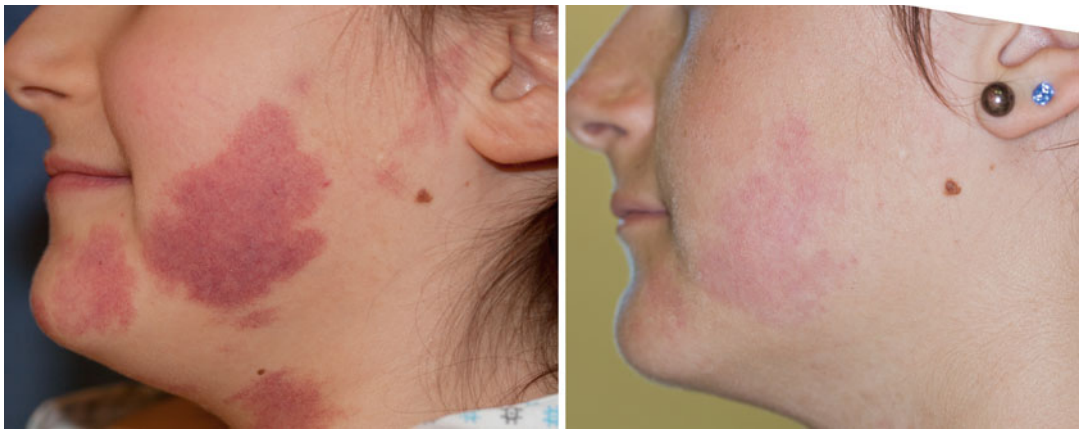


Fig. 103.1 Capillary malformation of the face before and after three treatments with 595 nm FPDL

psychological damage and sometimes very marked functional disorder. Even less clinically significant cases are capable, from early infancy, of producing negative effects on a child's cognitive, social and psychological development with inevitable repercussions in adult life. To this can be added the anxiety and sense of guilt that normally afflict the parents, emotional factors that can complicate problems of family equilibrium to the extent that this pathology can be considered a condition that is not limited to a merely aesthetic issue. For these reasons, requests for treatment are becoming ever more numerous, particularly now that the proliferation of new communications media makes it easier to access detailed information about the technological solutions available and the clinical issues that accompany them. It is known that this condition is associated with some syndromes (see Table 103.2), the most well known and frequently occurring is Sturge-Weber syndrome, which can be observed in particular in patients with a port wine stain affecting the part of the skin corresponding to the first branch (V_1) of the trigeminal nerve.

General Principles of Treatment

Traditional attempts at therapy (surgery, radiation therapy, cryotherapy, diathermic coagulation, dermabrasion or simple cosmetic camouflage) have always left both patients and therapists dissatisfied, and these have often caused blemishes that are even more unsightly than at the start. The first attempts at treating CMs with laser equipment (CO_2, Argon and Nd:YAG) were equally disappointing both because of their lack of effectiveness

and because of the resultant scarring, sometimes very serious, resulting from the application of the flash lamp. It was only in the 1980s and 1990s that greater knowledge of selective photothermolysis led to the development of an apparatus specifically designed for CM treatment, the dye laser, which very soon became the therapeutic gold standard for the treatment of this pathology.

The Dye Laser

Dye lasers belong to a class of equipment whose active medium is an organic dye in a liquid state, normally in an alcohol solvent. The dye is made to circulate rapidly in a cylindrical cell excited by a flash lamp as is the case for solid-state lasers or Argon or Nd:YAG lasers. The apparatus used in dermatology uses mainly *rhodamine 6G*: the dye is excited by a high-intensity flash lamp from which the laser takes its international name *flash lamp-pumped dye laser* (FLPD), and the result is the emission of light at a wavelength of 595 nm, the ideal compromise between selectivity and depth of penetration within the skin. The target for CM treatment is the oxyhaemoglobin contained in the malformed capillary bed. According to the studies by Greenwald and Tan, the first appreciable results after exposure to laser light were confined to the superficial plexus (0.5 mm) and were characterised by an aggregation of erythrocytes, breakage of the vessels and haemorrhaging. Deeper down (0.5–1.1 mm) a disseminated infiltration of polymorphonucleates was observed, mainly perivascular and alternating with areas of lymphocyte infiltration. One week after the treatment, the vessels had been replaced by a fine granular tissue, and at the level of the papillary dermis, they presented a lumen of a smaller diameter. One month later, no abnormally dilated capillaries were observed: the treated areas presented a lumen of a small diameter, thin walls and a notably greater quantity of endothelial cells and pericytes. The epidermis showed no alterations after 30 days from treatment. In this study, using a 577 nm apparatus, the minimum flux needed to produce tangible alterations was estimated as 3 j/cm^2, while the more considerable alterations were found starting from 5 j/cm^2. Today the most commonly used starting flux, which varies according to the specifications of the equipment used, is between 5.6 and 10.12 j/cm^2. The ideal diameter of the spot is considered to be between 7 and 10 mm. The universally adopted exposure time, from the first experiences of CM treatment, is 450 μs, the lowest thermal release time (TRT) threshold for the cutaneous capillary plexus. Using a wavelength of 595 nm, this can be increased to 3.0 ms, making it possible to act on vessels of a larger size. These exposure times result in the immediate appearance of the characteristic purple colouration that represents an important end point for the treatment. Checking the tonality of the purpura offers the therapist the opportunity to make an indirect assessment of its efficacy. Any evidence of greyish areas within the typical purple colouration most probably represents an area of hyperexposure to the laser light, while reduced colouration probably suggests too low a flux or an inadequate target. The purpura regresses in 10–14 days, but this can be followed, some days after treatment, by the appearance of small water blisters which then give way to crusty surface scabs. Although these phenomena disappear rapidly, they appear quite dramatic when they first appear, and therefore it is advisable to show patients or their family some photographs illustrating the different stages in the evolution of these phenomena.

When to Begin Treatment, Success Rate and Adverse Side-Effects

Personal experience and numerous publications on this subject confirm that treatment should be undertaken as early as possible. Early treatment is more successful because the capillary bed is more superficial, the diameter of the vessels smaller and the epidermis is thinner, thus enabling greater light penetration and last but not least, the more limited extent of the lesions, making it possible to cover a greater area in the same session. Not only is the therapeutic success more obvious, but fewer treatments are required than in adult-

hood. The location of some CMs, such as on the lower limbs, can be completely untreatable in an adult, but there may be some hope of improvement if treated at an early age. For these reasons, the first intervention should be planned to start from the first months of life with the prospect of significant clearing in a few sessions spaced 4–5 months apart. Depending on the response, it may then be necessary to schedule some "maintenance" treatment sessions at a frequency to be determined according to the clinical development of the condition. Regardless of the amount of clearing obtained, periodic laser treatment is capable of arresting or reducing such involution phenomena as thickening and cobbling that can be observed in the most deep-seated conditions. The treatments are given under a general anaesthetic to the youngest children and those with lesions on the face. In these cases the eyes must be protected with a metal screen, particularly if the area to be treated is the eyelids or the area around the eyelids. Adults are quite able to withstand treatment in outpatients without the need for a local anaesthetic or sedation.

The success rate reported in the numerous published works on this topic can vary quite dramatically, this being largely influenced by the age of the patient and the size and location of the lesions. A positive judgement of the treatment expressed by patients or their families can exceed 80 % for facial lesions in paediatric patients, but this decreases notably for adults and for lesions on the extremities. The size of the lesions, particularly in adult patients, seems to affect the response to the treatment in a linear way, in particular for affected areas over 100 cm^2. Adults too can respond very well to treatment, particularly in cases with limited lesions, while there is a very low response for more extensive lesions, particularly when these affect the extremities. Despite the considerable aesthetic improvement, complete clearing of CMs has only been observed in about 10 % of cases.

Adverse side effects are very rare, under 1 % of cases, but they are possible, and therefore this must be clearly explained before undertaking treatment. Most unwelcome are those represented by hypertrophic and keloid scarring that is later particularly observable in treatments to the neck. Atrophic scarring has also been reported, generally reversible over a period of 12–18 months. Moreover post-inflammatory hyperpigmentation and hypopigmentation can be observed, usually transitory and largely influenced by the skin phototype. Indeed, melanin can compete with haemoglobin in the wavelengths between 585 and 590 nm and partially absorb the laser energy. Pigmentation disorders after treatment are therefore more common in darker phototypes and are also influenced by the degree of tanning present when the therapy is applied.

Recurrence of Vascular Manifestations

Although this methodology today represents the benchmark treatment for CM conditions, two main problems still exist: the recurrence of the vascular manifestations and the cases that fail to respond to treatment.

In the years following treatment, the vascular condition gradually reverts in a large number of the cases treated, something that has been noted and confirmed by studies that use objective assessment methods. This fact must therefore be clearly explained before undertaking treatment, since it is likely that further "maintenance" sessions will be needed over the years. Despite this evidence, the majority of patients state that they are satisfied with the treatment, apart from the partial revascularisation. The result is most probably due to the gradual onset of the return of colouration and thus to the changes in perception associated with this.

Alternative Treatments

Some cases, between 20 and 30 %, according to the literature, show little or no response to FPDL treatment, and to date, it is virtually impossible to predict, prior to treatment, which lesions will show the best response, despite the various instrumental approaches suggested to remedy

this problem, principally Doppler sonography and videodermatoscopy. When there is a poor response, substantial benefits cannot be obtained by changing the parameters of the apparatus, such as exposure time or flux, although the double-pass technique, at 595 and 585 nm, does seem more promising.

Other lasers have been proposed as complementary or as alternatives to the dye laser when there is no response, among them the alexandrite 755 nm and the Nd:YAG 1,064 long pulse lasers. Even though the results are still limited and contradictory, they appear to provide useful support in the treatment of CM conditions. Consideration is also being given to the use of IPL (intense pulsed light) equipment, supported by some interesting work and, more recently, the use of photodynamic therapy. In addition to the use of complementary or alternative apparatus to the dye laser, further research is being done on some drugs such as angiogenesis inhibitors, rapamycin and imiquimod.

Haemangiomas

Definition

Infantile haemangiomas (IHs) are very common benign vascular lesions composed of endothelial cells. They are found in approximately 10 % of all newborns and infants up to the age of 12 months (20 % in premature infants). They are three to four times more common in females.

Basic Concepts of Pathogenesis

The pathogenesis of infantile haemangioma, in spite of having been recently reviewed, is still not completely understood, although it has been postulated that growth factors and hormonal and mechanical influences affect the abnormal proliferation of endothelial cells.

Numerous studies support the hypothesis that the primary defect is intrinsic to endothelial cells in that the underlying factor in the development of the tumour is a mutation in a critical gene in a precursor stem cell, and the clonal expansion of this single cell carrying a somatic mutation leads to haemangiogenesis. In the proliferation stage of a haemangioma, there is rapid proliferation of new blood vessels that arise as clonal primitive stem cells differentiating into endothelial cells and pericytes, and there is an increase in the expression of proangiogenic factors, such as VEGF, bFGF, PDGF, IGF-2, HIF-1alpha, MMP-2 and MMP-9. In particular, VEGF (vascular endothelial growth factor) seems to play a key role in the pathogenesis of haemangiomas in that it stimulates both proliferation and migration, increases vascular permeability, stimulates angiogenesis and inhibits apoptosis.

In contrast, the regression phase is characterised by a reduced expression of these factors and the endothelial cells, followed by lobular deposition of fibrofatty tissue.

VEGF expression is also increased by hypoxia: tissue hypoxia seems to be the most powerful inducer of vasculogenesis and angiogenesis involved in the pathogenetic mechanism. Recent studies have shown an association between placental hypoxia and haemangioma.

An alternative theory implicates the expression of placental vascular epitopes in haemangioma in which high levels of immunostaining are displayed for the GLUT1 glucose transporter, a surface protein that is highly expressed in most embryonic and foetal endothelial cells but lost in most tissue, except at blood-tissue barriers, including microvessels in the central nervous system and the placenta. It has been hypothesised that embolisation of placental endothelial cells to the foetus plays a role in the pathogenesis of haemangiomas, because this would explain the exclusively perinatal or congenital presentation of this pathology.

The role of the renin-angiotensin system has recently been explored with beta-blockers causing a reduction in renin activity. The effect of propranolol on haemangioma is not currently completely understood, but with improving knowledge of the pathogenesis of infantile haemangioma, several possible mechanisms for the action of the beta-blocker have been found. It is believed that propranolol leads to suppression of angiogenesis, through a reduction in the expres-

sion of such proangiogenic factors as VEGF, vasoconstriction of the capillaries and the induction of apoptosis.

Clinical Presentation

IHs generally appear in the first 2 weeks of life, and they typically evolve with a phase of rapid proliferative growth up to the fourth to sixth months of life, followed by a slow spontaneous involution phase that is complete by the fifth year in 50 % and the seventh year in 70 % of cases, but in 30 % of cases, the regression phase can be prolonged up to the ninth to tenth year of life.

RICH (rapid involuting congenital haemangiomas), whose proliferation stage occurs during endouterine life and that have reached their maximum size at birth, subsequently regressing over the first 2 years of life, are a separate type of haemangioma and are not considered a variant of IH.

While IHs can be located on any area of the skin, the majority appears on the head and neck (60 %), followed by the trunk (25 %) and limbs (15 %).

Clinically superficial IHs present as macules or papules that are pink or red in colour, at times preceded by blanching of the involuted skin followed by fine telangiectasias. During the proliferative growth phase, IHs tend to become raised, well demarcated, a bright red in colour, plaque or tumour-like, with a smooth lobulate surface.

In addition to superficial IHs located on the dermis, there are deep IHs located subcutaneously that present as masses covered by normal skin, sometimes of a bluish colour that can be compressed by pressure. Mixed IHs also exist that are superficial and deep and that have the clinical characteristics associated with both types.

Regression is expressed clinically, with a lessening of the depth in colour of the superficial component until greyish areas appear, especially at the centre, tending to become more extensive with the gradual reduction of the subcutaneous mass that becomes less consistent, more flaccid and exhibits less expansion during increased intravascular pressure (e.g. crying).

At the end of the regression phase, the majority of cases exhibit permanent results such as telangiectasias, dilated superficial veins, epidermal atrophy and excess skin.

Complications

Ulceration and Bleeding

Ulceration and bleeding are the most common complications.

Ulceration occurs in 10–25 % of cases and is most frequent for IHs located in folds, the anogenital area and on the lips, especially the lower lip. In these areas an increase in local moisture and rubbing can favour the erosion of IHs, particularly mixed IHs – combined superficial and deep IHs. Moreover, ulceration occurs most frequently in IHs in the rapid proliferation stage with taut surfaces.

It may take months to heal these with constant intervention and scarring as the outcome.

While bleeding is frequent, in some 40 % of cases, this is usually mild and transitory, and it can be easily arrested simply by continuous compression for 3–4 min. Serious haemorrhage is very rare.

Secondary infection can occur and this is the main cause of painful conditions.

An ulcerated lip IH can hinder feeding and lead to poor oral intake.

Treatment includes local medication, oral antibiotics, pulsed dye laser treatment and, in some cases, also surgical excision. The best treatment is currently considered to be oral propranolol which has proven efficient at controlling the associated pain and promoting tissue repair in 2–6 weeks.

Functional Impairment

Visual obstruction must always be considered when an IH affects the eyelids, particularly the upper lid, or the periorbital area in general.

Periorbital haemangiomas are often the cause of secondary astigmatism due to alterations of

the corneal curvature. Less frequent are strabismus and visual axis obstruction which can result in amblyopia and permanent vision loss.

In all cases in which the periorbital area is affected, it is necessary to arrange an early visit to an oculist.

Therapy is indicated not only in cases of detected or suspected visual impairment but also in all situations considered at risk, and propranolol administered orally is currently considered the first-line treatment in such situations.

IH of the upper lip or intranasal area can hinder nasal breathing.

Even when IHs are only superficial, located on the lower third of the face and in the cervical and chin area, particularly if these are bilateral, they can be associated with IHs of the upper airway and may be suspected in cases of sleep apnoea, stridor or a hoarse cry.

The diagnosis can be confirmed by laryngoscopy or by MRI. However, even when there are no symptoms, all newborns with IHs located on the lower third of the face should be referred for an ENT consultation in order to make an accurate assessment of the airways.

In these cases, oral propranolol is also the first choice of treatment.

Multiple Cutaneous Haemangioma

In cases of multiple cutaneous haemangioma, with the presence of more than five, there is a risk of hepatic haemangioma, which must be assessed by way of abdominal ultrasonography. Hepatic haemangioma is usually asymptomatic and does not require therapy. However, if present, careful follow-up is recommended with serial ultrasounds to monitor its size.

In cases of ten or more haemangiomas (diffuse neonatal haemangiomatosis), not just the liver but all the visceral organs may be affected with life-threatening potential. The main cause of early mortality is congestive heart failure because of the reduction in the circulating haematic mass. In these cases a complete imaging study (MRI, ultrasonography) must be performed. Treatment involves the use of steroids in general, interferon alpha and, above all, propranolol.

Associated Malformations

Large segmental haemangioma of the face (>5 cm in diameter), mainly if this involves the frontal-temporal or mandibular areas, in approximately 30 % of cases, is associated with PHACE syndrome, an acronym denoting posterior fossa malformations, haemangiomas, arterial anomalies, cardiac anomalies, eye abnormalities and, rarely, sternal clefting or supraumbilical raphe. One or more of these extracutaneous congenital anomalies may be present. All patients with a large facial segmental haemangioma should be investigated with MRI and MRA of the head and neck, echocardiogram and ophthalmologic evaluation. Treatment with propranolol may be started but with extreme caution because of the documented risk of stroke and ischaemia in cases characterised by reduced arterial pressure. The recommended regimen is three daily doses, starting with the minimum then gradually increasing.

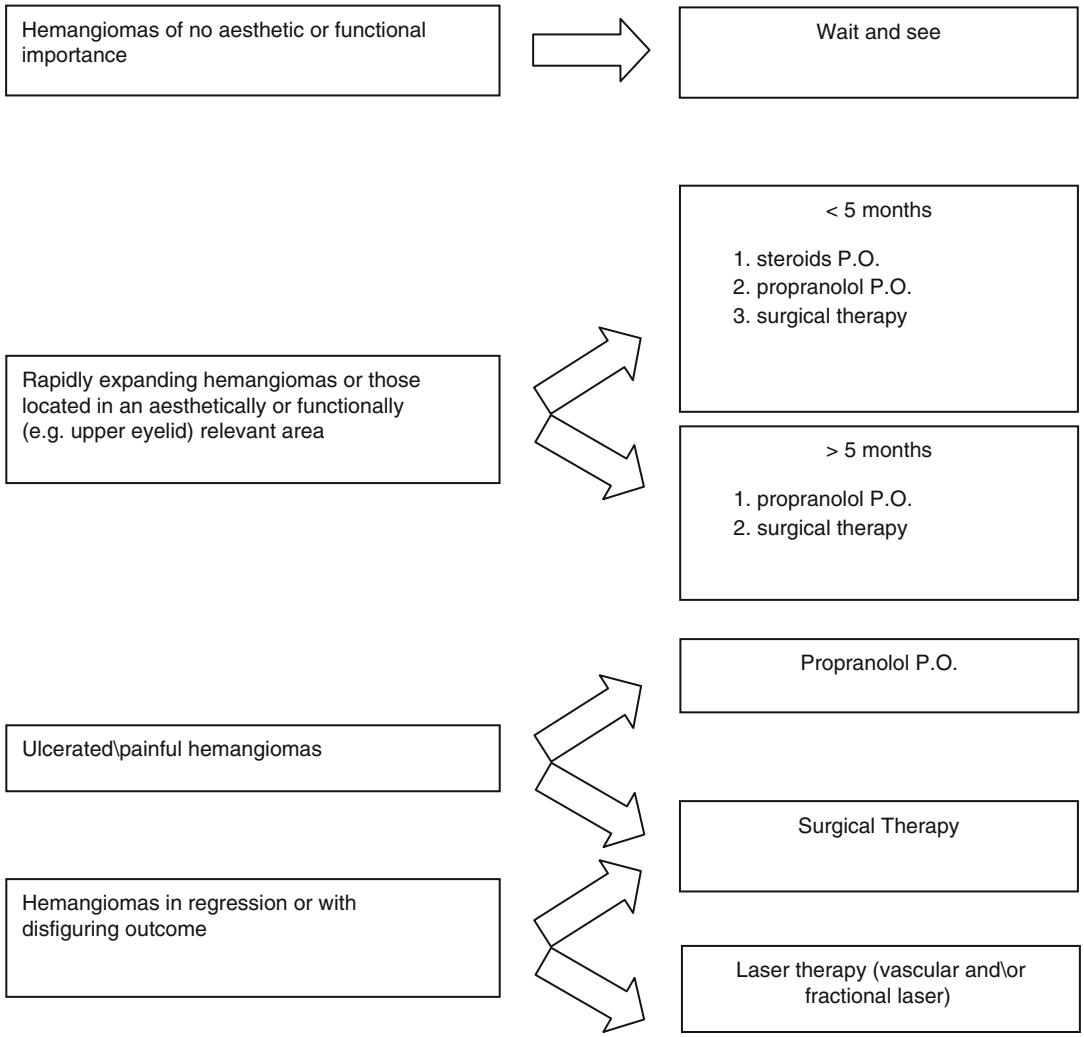
Large segmental IH involving lumbosacral or perineal regions may be associated with other underlying congenital anomalies as described in LUMBAR syndrome (lower body haemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, renal anomalies), PELVIS syndrome (perineal haemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, skin tag) and SACRAL syndrome (spinal dysraphism, anogenital, cutaneous, renal and urological anomalies, angioma of lumbosacral localisation). All these acronyms refer to the same group of malformations that can be associated in extremely variable ways.

In all cases without neurological symptoms, without clinical evidence of sinus or ulceration before the first 3 months of life, intervention may be limited to an ultrasound examination, delaying a spinal MRI with contrast.

General Principles of Treatment

Currently all authors are in agreement, maintaining that, in the majority of cases of haemangioma in which, depending on its location, size and

Table 103.3 Management of haemangioma: current treatment options in M. Bufalini Hospital, Cesena, Italy



stage of evolution, a good aesthetic outcome can be predicted at the end of the spontaneous involution stage, there are no indications for medical or surgical treatment. No treatment should be given, adopting a "wait and see" approach in all cases in which no functional impairments or disfigurements are present or predicted.

The major goals for IH management have recently been identified as minimising physiological and psychological distress, prevention of life-threatening complications or any complications that obstruct vital structures, such as the airway or visual pathway and treatment of such complications if they arise, in addition to prevention of disfigurement due to residual skin changes after the involution phase.

The initial decision is whether to treat with local or systemic therapy and the identification of patients who require surgical therapy. In general, local agents are best employed for small, superficial and localised haemangiomas, while systemic therapy is reserved for larger haemangiomas, those showing more aggressive growth and those carrying a high risk of functional impairment. Surgery is indicated for cases in which medical treatment has proven insufficient to produce the expected improvement in a short time, for example, painful ulcerated haemangioma, or haemangioma causing closed palpebral ptosis, and to correct unwanted results, generally at the end of the involution stage but sometimes before that if there is major psychological distress. See Table 103.3.

Topical Treatments

Several topical agents have been proposed for IH. Recent studies have supported the efficacy of timolol maleate 0.5 % gel-forming solution for treating small and superficial haemangiomas, demonstrating a reduction in redness and thickness within the first 2 weeks. Topical imiquimod cream may also be considered in early IH of the head and neck; possible complications to be considered include irritation, crusting and ulceration. Intralesional steroids maintain a useful role as a local treatment for select cases, particularly for early localised haemangiomas of the lip or nasal tip: triamcinolone is usually employed, and the doses should not exceed 1–2 mg/kg per injection.

Systemic Treatments

None of the pharmacological treatments in current use to combat the growth of haemangiomas or to encourage their regression have obtained official recognition and are therefore to be considered off-label.

Until recently oral corticosteroids were the mainstay of treatment for IH, but in the last few years, propranolol has dramatically changed the management of this pathology. It is now considered by most experts to be first-line therapy when systemic treatment is indicated.

Corticosteroids

The efficacy of steroids in the treatment of IH is extensively documented. Prednisone or prednisolone is usually administered at doses of 2–5 mg/kg/day as a single daily dose. Betamethasone can also be used at a dose of 0.10–0.30 mg/kg/day. They are effective in halting haemangioma growth during the proliferation phase. This therapy should be given either continuously or in cycles of 15–20 days alternating with a 7-day break until the end of the proliferation stage and then gradually decreasing. The possible side effects depend largely on the daily dose and duration of the treatment. These can include gastrointestinal upset and irritability, weight gain, a cushingoid appearance, hypertension, growth delay, adrenal suppression and immunosuppression by height. In doses of 2–3 mg/kg/day in a 15-day cycle, the side effects are generally reduced to easy irritability and insomnia. Moreover, it must not be forgotten that the normal vaccination programme should be changed, arranging for the vaccine to be administered no less than 15 days after the last cortisone treatment.

Propranolol

Propranolol is a non-cardioselective beta-blocker without any intrinsic sympathomimetic action. The efficacy of the treatment is almost constant and rapid, particularly in the proliferation stage, showing improvements within 2 months of the start of therapy. Because it is easy to witness renewed three-dimensional growth of the haemangioma when the therapy is suspended before the end of the proliferation stage, the current recommendation is to proceed with therapy until at least the end of the first year of life.

The action mechanism is not fully understood. However, the drug produces effects of vasoconstriction, inhibition of the renin-angiotensin system with consequent inhibition of the proliferation of immature endothelial cells, modulation of VEGF secretion with consequent blocking of endothelial proliferation and the induction of apoptosis.

Despite there not being a unanimously shared protocol, consensus guidelines from a multidisciplinary expert panel have recently proposed brief inpatient hospitalisation for monitoring during induction of the treatment, with initial dosing starting at 0.5 mg/kg/day divided into three daily doses, increasing slowly to the desired dose. The goal for oral propranolol dosing is 2–3 mg/kg/day divided into three doses. Side effects included sleep disturbance, cold hands and feet, hypotension, bradycardia and symptomatic hypoglycaemia. The medication should be administered after feeding to prevent hypoglycaemic episodes.

Other centres recommend a preliminary echocardiogram and an electrocardiogram, together with monitoring of cardiac frequency, arterial

pressure, respiratory frequency and glycaemia. Some experts recommend an initial dose of 1 mg/kg/day in two daily doses.

The contraindications are those already known for propranolol: asthma, bradycardia (<45 beats a minute), arterial hypotension, Raynaud phenomenon and a predisposition for hypoglycaemia.

Other therapies in sporadic cases are represented by interferon alpha and vincristine. These are medications that act very slowly and are haemotoxic and neurotoxic.

Laser Treatment

Laser treatment, mainly delivered by a flash lamp-pumped pulsed dye laser (PDL) 595 nm, is generally useful for haemangioma in the flat macular stage and for correcting telangiectatic effects at the end of the involution stage. It has also been proposed as a treatment for ulcerated haemangiomas, although orally administered propranolol is currently considered the most advantageous treatment.

An ablative fractional carbon dioxide laser has recently been used to improve anetodermal effects and scarring at the end of the involution stage (Fig. 103.2).

Surgical Excision

Surgical treatment of involuted haemangiomas is quite common because the natural evolution of the condition does not always produce satisfactory results. Indeed, cutaneous defects, such as

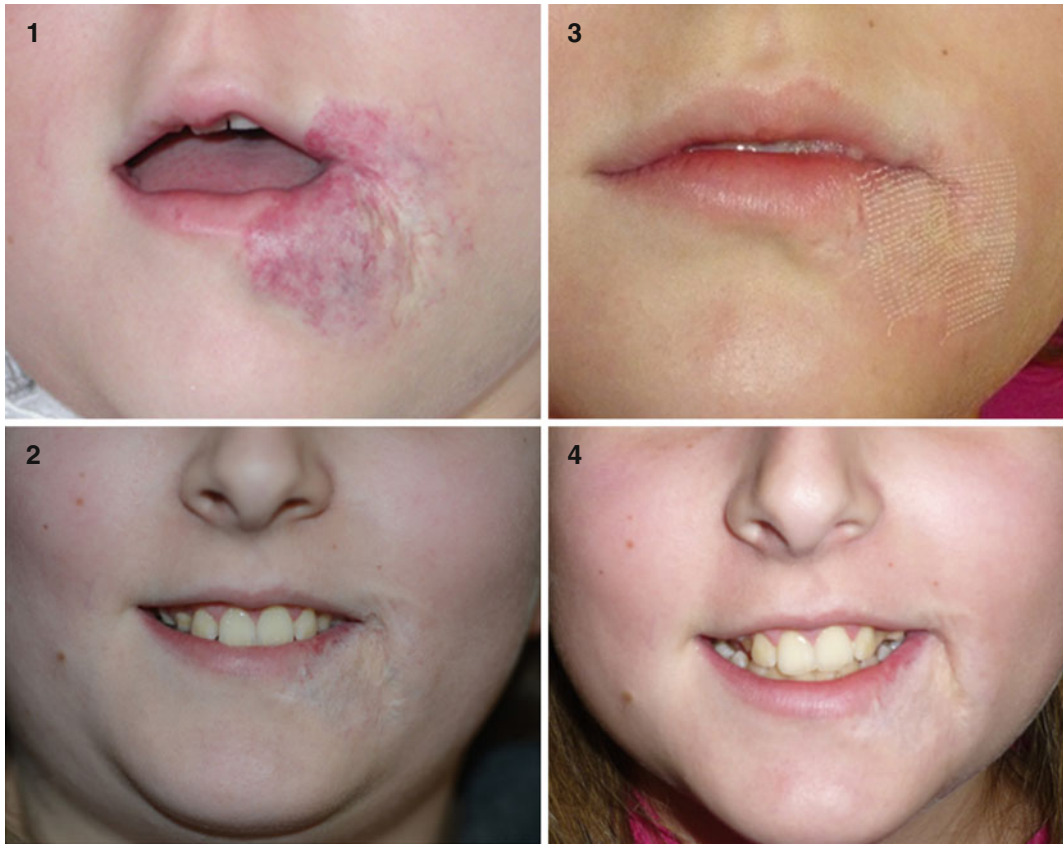


Fig. 103.2 Involuted haemangioma with atrophic skin and telangiectasias. Before treatment (*1*) after three sessions with 595 nm FPDL (*2*). Additional fractional CO2 laser treatment (*3*) with satisfactory final result (*4*)

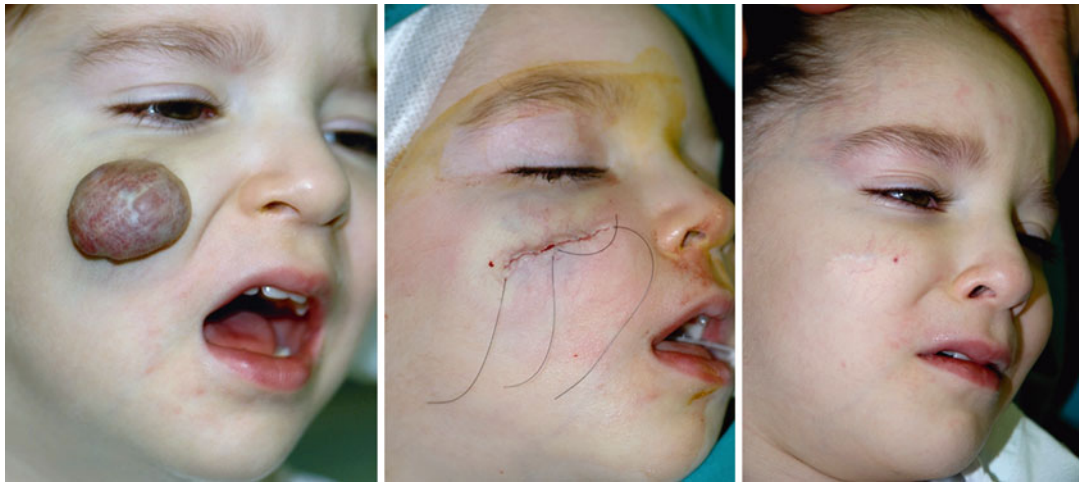


Fig. 103.3 Surgical treatment of disfiguring regressed haemangioma of the cheek

atrophic scarring, anetodermic and tumoral fibrofatty skin, often result at the end of the involution stage with significant cosmetic or functional impairment.

Surgical treatment is also suggested for ulcerated and painful haemangiomas, if medical treatment proves ineffective, for haemangiomas causing functional alterations, such as haemangiomas that cause palpebral ptosis with obstruction of the visual field and that have not responded to medical treatment.

In more general terms, surgical treatment should be considered, even before the end of the involution stage, in all cases in which it could bring improvements or prevent permanent effects with a major aesthetic impact. Because the presence of cosmetically disfiguring lesions in early childhood can have serious psychosocial repercussions, the state of the haemangioma should be assessed at the age of 3–4 for relevant permanent after-effects. In all cases in which it is reasonable to predict an unfavourable outcome, as, for example, large haemangiomas or those which have shown notable three-dimensional growth with stretching of the associated skin, the possibility of producing a better outcome with surgical treatment should be considered (Fig. 103.3).

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Vitiligo

104

Electra Nicolaidou, Andreas D. Katsambas, and Torello M. Lotti

Key Points

- Vitiligo is an acquired chronic disease characterized by circumscribed depigmented macules and patches that result from a progressive loss of functional melanocytes.
- Autoimmune processes, deficiency of melanocyte growth factor, enzymatic self-destruct mechanism and abnormal neurogenic stimulus leading to dermatomal melanocyte destruction have been postulated as possible pathogenetic factors.
- The course of vitiligo is unpredictable.
- At present, no entirely effective treatment is available.
- Cosmetic cover-up alone is quite acceptable to some patients with vitiligo.
- Topical corticosteroids and topical calcineurin inhibitors can be used alone or in combination in localized disease.
- Phototherapy is the treatment of choice in generalized disease.
- Narrowband UVB phototherapy has superseded psoralen plus UVA (PUVA) photochemotherapy in the treatment of vitiligo because it has been shown to be clinically more effective and it is characterized by a better side effect profile.
- Surgical treatment with autologous transplantation techniques may be an option for patients with limited and stable disease.
- Depigmentation should be considered when vitiligo patients have >80 % cutaneous involvement and are recalcitrant to repigmentation.

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Definition and Epidemiology

Vitiligo is an acquired chronic disease characterized by circumscribed depigmented macules and patches that result from a progressive loss of functional melanocytes.

It affects approximately 0.5–2 % of the general population and it occurs in all races and both sexes. Vitiligo onset during childhood (<12 years old) is common. Most studies report

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_104, © Springer-Verlag Berlin Heidelberg 2015

a disease onset before the age of 12 in about 25–30 % of patients.

In 20 % of vitiligo cases, a family history can be detected. Several studies indicate the importance of genetic factors in the development of vitiligo, which represents a heterogeneous genetic disease with environmental influences.

Basic Concepts of Pathogenesis

Vitiligo is a multifactorial disorder, characterized by selective destruction of the melanocytes in the depigmented patches.

Autoimmune processes (i.e. presence of circulating organ-specific autoantibodies, evidence of autoantibodies to normal human melanocytes, decrease of T-helper cells), deficiency of melanocyte growth factor, enzymatic self-destruct mechanism and abnormal neurogenic stimulus leading to dermatomal melanocyte destruction have been postulated as possible pathogenetic factors. It is likely that vitiligo vulgaris in humans represents a multitude of pathophysiological mechanisms, i.e. a variety of different diseases. A "convergence theory" in which different causal factors may act independently or synergistically to induce disappearance of melanocytes is a reasonable possibility. In some patients, vitiligo is associated with other diseases, mainly of autoimmune nature, like alopecia areata, thyroiditis, pernicious anaemia, diabetes and Addison's disease. Appropriate studies for these conditions are recommended when there is clinical suspicion.

Clinical Presentation

Lesions are round or oval macules, sharply demarcated and pure white. They are distributed, usually symmetrically, around orifices (lips, eyes, anogenital areas), over bony prominences such as the wrists, elbows and knees and in intertriginous areas. In affected areas, the hair usually is also white. Margins of the lesions may become hyperpigmented. At times, the pure white patches are surrounded by an area of the skin that is intermediate in colour before merging in the normal-coloured skin. This is known as trichome vitiligo and is mostly seen in black people. Vitiligo can be classified into two major clinical types, segmental and nonsegmental, according to the distribution of lesions.

The course of vitiligo is unpredictable. In some cases, the lesions remain stable over many years (mostly segmental vitiligo), but in others, they can enlarge in size while new patches appear to involve large portions of the skin surface (mostly nonsegmental type). However, spontaneous repigmentation may occur in 10–20 % of patients, mainly in sun-exposed areas. Repigmentation usually begins perifollicularly creating pigmented spots that gradually may enlarge and coalesce.

Diagnosis

Skin biopsy with special staining for melanocytes is the only significant examination but usually is not necessary. Histology reveals the absence of melanocytes which appear to be replaced by Langerhans cells in the lesions. A lymphomonocytic infiltrate is sometimes present in the marginal areas.

Differential Diagnosis

Wood's light examination should be part of the evaluation of every patient with vitiligo. It is most useful to differentiate the pure white appearance of the amelanotic vitiligo macules from the tan-white or grey-white colour of the relatively hypomelanotic disorders, presented in the table below:

Pityriasis alba	Fine scales on the lesions
Postinflammatory leucoderma	Irregular mottling of hyperpigmented and hypopigmented blotches
Tinea versicolor	Microbiology, Wood's lamp
Piebaldism	Hyperpigmented macules within the depigmented areas
Naevus depigmentosus	Present at birth, unilateral, stable

(continued)

Morphea	Speckled appearance, palpable induration, scleroatrophy
Hypomelanocytic leprosy	Anaesthetic macules
Chemical leucoderma	History of repeated exposure to phenols and sulphhydryls
Idiopathic guttate hypomelanosis	Numerous, small, white macules mainly distributed on the legs of dark-skinned individuals
Tuberous sclerosis	Congenital, dull to off-white confetti macules, seizures and mental retardation

General Principles of Treatment

- At present, no entirely effective treatment is available. Regardless of the treatment used, repigmentation may be slow and never be complete.
- Many patients will require only reassurance and advice on the use of the sunscreens and cosmetic camouflage. Active treatment is indicated in patients who have a marked cosmetic disability, particularly those whose lifestyle, self-esteem and productivity have been affected by the disease.
- New patches are possibly triggered by physical trauma (Koebner phenomenon), especially during spreading phases. It is recommended to avoid medical or surgical cosmetic procedures which can traumatize skin like deep peeling, lifting, etc.
- With the existing treatment methods, different results are obtained at different sites of involvement, i.e. vitiliginous patches over bony prominences respond poorly, while lesions on the face and body respond much better.
- If the involved site has no hair follicles, therapy usually fails because hair follicles seem to be necessary to supply new melanocytes.
- Treatment method should be chosen after consideration of the age of the patient, the areas involved and the extent of the disease.
- Spontaneous repigmentation occurs in about 10–20 % of patients and usually is only partial.
- Avoidance of the sun is highly recommended, especially in patients with widespread disease. Broad-spectrum sunscreens (SPF30 or greater) should be applied to all exposed skin, 30–60 min prior to sun exposure to decrease the short- and long-term effects of UV radiation and to reduce the contrast between the normal skin and the vitiliginous areas.

Recommended Therapies

(a) Cosmetic camouflage
(b) Repigmentation
(c) Depigmentation (extremely widespread disease – greater than 50 % of the body surface area)

Cosmetic Camouflage

Cosmetic cover-up is quite acceptable to some patients with vitiligo. Camouflage may be achieved with various cosmetics and stains containing mainly aniline dyes and dihydroxyacetone (DHA). "Quick Tan" preparations containing dihydroxyacetone (3–5 %) are produced by many cosmetic firms. DHA is a sugar that binds with the amino acids of the corneum layer inducing the production of coloured components that change from yellow to brown giving the skin a tanned effect. DHA dyes are easy to apply; they are neither dirty nor greasy. The pigmentation appears a few hours later and the application has to be repeated until the desired result is obtained. These dyes do not provide protection against UV radiation and phototherapy can be used. When cosmetics and make-up are used, the contribution of a professional cosmetician is of great help in demonstrating how to choose and apply the appropriate product.

Topical Treatments

Topical Corticosteroids

Topical corticosteroids (TC) are a first-line treatment for localized areas of vitiligo for both children and adults. A meta-analysis showed that half of patients with vitiligo affecting less than 20 % of body surface area achieved >75 % repigmentation with either super-potent or potent TC. Cutaneous atrophy was observed in 14 % and 2 % of patients, respectively. Other local side effects of TC include telangiectasia, hypertrichosis, acneiform eruptions and striae.

Newer potent TC such as mometasone furoate and methylprednisolone aceponate are largely devoid of these side effects and they also present negligible systemic side effects, so they should be preferred.

Currently, there are no studies available on the optimal schemes of TC treatment in vitiligo patients. Continuous treatment schemes can be used for up to 3 months, while discontinuous ones (15 days per month) may be used for up to 6 months. Facial lesions can be treated as effectively and with fewer side effects with calcineurin inhibitors. The latter can also be used in conjunction with TC for both facial and body lesions.

Topical Calcineurin Inhibitors

Tacrolimus and pimecrolimus are topical calcineurin inhibitors (TCI) that are useful in treating vitiligo patients because they have immunomodulatory effects without the side effects of TC.

Calcineurin is an intracellular protein which acts as a transcription factor for cytokines such as interleukin-2 and tumour necrosis factor-alpha (TNF-α). Tacrolimus and pimecrolimus, through inhibition of calcineurin, affect the activation/maturation of T cells and inhibit the production of cytokines, such as TNF-α. Patients with vitiligo have elevated TNF-α and tacrolimus treatment decreases tissue counts of TNF-α. Moreover, TCI enhance melanocyte migration and differentiation.

Tacrolimus and pimecrolimus are approved for patients with atopic dermatitis older than 2 years of age. Tacrolimus 0.03 % is approved for children 2–15 years of age. However, the off-label use of TCI has been shown to be safe and effective in the treatment of vitiligo, in both adults and children. Compared to TC, TCI provide similar to slightly inferior results. Tacrolimus provides similar to slightly higher response rates, compared to pimecrolimus. Face and neck lesions respond best. Twice-daily applications are recommended and occlusion may help with recalcitrant lesions on the extremities. If effective, prolonged treatment (e.g. longer than 12 months) may be proposed.

The combination of TCI and phototherapy or sun exposure is currently not recommended by the US Food and Drug Administration, to avoid a synergistic immunosuppressive effect. However, several studies have shown a synergistic effect between narrowband UVB phototherapy or 308-nm excimer laser and tacrolimus.

The most common side effects of TCI are local reactions, such as burning sensation, pruritus and erythema. Today, there is no evidence to suggest that there is an elevated risk of nonmelanoma skin cancer or lymphoma in adults or children under tacrolimus treatment.

Phototherapy

Ultraviolet (UV) radiation has been used extensively to treat patients with vitiligo. It is believed that UV has both immunosuppressive and melanocyte stimulatory effects.

UVB Phototherapy

1. Narrowband UVB Phototherapy

   Narrowband UVB (NB-UVB) radiation was used initially for the treatment of psoriasis, after the observation that wavelengths around 311 nm provoked less erythema and, at the same time, were most effective for complete clearance of psoriasis lesions. NB-UVB light sources emit polychromatic light, but the 311–313-nm wavelength range predominates in the emission spectrum.

   During the past decade, NB-UVB phototherapy has superseded psoralen plus UVA (PUVA) photochemotherapy in the treatment of vitiligo because it has been shown to be clinically more effective and it is characterized by a better side effect profile.

There is no universally accepted protocol for NB-UVB, so treatment protocols differ from study to study. Sessions are performed twice or thrice weekly, on nonconsecutive days. The initial dose ranges from 100 to 280 mJ/cm^2. The dose is subsequently increased in most studies by 10–20 % per session. In many studies, the dose is held constant when mild erythema develops. Generally, after the first few sessions, the rate of increase is individualized for each patient.

Overall response of vitiligo to NB-UVB has been variable. More than 75 % repigmentation (which is considered cosmetically acceptable repigmentation) has been achieved by 12.5–75 % of treated patients in different studies, after approximately 1 year of treatment (Fig. 104.1). Facial lesions and patients with skin phototype III–V respond better to treatment. Treatment is usually continued as long as there is ongoing repigmentation or over a maximum period of 1–2 years.

Combination of NB-UVB with topical corticosteroids may provide better results. Potent topical steroids could be applied once daily for 3 weeks per month for the first 3 months of treatment.

Acute adverse effects during NB-UVB are not frequent, include only erythema, pruritus and xerosis and usually resolve after topical applications of emollients. Chronic adverse effects of NB-UVB include photo-ageing and photocarcinogenesis. NB-UVB has been shown to induce DNA damage in cell cultures, as well as in human skin and animal models, a mechanism that leads to carcinogenesis. However, a recent study did not provide evidence for an increased skin cancer risk in psoriasis patients treated with either broad-band or NB-UVB. In another study, no increased risk for melanomas or squamous cell carcinomas was detected in patients receiving NB-UVB for diseases other than vitiligo, but an increased risk was evident for basal cell carcinomas. No data are available so far regarding carcinogenesis in vitiligo patients treated with NB-UVB, but since the development of skin cancer in vitiligo patients seems to be rare, it is rational to expect that vitiligo patients will not have an increased risk compared to other patients receiving NB-UVB. Until more data are available, NB-UVB is considered less carcinogenic than PUVA, but still it should be used cautiously and patients receiving long-term therapy should be followed up regularly.

2. Narrowband UVB Focused Microphototherapy
It is possible to treat exclusively vitiligo patches avoiding normally tanned skin especially in children and if the surface affected does not exceed 20 % of the total body surface. A phototherapy device (BIOSKIN®) allows selective narrowband UVB (311-nm) treatment limited to the white patches. The main characteristics of the BIOSKIN® generator are that it produces UVB rays, in a spectrum of 300–320 nm, with maximum emission at 311 nm; the energy displayed by the UVB generator is 10–100 mJ/

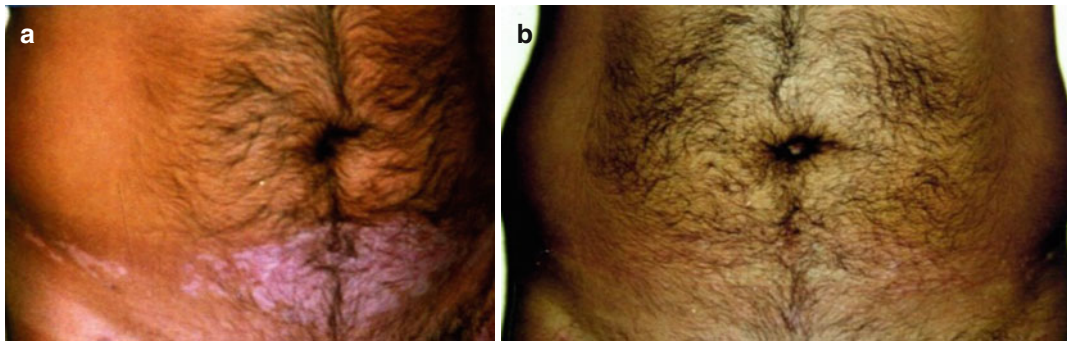

Fig. 104.1 Vitiligo lesions on the abdomen before (**a**) and after 8 months treatment with narrowband UVB phototherapy (**b**)

cm²/s and the diameter of the light spot is 1 cm. This device has been particularly efficient in the treatment of limited affected areas and segmental vitiligo. This technique has several advantages: it does not increase the colour contrast between normally pigmented skin and affected skin, and the total irradiation dose is minimal depending on the percentage of body surface affected. The method consists of weekly sessions of irradiation of all vitiligo patches. The dose is 20 % lower than MED, which is measured before the beginning of the treatment. This phototherapy treatment permits a differentiated irradiation. Thus, it is possible to irradiate the hands and feet with a dose five or six times higher than the dose used for eyelids.

UVA Photochemotherapy

1. Topical UVA Photochemotherapy
   Topical psoralen photochemotherapy may be considered for patients with limited involvement (less than 20 % of the body surface) or localized disease. It can be used to treat both children over 2 years old and adults. Dilutions of 1 % 8-methoxypsoralen are made with alcohol or lotions for final concentrations of 0.01–0.1 % in order to minimize adverse phototoxic reactions. The preparation is applied to the vitiliginous areas 30 min prior to exposure to UVA. The initial UVA dose is 0.12 or 0.25 J/cm² and is increased by increments of 0.12 or 0.25 J/cm² weekly according to the patient's skin type. After a moderate asymptomatic erythema is achieved, the UVA and psoralen dosage should be maintained at a constant level to retain the minimal degree of erythema. Treated areas should be washed with soap and covered with broad-spectrum sunscreen before the patient leaves the physician's office. Treatments are given once or twice per week. The psoralen should be applied by hospital or medical personnel and not by the patient. For 6–8 h after the treatment, unnecessary exposure to sunlight must be avoided because of the high potential of developing severe phototoxic reactions. Hyperpigmentation may develop in perilesional normal skin during treatment; this is a temporary phenomenon that resolves after the treatment stops.

   The major side effects of topical photochemotherapy are a severe phototoxic reaction and blistering, and patients should be warned of this before the treatment begins. If erythema and blistering develop, treatments are stopped until the reaction subsides. Upon reinstitution of therapy, the UVA exposure is usually decreased to half the previous dosage.

   Topical PUVA cannot be considered a first choice treatment for any type of vitiligo. However, topical PUVA is preferable to oral PUVA in patients with hepatic and gastrointestinal (uncertain absorption) disorders, cataract, poor eye protection and poor compliance and when shorter irradiation times are necessary (children and claustrophobic individuals).
2. Oral UVA Photochemotherapy
   Oral photochemotherapy is currently used in adult patients with generalized vitiligo as a second-line therapy, after NB-UVB.

   Contraindications for oral photochemotherapy include abnormal liver function, ocular defects including cataracts and pregnancy. In addition, the presence of photosensitivity disorders contraindicates the use of both oral and topical PUVA. Oral psoralens are not usually recommended for children under 12 years of age. Before therapy is begun, the following tests are required:

   Blood count
   Erythrocyte sedimentation rate
   Antinuclear antibodies
   Liver function tests
   A baseline ophthalmologic examination

   All these examinations should be repeated yearly. The maximum recommended 8-methoxysporalen dose is 0.6 mg/kg. It should be taken orally 2 h before UVA exposure. Patients may occasionally experience some gastrointestinal irritation (nausea, vomiting, abdominal pain) with psoralen, which becomes less frequent when the drug is taken after food. An initial dose of 1–2 J/cm² is generally given, with subsequent increments of 1 J/cm² at every other visit until moderate asymptomatic erythema is observed. The dose of UVA must be adjusted, depending on the sensitivity of the individual patient. Treatments

are given twice weekly but never on 2 consecutive days.

Protective UVA glasses should be worn for 24 h after oral psoralen intake. As a UVA source, PUVA cabinets are usually used (320–400-nm-emitting fluorescent tubes).

If the patient is unable to come to the physician's office for treatment, trioxysalen (4,5,8-trimethylpsoralen), in a dose of 0.6 mg/kg, and sunlight are suggested. An initial sun exposure of 5 min is recommended. The best time for sun exposure is from 10 a.m. to 2 p.m. Subsequent exposures are increased in increments of 5 min with each treatment until a mild erythema is attained, after which the exposure times are held constant until an increase is necessary to maintain the erythema. Treatments are given three times weekly but not on 2 consecutive days.

Trioxysalen is less phototoxic than 8-methoxypsoralen and less effective as a repigmenting agent. Patients should apply broad-spectrum sunscreens to the treated areas immediately after the treatment and limit further sun and UVA exposure.

PUVA-induced repigmentation is permanent in the majority of patients, but some may require maintenance treatment. Psoralen photochemotherapy induces maximal repigmentation of the face and neck; intermediate responses on the trunk, arms and legs; and minimal responses on the hands and feet. Treatment should be continued for at least 6 months to a year before the patient is classified as recalcitrant. Often as many as 200–300 treatments are required to produce a uniform repigmentation of the vitiliginous areas.

PUVA photochemotherapy carries a slightly elevated risk for both nonmelanoma skin cancer and melanoma. Long-term treatment may induce xerosis, "PUVA lentigines" and premature photo-ageing. The maximum recommended lifetime exposure to PUVA should be limited to 1,000 J/cm^2.

Laser Therapy

The best studied and most used laser therapy for vitiligo is the xenon chloride monochromatic excimer laser, which emits a monochromatic light of 308 nm and induces photobiological effects similar to NB-UVB. Several studies have shown response of vitiligo patches to excimer laser and it has been approved by the US Food and Drug Administration for the treatment of both vitiligo and psoriasis. Sessions are performed 2–3 times a week for a period of 4–36 weeks.

Compared to NB-UVB phototherapy, excimer laser has been reported to have better clinical outcomes. Repigmentation greater than 75 % is usually reported for 15–50 % of treated lesions. Location of lesions seems to be the best predictor of response: lesions on the face, neck and trunk respond in a better way than lesions on extremities. Lesions on the hands and feet tend to have the least favourable prognosis. Combination of laser treatment with either topical hydrocortisone or topical tacrolimus provides better results than laser treatment alone.

The sessions are generally well tolerated and side effects are minimal. Mild to severe erythema is usually reported, while blisters and pruritus are observed occasionally. Excimer laser permits the selective treatment of only lesional skin and ensures no unnecessary treatment of healthy skin. Thus, the patient receives less radiation. Furthermore, the unsightly tanning of all perilesional skin is avoided and perilesional tanning is usually limited to small areas around the lesion that have received the laser pulse during treatment. On the other hand, this selectivity makes the treatment of extensive vitiligo very time consuming and may not prevent the occurrence of new lesions at untreated body sites. Finally, another drawback of laser treatment, compared to NB-UVB, is its high cost.

Systemic Treatments

Systemic Corticosteroids

The use of systemic corticosteroids for therapy of vitiligo is useful, considering the relationship between benefits and side effects, mainly for the treatment of active, rapidly progressive generalized disease. In these patients, oral mini-pulse therapy with betamethasone or dexamethasone in a dose of 2.5–7.5 mg for 2 consecutive days per week for up to 6 months has shown the ability to

arrest the progression of the disease and to induce repigmentation. Oral mini-pulse steroid therapy can also be used as an adjunct to phototherapy in the first months of treatment.

Surgery

Surgical treatment with autologous transplantation techniques may be an option for patients that fulfil the following criteria:

(a) Stable disease for at least 6 months
(b) Unsatisfactory response to medical treatment
(c) Absence of Koebner phenomenon
(d) No tendency for scar formation
(e) Age above 12 years

Melanocyte transplantation techniques include punch grafts, split-thickness skin grafts, suction blister grafts and autologous melanocyte suspension transplants. Surgical techniques can be combined with phototherapy for best results.

Adverse outcomes include scarring, graft failure, infection, cobblestone texture and variegated pigmentation.

Depigmentation

Depigmentation should be considered when vitiligo patients have >80 % cutaneous involvement and are recalcitrant to repigmentation. The process is permanent and irreversible, and the patient will be permanently photosensitive. For these reasons this form of therapy should be considered for patients over 40 years old who have had an adequate trial of phototherapy and have failed or are unwilling to undergo repigmentation therapy. The dermatologist must feel confident that complete depigmentation will be not only cosmetically satisfactory but also psychologically acceptable, especially in black patients:

- *Monobenzyl ether of hydroquinone* (MBEHQ) is used as a depigmenting agent (Fig. 104.2). It destroys melanocytes. The treatment starts with 10 % concentration of MBEHQ by diluting the full-strength preparation with any water-soluble vehicle. The preparation is then applied to the pigmented areas twice daily. The concentration is increased by 5 % every 1 or 2 months until the patient is using 20 % MBEHQ.

  Patients should be advised that effective treatment may require several months to 1–2 years of therapy. The major side effect of MBEHQ therapy is dermatitis, which usually responds rapidly to topical applications of steroids. Other common side effects include contact dermatitis, pruritus, xerosis, greying of the hair and, following application to periocular skin, conjunctival melanosis and corneal pigment deposition.
- *Laser depigmentation.* The Q-switched ruby laser (694 nm) is capable of destroying selectively melanin and melanocytes. The

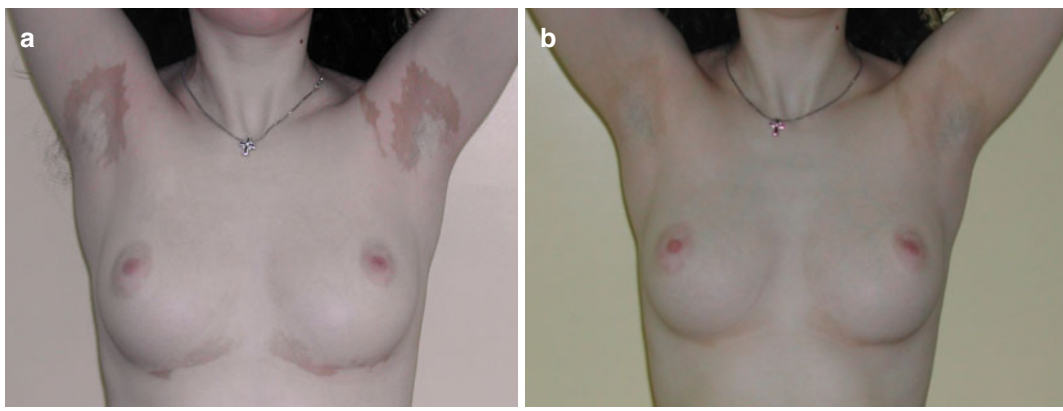

Fig. 104.2 Generalized vitiligo with a few islands of normally pigmented skin before (**a**) and after 6 months depigmentation treatment with 20 % monobenzyl ether of hydroquinone (**b**)

established method consists of a previous test session to evaluate the safety and efficacy of this technique on the patient. The response to this test is evaluated 2 months after the test, and if there is no response, laser depigmentation should be discouraged.

If the depigmentation test has caused significant depigmentation, the treatment can be continued until the desired bleaching effect has been achieved. This technique is safe (no drug is required). The contraindications are the same as those for depigmentation with bleaching agents.

Alternative and Experimental Treatments

L-Phenylalanine

When taken orally (1–3 g/day for 12–36 weeks) and followed by UVA irradiation, it is a promising agent for the treatment of childhood vitiligo.

Topical Khellin

Khellin is a furanochromone chemically related to psoralens. Khellin has been used in combination with sunlight or in combination with UVA (KUVA). Khellin can be administered either topically (2 % solution in 90 % acetone and 10 % propylene glycol) or systematically (100 mg) followed by UVA irradiation 1–2 h later, three times a week. The results are variable. Regular monitoring of liver enzymes should be performed and the treatment should be stopped if liver enzyme levels increase.

Pseudocatalase

Due to the report that patients with vitiligo have very low catalase activity, a group of investigators applied a vehicle with pseudocatalase twice daily, followed by a twice-weekly total body suberythema UVB irradiation. Excellent repigmentation was noted in 90 % of patients after almost 15 months. However, subsequent studies and especially a randomized, double-blind, placebo controlled clinical trial failed to show any benefit in adding pseudocatalase to NB-UVB treatment.

Melagenina

Melagenina is an alcoholic extract of human placenta. The active ingredient is an α-lipoprotein of low molecular weight. Melagenina is applied topically three times a day. One of the daily applications is followed by a 15-min solar or infrared exposure. The results are rather conflicting and the use of melagenina still remains experimental until random double-blind studies are done for both efficacy and safety.

Traditional Chinese Medication

Although some Chinese physicians believe that the administration of some Chinese medicinal herbs may be beneficial for vitiligo, lack of scientific data renders these treatments experimental.

Permanent Tattooing

Permanent dermal micropigmentation using a nonallergic iron oxide pigment can permanently tattoo recalcitrant areas of vitiligo (i.e. the hands, perioral region and hairline).

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Vulvar Diseases

105

Silvestrs Rubins, Ilze Viberga, and Andris Rubins

Key Points

- The vulva is a gynecologic organ with dermatologic anatomy. The spectrum of potential vulvar diseases is large, although only few of them are uniquely vulvar.
- Vulvar infections are the most common, while vulvar cancer is very rare.
- There is no uniform classification of vulvar disease. Vulvar dermatoses are grouped according to the principles of willanism. The vulva is also an important signaling organ of endocrine and genetic pathology.
- Diagnostic and therapeutic arsenal is large. Nevertheless only few drugs are marketed as vulvar or for vulvar conditions.
- New achievements in microbiology, pharmacology, molecular biology, and oncology can improve the prognosis and quality of life in many vulvar diseases substantially.

Abbreviations

ACT	Adoptive cell transfer
AJCC	American Joint Committee on Cancer (2009 Melanoma Staging and Classification)
CAH	Congenital adrenal hyperplasia
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
ELPV	Erosive lichen planus of the vulva
FGM	Female genital mutilation
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GUD	Genital ulcer disease
HPV	Human papillomavirus
HVLNE	Hemivulvectomy with superficial inguinal lymphadenectomy
ISSVD	International Society for the Study of Vulvovaginal Disease
LGV	Lymphogranuloma venereum
LS	Lichen sclerosus
LSC	Lichen simplex chronicus
PCR	Polymerase chain reaction
PSA	Prostate-specific antigen
RVLNE	Radical vulvectomy with inguinofemoral lymphadenectomy
SCC	Squamous cell carcinoma
SJS	Stevens-Johnson's syndrome
STI	Sexually transmitted infection
SLN	Sentinel lymph nodes
TIL	Tumor-infiltrating lymphocytes
VIN	Vulvar intraepithelial neoplasia

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_105, © Springer-Verlag Berlin Heidelberg 2015

VLP Vulvar lichen planus
VVS Vulvo-vestibulitis syndrome
WLE Wide local excision

Definition

The vulva is the female external genitalia and includes the mons pubis, labia majora, labia minora, clitoris, vestibulum, and vestibular glands. Arterial blood to the vulva is provided by the internal pudendal artery and venous return by pudendal veins. Vulvar lymphatics drain to inguinal and femoral nodes. Lymph from the midline vulva drains bilaterally. Innervation of vulva are performed by three nerves: ilioinguinal, posterior femoral cutaneous, and pudendal. The vulva lies in close proximity to the lower abdomen, inguinal and perianal regions, vagina, urethra, and anus. The microbial diversity and load of the vulvar area are much higher than in other parts of the skin. A papillary dermis is absent in the clitoris and labia minora.

Clinical Presentation

Vulvar Ulcers

Genital ulcer disease (GUD) is a general term used to describe genital ulcers in both sexes. Vulvar ulcers may have multiple causes (Table 105.1). Syphilis ulcer is typically a single, not painful, infiltrated lesion accompanied by unilateral inguinal lymphadenopathy. Herpetic ulcers are numerous, painful erosions or ulcers covered with whitish film accompanied with inguinal lymphadenopathy. Vulvar involvement can occur also in herpes zoster and varicella. Ulcus molle has a painful, purulent ulcer and purulent inguinal lymphadenopathy. In donovanosis or granuloma inguinale, multiple granulomatous ulcers and inguinal mass or pseudobubo are observed. Lymphogranuloma venereum (LGV) develops in three phases: from papule to ulcer, then to red and swollen inguinal lymph nodes, and finally to genital elephantiasis. Tuberculosis can also present itself with vulvar ulcers and mimic sexually transmitted infection (STI). In vulvar diphtheria, ulcers are covered with a pseudomembrane and there are additional nasopharyngeal and systemic signs. Primary cytomegalovirus (CMV) infection can cause acute, painful vulvar ulcers.

In Behçet's disease, painful genital ulcers can be one of the diagnostic symptoms in addition to other extragenital signs, e.g., oral ulcers, uveitis, positive pathergy test, and skin lesions. Ulcus vulvae acutum or Lipschütz ulcer is a rare, purulent, necrotic vulvar ulcer which most often develops together with flu-like illness in prepubertal girls. The etiology of Lipschütz ulcer is not known but possibly involves Epstein-Barr virus (EBV), CMV, mumps virus, and influenza A infection. Mycoplasma pneumonia can be associated with acute, extensive, painful, destructive vulvar ulcers in adult women. Ulcerative vulvitis in Reiter's syndrome is another rare form of vulvar ulcers with additional signs of conjunctivitis, arthritis, and psoriasiform skin lesions. Crohn's disease can involve the vulva and cause deep ulcers and formation of fistulas. Pyoderma gangrenosum very rarely involves the vulva and typically has painful, necrotic ulcers. Invasive vulvar cancer and other vulvar neoplasias can cause ulcers. Idiopathic vulvar ulcers can be HIV/AIDS associated. Other miscellaneous causes of vulvar ulcers include opportunistic infections, radiation, drugs, postsurgical wounds, chemicals, biologic substances, and mixed infections.

Diagnosis of vulvar ulcers is based on clinical appearance, symptoms, and laboratory methods such as microscopy, culture, polymerase chain reaction (PCR), and biopsy. Treatment follows established guidelines in known cases. Ulcers of unknown etiology are managed by local corticosteroids, peroral antibiotics, and immunosuppressive drugs.

Vulvitis and Vestibulitis

Vulvitis, vestibulitis, or vulvo-vestibulitis is an inflammation of the outer female genitals, presenting as redness, itching, burning, pain, and dyspareunia. Vulvitis is rarely isolated but

Table 105.1 Diagnosis and management of infectious vulvar ulcers and vulvitides

Pathology	Etiology	Diagnostic tests	Treatment
Syphilis ulcer	*Treponema pallidum pallidum*	Dark-field microscopy	Benzathine penicillin G 2.4 MU IM single injection (for primary syphilis)
		PCR	Alternatives: tetracycline, doxycycline, erythromycin (all PO)
Herpes ulcer	*Herpes simplex virus 1, 2*	Serology – HSV 1 and HSV 2 IgM Immunofluorescence PCR	Famciclovir – 125–1,000 mg PO 2–3× daily, 1–7 days Valaciclovir – 500–1,000 mg PO 2–3× daily, 3–7 days
Candida vulvitis	*Candida albicans ~90%* *Candida glabrata – 2–10%* *Candida krusei – 1–3%*	KOH microscopy, culture, PCR	Systemic treatment for acute infection: Fluconazole 150 mg PO single dose Itraconazole 200 mg PO 2× daily, 3 days Ketoconazole 400 mg PO 2× daily, 3 days (For local treatment, please see Table 105.6)
Streptococcal ulcer/ vulvitis	Group A beta-hemolytic streptococcus Group B streptococcus	Microscopy, culture	Penicillin V 500 mg PO 3× daily, 14 days Erythromycin 500 mg PO 3× daily, 14 days (For local treatment, please see Table 105.6)
Donovanosis	*Klebsiella granulomatis*	Microscopy, Giemsa stain, Donovan bodies Culture PCR	Azithromycin 1 g PO 1× weekly, 3–4 weeks Erythromycin 500 mg PO 4× daily, 21 days Ofloxacin 200 mg 2× a day PO for 21 days Ciprofloxacin 500 mg PO 2× daily, 21 days
Lymphogranuloma venereum	*Chlamydia trachomatis*, serovars L1, L2, L2a, L3	PCR, culture	Doxycycline 100 mg 2× day PO for 21 days Erythromycin 500 mg 4× a day PO for 21 days Azithromycin 1 g 1× a week PO for 3 weeks
Ulcus molle	*Haemophilus ducreyi*	Gram-stain microscopy, culture, PCR	First choice: Azithromycin 1 g PO single dose Ceftriaxone 250 mg i.m. single injection Alternative: Ciprofloxacin 500 mg 2× day PO for 3 days Erythromycin 2 g per day PO for 7 days

Fig. 105.1 (**a**) Erosive papules and condylomata lata on labia majora and edema indurativum and erosions of labia minora; secondary syphilis. (**b**) Condylomata lata on labia majora and minora; secondary syphilis. (**c**) Condylomata lata on labia majora and perineum; secondary syphilis

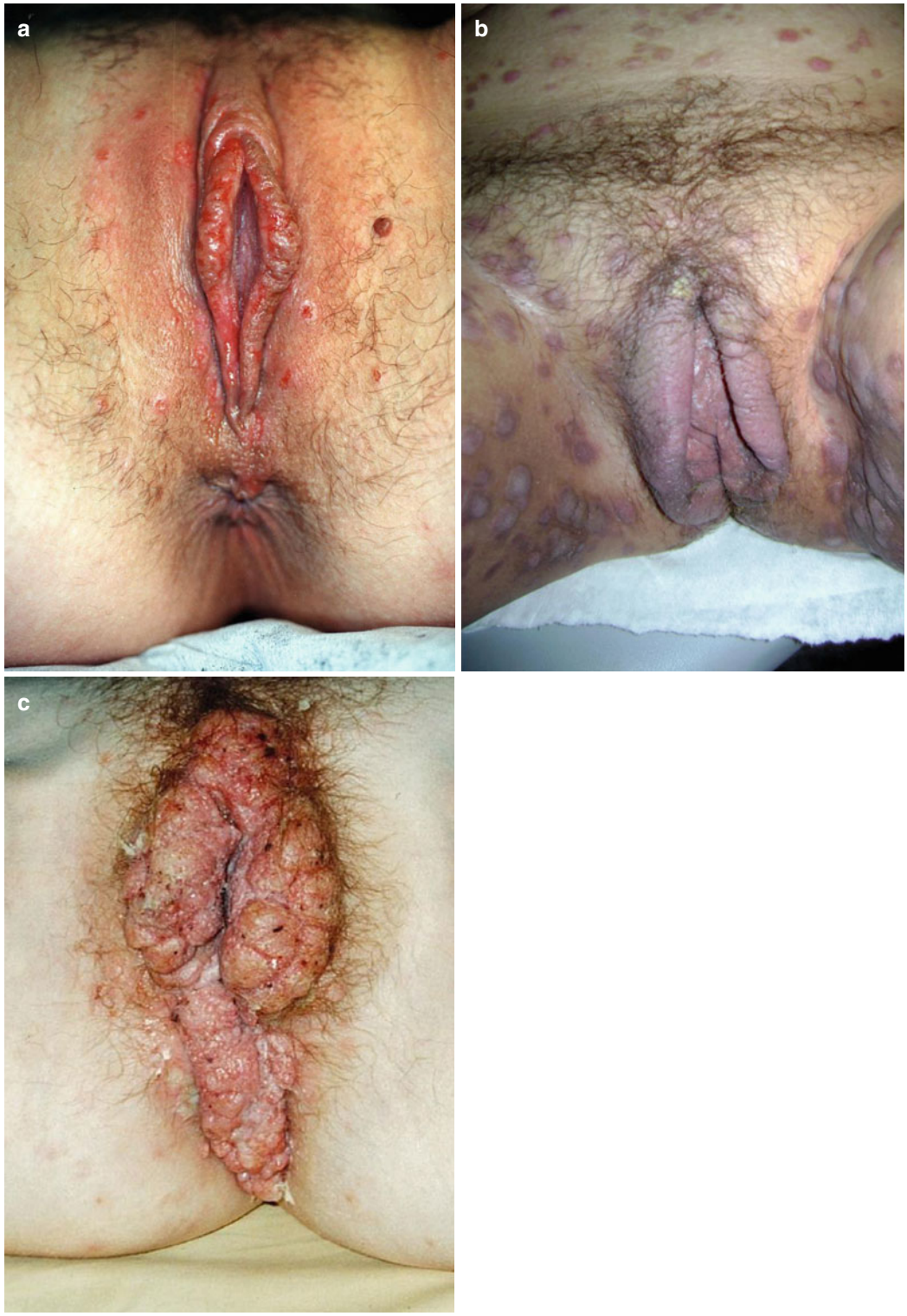

Fig. 105.2 (**a**) Erosive papules on labia majora and minora; secondary syphilis. (**b**) Condylomata lata, secondary syphilis. (**c**) Condylomata acuminata, HPV infection

usually develops secondary to a vaginal process (vulvovaginitis) inguinal or perianal pathology. Candida vulvitis or vulvovaginitis is the most common type of infectious vulvitis. Predisposing factors are numerous: asymptomatic carriage, peroral antibiotic use, contraceptives, diabetes, and HIV/AIDS. Treatment is with either local or systemic antifungals; both of them are equally effective. Streptococcal vulvitis or vulvovaginitis due to group A β-hemolytic streptococcus is more often seen in prepubertal girls than adult women, often recurrent, and usually associated with nasopharyngeal or gastrointestinal carriage of bacteria. The treatment is antibacterial. Vulvitis circumscripta plasmacellularis or Zoon's vulvitis is a disease of unknown etiology characterized by shiny, red-brown macules on the labia. Treatment options include high-potency topical corticosteroids, topical calcineurin inhibitors, 5 % imiquimod cream, cryotherapy, intralesional injections of triamcinolone, or interferon alpha. Postcoital or seminal vulvitis occurs after unprotected intercourse as either localized vulvar urticaria, vulvar angioedema or generalized urticaria, or facial angioedema. A pathogenic mechanism is type I hypersensitivity reaction possibly caused by prostate-specific antigen (PSA). Acute and subacute vulvar eczema (allergic or irritant), manifests itself clinically as vulvitis. Inguinal erythrasma, intertrigo, and tinea inguinalis can spread from the inguinal region to the labia majora to cause vulvitis. Vulvar psoriasis can have a chronic, symmetrical vulvitis without vaginitis. Diagnosis and treatment of primary cause improves or cures vulvitis. For idiopathic cases topical corticosteroids or calcineurin inhibitors are commonly used.

Vulvar Dermatoses

According to the ISSVD (International Society for the Study of Vulvovaginal Disease) 2011 classification, all vulvar dermatoses are divided into eight main groups (with further subdivision) (Table 105.2): (1) skin-colored lesions; (2) red lesions, patches and plaques; (3) red lesions, papules and nodules; (4) white lesions; (5) dark-colored lesions; (6) blisters; (7) erosions and ulcers; and (8) edema. Histologically the ISSVD recognizes eight patterns of pathological reactions in the vulva: spongiotic, acanthotic, lichenoid, sclerotic, vesiculobullous, acantholytic, granulomatous, and vasculopathic.

Dermatoses which can be seen in the vulva (besides the already mentioned ulcers and vulvites) are numerous: different erythemas, intertrigo, erysipelas, vitiligo, pityriasis versicolor, lichen planus, lichen simplex chronicus, vulvar lentigo, melanoma, psoriasis inversa, condylomata acuminata, Bowenoid papulosis, squamous cell carcinoma, basal cell carcinoma, condylomata lata, molluscum contagiosum, Fox-Fordyce diseases, seborrheic dermatitis, scabies, pubic lice, seborrheic keratosis, furuncle, acne inversa, epidermoid cyst, vulvar polyp, herpes simplex, herpes zoster, varicella, lupus erythematosus, pemphigus vulgaris, bullous pemphigoid, Hailey-Hailey disease, Darier's disease, and Stevens-Johnson's syndrome (SJS). Vulvar involvement can occur in pathologies of other organs and systems, e.g., diabetes (candida vulvitis), Crohn's diseases (ulcers, vulvitis, edema), and HIV/AIDS (secondary ulcers, vulvitis, tumors). Drug eruptions in the vulva most commonly present as fixed drug eruption (erythema fixatum), erythema multiforme, and SJS. Bullous and acantholytic diseases such as pemphigus vulgaris vegetans, Hailey-Hailey disease, and Darier's disease can also involve vulva. Diagnostic principles and treatments used in vulvar dermatoses are similar to other parts of the body.

Pathologies of Vulvar Glands

Bartholin's gland is located in the lower third of the vulva. Its main purpose is to lubricate the labial opening of the vagina. Bartholin's gland pathologies are obstruction of the duct, inflammation, cyst, abscess, benign tumors (nodular hyperplasia, adenoma, adenomyoma), and adenocarcinoma.

Bartholin's gland cyst and abscess is an interlabial mass or two bilateral lesions. Bartholin's gland abscess is typically caused by *E. coli*, *Bacteroides*, and *Prevotella* species, as well as

Table 105.2 ISSVD 2011 classification of vulvar dermatological disorders

1. Skin-colored lesions	(a) *Skin-colored papules and nodules* – papillomatosis of the vestibule and medial labia minora (a normal finding; not a disease), molluscum contagiosum, warts (HPV infection), scar, vulvar intraepithelial neoplasia (VIN), skin tag (acrochordon, fibroepithelial polyp), nevus (intradermal type), mucinous cysts of the vestibule and medial labia minora, epidermal cysts, mammary-like gland tumor (hidradenoma papilliferum), Bartholin's gland cyst and tumor, syringoma, basal cell carcinoma
	(b) *Skin-colored plaques* – lichen simplex chronicus and other lichenified diseases, vulvar intraepithelial neoplasia
2. Red lesions: patches and plaques	(a) *Eczematous and lichenified diseases* – allergic contact dermatitis, irritant contact dermatitis, atopic dermatitis (Fig. 105.3b), eczematous changes superimposed on other vulvar disorders, diseases clinically mimicking eczematous disease, lichen simplex chronicus, lichenification superimposed on an underlying preceding pruritic disease
	(b) *Red patches and plaques* (no epithelial disruption) – candidiasis, psoriasis, vulvar intraepithelial neoplasia, lichen planus, plasma cell (Zoon's) vulvitis, bacterial soft tissue infection (cellulitis and early necrotizing fasciitis), extramammary Paget's disease
3. Red lesions: papules and nodules	(a) *Red papules* – folliculitis, wart (HPV infection), angiokeratoma, molluscum contagiosum (inflamed), hidradenitis suppurativa (early lesions), Hailey-Hailey disease
	(b) *Red nodules* – furuncles, wart (HPV infection), prurigo nodularis, vulvar intraepithelial neoplasia, molluscum contagiosa (inflamed), urethral carbuncle and prolapse, hidradenitis suppurativa, mammary-like gland adenoma (hidradenoma papilliferum), inflamed epidermal cyst, Bartholin's duct abscess, squamous cell carcinoma, melanoma (amelanotic type)
4. White lesions	(a) *White papules and nodules* – Fordyce spots, molluscum contagiosum, wart, scar, vulvar intraepithelial neoplasia (VIN), squamous cell carcinoma, milium, epidermal cyst, Hailey-Hailey disease
	(b) *White patches and plaques* – vitiligo, lichen sclerosus, postinflammatory hypopigmentation, lichenified disease, lichen planus, vulvar intraepithelial neoplasia (VIN), squamous cell carcinoma (SCC)
5. Dark-colored lesions	(a) *Dark-colored patches* – melanocytic nevus, vulvar melanosis, postinflammatory hyperpigmentation, lichen planus, acanthosis nigricans, melanoma in situ
	(b) *Dark-colored papules and nodules* – melanocytic nevus, warts (HPV infection), vulvar intraepithelial neoplasia (VIN), angiokeratoma, hidradenoma papilliferum, melanoma
6. Blisters	(a) *Vesicles and bullae* – herpesvirus infections (herpes simplex, herpes zoster), acute eczema, bullous lichen sclerosus, lymphangioma circumscriptum, immune blistering disorders
	(b) *Pustules* – candidiasis, folliculitis
7. Erosions and ulcers	(a) *Erosions* – excoriations, erosive lichen planus, fissures arising on normal tissue (idiopathic, intercourse related), fissures arising on abnormal tissue (candidiasis, lichen simplex chronicus, psoriasis, Crohn's disease, etc.), vulvar intraepithelial neoplasia (eroded variant), ruptured vesicles, bullae and pustules, extramammary Paget's disease
	(b) *Ulcers* – excoriations (related to eczema, lichen simplex chronicus), aphthous ulcers (Lipschütz ulcer, secondary to other diseases – Crohn's, Behçet's), Crohn's disease, herpesvirus infection, ulcerated squamous cell carcinoma, primary syphilis (chancre)
8. Edema	(a) *Skin-colored edema* – Crohn's disease, idiopathic lymphatic abnormality (congenital Milroy's disease), postradiation and postsurgical lymphatic obstruction, postinfectious edema (esp. staphylococcal and streptococcal cellulitis), postinflammatory edema (esp. hidradenitis suppurativa)
	(b) *Pink or red edema* – venous obstruction (e.g., pregnancy, parturition), cellulitis (primary or superimposed on already existing edema), inflamed Bartholin's duct cyst/abscess, Crohn's disease, mild vulvar edema (may occur with any inflammatory vulvar disease)

Neisseria gonorrhoeae, *Chlamydia trachomatis*, and *Pseudomonas aeruginosa*. Treatment modalities for Bartholin's duct cyst and abscess include gland incision and drainage, catheterization (fistulization), marsupialization, and excision. Catheterization and marsupialization are the most effective methods, while aspiration alone is the least effective with the highest recurrence rate. CO_2 laser vaporization can achieve a cure rate of above 95 % in a single session. Rectovaginal fistula can occur after surgical removal of Bartholin's gland.

Skene's gland and duct are periurethral structures histologically and functionally resembling the male prostate and are called female prostate. Skene's gland is also the principal source of prostate-specific antigen (PSA) in female. Main pathologies are Skene's cyst, pseudocyst, abscess, calculi, and carcinoma. Skene's duct cyst can have symptoms of superficial, external dyspareunia and voiding difficulties. Skene's abscess presents as vulvar pain, enlarged labium majus, and erythema around the urethra. Diagnosis is clinical and done with ultrasound and MRI. Treatment is incision and drainage or excision. Paraurethral cyst arising from Skene's glands can also be seen in female newborns. Clinically it usually looks as a round, yellowish interlabial nodule. Diagnosis can be made in prenatal ultrasound. Invasive treatment is similar to adults, although a nonsurgical approach is more relevant, because paraurethral cysts often disappear spontaneously in the first year of life.

Fox-Fordyce is a disease of apocrine glands with folliculocentric papules and pruritus. Physical trauma can contribute to its development including laser hair removal. Treatment is with different topical agents (retinoids, clindamycin, corticosteroids) and oral retinoids or contraceptives. In resistant cases, mechanical destruction or surgical removal of apocrine glands can be done.

Acne inversa or hidradenitis suppurativa can affect the vulva in females and is characterized by recurrent, painful, deep-seated nodules and abscesses of apocrine gland-bearing skin. Diagnosis and staging is aided by ultrasound. Treatment includes systemic antibiotics, retinoids, and biologics. In advanced cases only radical surgery and grafting are curative.

Vulvar Edema and Vascular Pathology

Vulvar edema can be caused by infections, neoplasia, pregnancy, systemic diseases, drugs, allergies, medical and surgical procedures, and many other acquired or congenital factors. It can be mild, massive, unilateral, or bilateral with or without vulvar redness, ulcers, erosions, lymphadenopathy, and systemic signs. Common causes of vulvar edema are genital herpes, syphilis (*edema indurativum*), donovanosis, and postsurgical or postradiation lymphedema; less often causes are tuberculosis, Crohn's disease, acquired lymphangioma circumscriptum, and congenital vulvar lymphedema. Massive vulvar edema with ascites can precede preeclampsia and eclampsia in pregnancy. Vulvar elephantiasis can be seen in filariasis, LGV, tuberculosis, donovanosis (pseudo-elephatiasis), localized lympedema, malignancy, obesity, and trauma. Diagnosis of vulvar edema is usually clinical and anamnestical. Treatment can range from ice packs, wet dressings, and hydrotherapy to systemic drugs, hospitalization, intensive care, and surgery.

Arteriovenous malformation of the vulva is a pedunculated soft tissue mass most commonly located on the labia majus. Treatment is by simple excision. Vulvar varicosities can be one sided or bilateral. Pregnancy is the most common cause. Rare causes include pelvic congestion syndrome and Klippel-Trenaunay-Weber syndrome. Treatment is surgical removal and sclerotherapy.

The Clitoris, Mons Pubis, and Hair

The normal size of the clitoris is about 16 mm in adult females and 6 mm in full-term newborns. Acquired clitoral hypertrophy is most often caused by virilism and hyperandrogenemia; other causes include neurofibromatosis, pseudohypertrophy, hemangioma, angiokeratoma, and amebiasis.

Congenital clitoromegaly can be due to congenital adrenal hyperplasia (CAH), true hermaphroditism, female pseudohermaphroditism, 46,XY gonadal dysgenesis, and androgen exposure in utero.

The mons pubis is a place typical of some vulvar diseases. Pediculosis pubis is rather rarely seen in the industrialized world. Vulvar folliculitis – just the opposite – is very common. Vulvar furuncle and even carbuncle can also develop in the vulvar area. Other diseases typical in the mons pubis are molluscum contagiosum, scabies, melanocytic nevi, seborrheic keratoses, Bowenoid papulosis, seborrheic dermatitis, and trichomycosis. Hirsutism or male pattern pubic hair growth toward the umbilicus occurs in females in hyperandrogenic states of different causes.

Melano-Pigmentary Disturbances

It is estimated that one in every ten women has a pigmented vulvar lesion. Common benign pigmented vulvar lesions include vulvar melanosis, vulvar lentigo, postinflammatory pigmentation, nevi, pigmented seborrheic keratosis, pigmented follicular cysts, and vulvar tattoo. Dysplastic nevi or atypical melanocytic nevi of the genital type and cellular blue nevus can also be observed in the vulva. Pigmented vulvar intraepithelial neoplasia, malignant melanoma, and pigmented basal cell carcinoma are examples of malignant tumors. Dermoscopy is useful as a noninvasive tool to diagnose vulvar pigmentations. Histopathology offers additional diagnostic accuracy, especially for lesions that look similar in dermoscopy. Atypical, suspicious pigment lesions are usually excised.

Vitiligo in the vulvar area is rather common. Differential diagnosis is usually with vulvar pityriasis versicolor, lichen sclerosus, lichen simplex chronicus, amelanotic melanoma, and vitiligo-like depigmentations. Treatment of vulvar vitiligo includes calcineurin inhibitors and corticosteroids. Changes in genital pigmentation can be observed also in CAH, Addison's disease, neurofibromatosis, Dowling-Degos disease, and laser-assisted hair removal. Racial differences in vulvar pigmentation are also important.

Vulvar Lichens

The three most common forms are lichen simplex chronicus, lichen planus, and lichen sclerosus (Table 105.3).

Lichen simplex chronicus (LSC) clinically appears as lichenification of labial surfaces with fissures and slight scaling. Intense, sometimes unbearable itch is a chief complaint. The itch-scratch cycle maintains the pathological process. Etiologic factors can be numerous including atopic eczema, contact dermatitis (Fig. 105.3b), and other pruritic anogenital diseases. Many cases are idiopathic. Diagnosis is based on the clinical picture and skin biopsy. Established treatment is with ultrapotent corticosteroid ointments for 4–12 weeks. Second-line treatment is with topical calcineurin inhibitors. Other alternatives are peroral prednisolone and intramuscular triamcinolone.

Vulvar lichen planus (VLP) has three clinical forms in the vulva: classic or papulosquamous, erosive, and hypertrophic. Erosive lichen planus of the vulva (ELPV) is the most common type. Typical symptoms include burning, itch, and dyspareunia. Vaginal scarring and stenosis may occur in long-standing disease. Vulvovaginal-gingival syndrome is a subtype of ELPV, where erosive, desquamative lesions are seen on the vagina or gingiva, usually not simultaneously. First-line treatment for VLP is very potent topical corticosteroids, while alternative treatments are topical calcineurin inhibitors (pimecrolimus 1 % and tacrolimus 0.1 %). Very potent corticosteroids can achieve symptomatic relief in more than 70 %, but complete resolution in not more than 30 %. From all ELPV patients, about 5 % progress to VIN and 5 % to squamous cell carcinoma.

Lichen sclerosus (LS) (Fig. 105.3a) is a chronic disease of the anogenital region. Autoimmune factors such as autoantibodies to extracellular matrix or basement membrane zone, *Borrelia burgdorferi* infection, and hormonal and genetic factors can have a role in pathogenesis. Clinically LS often starts as sharp-demarcated erythema on the clitoris and upper part of the labia minora, then gradually

Table 105.3 Management of vulvar lichens

Pathology	First-line treatment	Second-line treatment	Third-line treatment/other recommendations
Lichen simplex chronicus	Clobetasol propionate 0.05 % ointment 1–2× daily to 2× weekly for 4–12 weeks or	Tacrolimus 0.1 % ointment/ cream 1–2× day; up to 2 years	Prednisolone 20–40 mg PO 1× daily AM for 7–14 days Triamcinolone acetonide 40–80 mg IM 1× daily to 1× monthly
	Clobetasol butyrate 0.05 % ointment 1× daily to 2× weekly for 4–12 weeks or Betamethasone valerate 0.1 % ointment 1× daily to 2× weekly for 4–12 weeks	Pimecrolimus 1 % cream 2× daily; up to 2 years	Avoidance of irritants and contact allergens Breakup of itch-scratch cycle: sedating antihistamines, sedating tricyclics, selective serotonin reuptake inhibitors Repair of epidermal barrier
Lichen planus	Clobetasol propionate 0.05 % ointment 1–2× daily to 2× weekly for 4–12 weeks or	Tacrolimus 0.1 % ointment/ cream 1–2× day; up to 2 years	Triamcinolone acetonide 10 mg/ml – 0.5–1 ml intralesionally Triamcinolone acetonide – 40–80 mg IM 1× daily to 1× monthly
	Clobetasol butyrate 0.05 % ointment 1× daily to 2× weekly for 4–12 weeks or Betamethasone valerate 0.1 % ointment 1× daily to 2× weekly for 4–12 weeks	Pimecrolimus 1 % cream 2× daily; up to 2 years	Prednisolone 20–40 mg PO 1× daily AM for 7–14 days Vaseline – to protect erosive surfaces against urine
Lichen sclerosus	Clobetasol propionate 0.05 % ointment 1–2× daily to 2× weekly for 4–12 weeks or	Tacrolimus 0.1 % ointment/ cream 1–2× day for up to 2 years	Topical estrogens Topical testosterone (rarely used due to virilization)
	Clobetasol butyrate 0.05 % ointment 1× daily to 2× weekly for 4–12 weeks or Betamethasone valerate 0.1 % ointment 1× daily to 2× weekly for 4–12 weeks	Pimecrolimus 1 % cream 2× daily; up to 2 years	Retinoids – local or systemic Phototherapy – UVA1, UVB, PDT Surgery for scarring and stenosis

involves all of the labia minora, and spreads to the labia majora and perineum, developing the classic LS picture, single or multiple porcelain-white plaques. Vaginal scarring and narrowing are typical complications of LS. First- and second-line treatment options are similar to other vulvar lichens – potent and very potent corticosteroids and topical calcineurin inhibitors, local or systemic retinoids, PDT, phototherapy, and surgery.

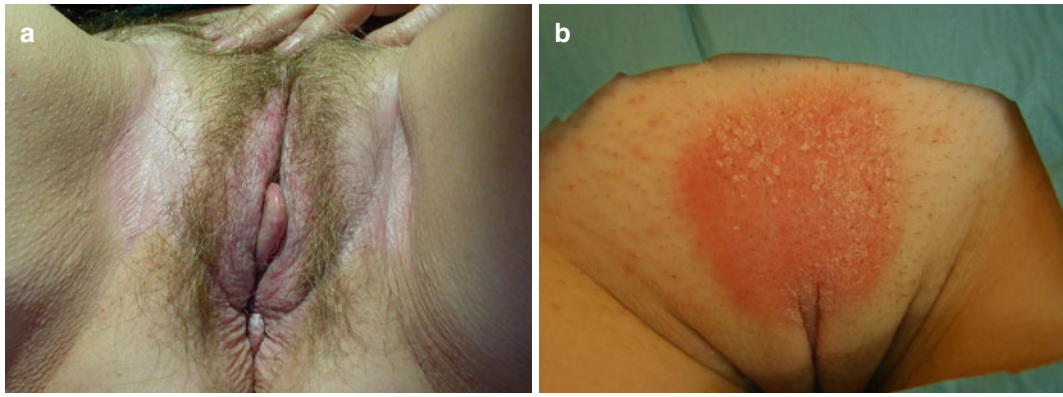

Fig. 105.3 (**a**) Lichen sclerosus. (**b**) Contact dermatitis

Benign Tumors of the Vulva

Due to different histological structures, the number of benign vulvar tumors is large. Some examples of benign vulvar tumors include epidermal cysts, hidradenoma papilliferum, syringoma, hemangioma, angiokeratoma, nevi, lipoma, vulvar polyp, angiomyofibroblastoma, vulvar endometriosis, primary Langerhans cell histiocytosis of the vulva, and many others. Their diagnosis and management is similar to other parts of the body.

Syringoma is a benign tumor from the intraepidermal portion of eccrine sweat ducts. A vulvar location is rare. Clinically, it appears as tiny, skin-colored papules, mainly on the labia majora. Diagnosis is verified histologically. Treatment includes CO_2 laser and radiofrequency. Angiomyofibroblastoma is another rare, benign, well-circumscribed mesenchymal tumor presenting as a nodule or mass on the labia majora. Differential diagnosis is with Bartholin's cyst, lipoma, and aggressive angiomyxoma. Diagnosis is by histology. Treatment is simple excision.

Vulvar Intraepithelial Neoplasia

Vulvar intraepithelial neoplasia (VIN) is a carcinoma in situ. According to the 2004 ISSVD classification, VIN is divided into three types: usual, differentiated, and unclassified. Usual-type VIN is further subdivided into warty, basaloid, and mixed (warty/basaloid) types. All VINs which neither belong to usual nor differentiated type are unclassified. VIN is replacing also terms such as Bowen's disease, erythroplasia of Queyrat, and Bowenoid papulosis. Usual-type VIN can be regarded as HPV-associated or HPV-caused diseases. Although the HPV positivity is not as high as in cervical cancer, more than 50 % of basaloid- and warty-type VINs are positive for HPV 16 and HPV 18 DNA. Differentiated-type VINs in 30–50 % of cases show association or develop in lichen sclerosus. The clinical picture of VIN is variable and unspecific – elevated, flat, warty, white, red, and brown lesions. The diagnosis of VIN is visual and by colposcopy, biopsy, and histology. Cytology is not reliable. HPV-DNA testing and presence of phosphorylated ribosomal S6 in biopsy can be of additional value to separate usual- and differentiated-type VIN. Treatment options for VIN include laser ablation or excision, skinning vulvectomy, wide local excision, and 5 % imiquimod cream topically. Wide local excision of VIN is regarded as the most effective method.

Cancers of the Vulva

Primary cancers of the vulva are rare and account for approximately 5 % of all gynecological malignancies and less than 1 % of all malignancies in women. Squamous cell carcinoma is the most common type of vulvar cancer at 90–95 %, followed by melanoma at 5 %, and adenocarcinomas and other cancers at 5 %.

Squamous Cell Carcinoma

Two different pathways are proposed for SCC development – HPV dependent and lichen sclerosus. In the first, high-risk types of HPV, e.g., HPV16, trigger usual-type VIN development and later warty/basaloid-type SCC. In the second, keratinizing SCC develops from differentiated VIN within a background of lichen sclerosus. Diagnosis and treatment of vulvar SCC is according to FIGO staging and treatment recommendation: early-stage vulvar cancer (FIGO I–II), intermediate-stage vulvar cancer (FIGO III), and locally advanced or metastatic (FIGO IV). A microinvasive carcinoma with less than 1 mm stromal invasion and less than 2 cm in size (FIGO stage IA) is surgically excised with a 1 cm resection margin without lymphadenectomy. For SCC invasion deeper than 1 mm, lymph node staging is done, and if sentinel lymph node is positive for metastasis, either unilateral or bilateral lymphadenectomy is performed. In intermediate or locally advanced tumor, treatment depends on tumor location, size, and invasion and lymph node status; main types of operations are wide excision and ipsilateral superficial lymphadenectomy, wide excision and bilateral inguinofemoral lymphadenectomy, and radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Metastatic vulvar SCC is treated with radiotherapy, chemoradiotherapy, and polychemotherapy. Erlotinib, an anti-EGFR tyrosine kinase inhibitor, has been used in clinical trials. Recurrence rate in SCC is high, especially with a tumor size of more than 35 mm, tumor-free surgical margin of less than 8 mm, and depth of stromal invasion of more than 4 mm. Chronic lymphedema and vulvar and groin wounds are typical posttreatment side effects.

Vulvar Adenocarcinomas

Primary vulvar adenocarcinomas are rare tumors classified into vulvar Paget's disease, sweat gland carcinomas, "breast-like"carcinomas, and vulvar apocrine adenocarcinoma. Vulvar Paget's disease or extramammary Paget's disease is the most common type of primary vulvar adenocarcinomas. Females 65–75 years of age are typically affected. Itching, eczema-like lesions on the labia, and enlarged inguinal lymph nodes are typical clinical presentations. Pruritus can be long-standing, with several years before diagnosis. Treatment is surgical excision, CO_2 laser, imiquimod and PDT, cryosurgery and PDT.

Skene's gland adenocarcinoma is a rare neoplasm of the female periurethral glands histologically resembling prostate adenocarcinoma. Diagnosis is made histologically. Immunohistochemical staining with PSA and preoperative and postoperative measurements of PSA are of diagnostic value. Treatment is by excision.

Bartholin's gland carcinoma is another rare neoplasm of the vulva. Histologically squamous, adenoid cystic, transitional, and combined types are recognized. Treatment is by hemivulvectomy with or without lymph node dissection, total vulvectomy and bilateral inguinofemoral lymph node dissection with or without radiotherapy and chemotherapy. Local recurrence and distant metastases are seen in one-third of patients.

Vulvar Melanoma

The vulva is the most common site of mucosal melanomas. Vulvar melanoma is the second most common vulvar malignancy after SCC. Postmenopausal women are typically affected. Vulvar melanomas differ from cutaneous and vaginal melanomas having a high percentage of c-KIT mutations.

Pigmented lesion or vulvar mass, pain, itching, and bleeding are characteristic symptoms of vulvar melanoma. Anatomical distribution favors the clitoris and labia minora in 60–70 %. Mucosal lentiginous melanoma, nodular melanoma, and superficial spreading melanoma are the three most common types in the vulva. About 10 % of vulvar melanomas are amelanotic or desmoplastic. Amelanotic melanomas can simulate lichen sclerosus or be associated with it. Differential diagnosis for amelanotic melanoma includes also VIN and SCC. Diagnosis of vulvar melanoma is established histologically with the help of immunohistochemistry. Clark, Breslow, or Chung system is used for microstaging. Correct and precise mapping of sentinel lymph nodes (SLN) in the inguinal and femoral area can be substantially improved with 3D fusion images of SPECT and CT scans. Positive SLN are found in 20–30 % of cases of vulvar melanoma. Molecular screening for activated c-KIT mutations shall be done.

Treatment depends on anatomical location, size of tumor, depth of invasion, and stage of disease (Table 105.4). Wide local excision is

Table 105.4 Treatment of vulvar premalignancies and cancer

VIN	Usual-type VIN	*First choice* WLE with 0.5 cm PM *Second choice* CO_2 laser excision or vaporization Simple vulvectomy Skinning vulvectomy *Others* Imiquimod 5 % cream 3× a week
	Differentiated-type VIN	*First choice* WLE with 0.5 cm PM *Second choice* CO_2 laser excision or vaporization Simple vulvectomy Skinning vulvectomy
SCC	FIGO IA FIGO IB FIGO II FIGO IIIA, IIIB, IIIC FIGO IVA, IVB	WLE with 1.0 cm PM WLE with 2–4 cm PM Ipsilateral or bilateral inguinal lymphadenectomy HVLNE or RVLNE with 5 cm PM Radiotherapy RVLNE with 5 cm PM Radiotherapy Chemotherapy – 5-FU or 5-FU + cisplatin RVLNE with 5 cm PM + pelvic exenteration Radiotherapy Chemotherapy – 5FU or 5FU + cisplatin Erlotinib – 150 mg/day PO Gefitinib – 250 mg/day PO Afatinib – 50 mg/day PO
Vulvar melanoma	AJCC IA AJCC IB AJCC IIA, IIB AJCC IIC; IIIA, IIIB, IIIC AJCC IV Metastatic	WLE with 1–2 cm PM WLE with 3–4 cm PM Inguinal lymphadenectomy IFN-alpha HVLNE or RVLNE with 3–4 cm PM Chemotherapy – DTIC Immunotherapy – IFN-alpha RVLNE with 5 cm PM Chemotherapy – DTIC Immunochemotherapy – DTIC + IFN-alpha RVLNE with 5 cm PM + pelvic exenteration Polychemotherapy (DVP, BHD, BOLD) Radiotherapy IL-2 – 600,000–720,000 IU/kg IV every 8 h, 14 doses; maximum 28 doses Imatinib – 400–800 mg PO daily Nilotinib – 400–800 mg PO daily Ipilimumab – 3 mg/kg IV every 3 weeks; total 4 doses Nivolumab – 10 mg/kg IV every 3 weeks; total 4 doses Lambrolizumab – 2–10 mg/kg IV every 2–3 weeks; total 4 doses Combined therapy: Ipilimumab + IL-2, ipilimumab + nivolumab

AJCC American Joint Committee on Cancer (2009 Melanoma Staging and Classification), *FIGO* Fédération Internationale de Gynécologie et d'Obstétrique, *HVLNE* hemivulvectomy with superficial inguinal lymphadenectomy, *PM* peripheral margin, *PO* peroral, *RVLNE* radical vulvectomy with inguinofemoral lymphadenectomy, *SCC* squamous cell carcinoma, *VIN* vulvar intraepithelial neoplasia, *WLE* wide local excision

preferred for thin lesions (<1 mm) and hemivulvectomy or radical vulvectomy with bilateral inguinofemoral lymphadenectomy for deeper lesions with nodal involvement. Local imiquimod therapy has been tried with partial success in vulvar melanoma.

For metastatic melanomas, dacarbazine monochemotherapy or polychemotherapy and adjuvant interferon alpha radiotherapy are used. Unfortunately, vulvar as well as mucosal melanomas have low response rate to chemotherapy. Radiotherapy may reduce the local recurrence but not the overall survival. In recent years several new therapeutic agents, classes of drugs, and treatments have been registered or are in clinical trials for metastatic melanoma, among them are CTLA-4 antibodies (ipilimumab, tremelimumab), interleukin-2 (vemurafenib, dabrafenib), anti-PD-1 (nivolumab, lambrolizumab), MEK inhibitors (trametinib), c-KIT inhibitors (imatinib, sorafenib), adoptive cell transfer, and combined therapies. Ipilimumab at 3 mg/kg alone or in combination with interleukin-2 or gp-100 has shown complete response in 6–17 % of patients, 2-year survival rate in 24 %, and 5-year survival rate from 13 to 23 %. Vemurafenib and other BRAF inhibitors are not really useful in vulvar melanomas, because they lack BRAF V600E mutations. For patients with metastatic vulvar melanoma, the highest hopes and expectations can be attributed to c-KIT inhibitors. In clinical trials imatinib 400–800 mg/day has shown complete response in 6 %, partial response in 23 %, and total disease control in 53 %; 1-year survival rate was achieved in 40–51 % and 2-year survival rate in 16–20 %. Similar results are obtained or will be expected with nilotinib. Adoptive cell transfer (ACT) is a new individualized method with high and durable response comparable to vemurafenib and ipilimumab. In ACT, tumor-infiltrating lymphocytes (TIL) are taken from the melanoma of the patient, cultured, and reinfused back. Response rate ranges from 20 to 70 % depending on the method. Prognosis in metastatic vulvar melanoma is generally worse than in cutaneous. Recurrence rate is 30–50 %. The average 5-year survival rate is 36 %.

Vulvar Itch and Vulvodynia

Vulvar itch or pruritus vulvae is a very common and important symptom. Besides anamnesis and clinical aspects, age of the patient is important. In young women vulvar pruritus is most often caused by infections and allergies – vulvovaginal candidiasis, enterobiasis, diabetes, scabies, pediculosis pubis, and vulvar eczema; in postmenopausal women it is more often caused by lichen sclerosus, VIN, and other benign and malignant tumors. Treatment is with local or systemic anti-infectives, corticosteroids, calcineurin inhibitors, surgery, and oncologic drugs.

Vulvodynia presents with vulvar pain, burning sensation, and dyspareunia without obvious physical cause. Formerly it was known as "burning vulva syndrome" and more correctly can be called "aidoiodynia." Some 10–20 % of females are estimated to be affected worldwide. Vulvodynia can be generalized involving all vulvar structures or localized to some parts, e.g., clitorodynia and hemivulvodynia. Vulvo-vestibulitis syndrome (VVS) is a type of focal vulvodynia. Disturbed pain perception, vulvar hypersensitivity, psychosexual problems, and vaginal infections are proposed pathogenic factors of vulvodynia. Diagnosis is based on anamnesis, clinical examination, pain assessment via Q-tip test, and tampon test. Treatment is done with amitriptyline cream, vaginal cream with conjugated estrogens, pelvic floor physiotherapy, biofeedback, cognitive-behavioral therapy, systemic amitriptyline, gabapentin, botulinum toxin A, posterior vestibulectomy, and simple vulvectomy.

Vulvar Injury, Mutilation, and Structural Pathologies

The vulva can be traumatized or deformed by sharp or blunt trauma, rape, sexual abuse, mutilation, diseases, chemicals, and other agents.

Female circumcision or female genital mutilation (FGM) is a ritual religious practice of some communities mainly in Africa and the Middle East. The top three countries practicing FGM are Egypt, Sudan, and Mali. The average age when

girls are circumcised is 10 years. Depending on the extent, FGM is graded into four types. The most common is FGM type II, when the clitoris and labia minora are removed. FGM is bound with many complications: psychosocial trauma, acute and chronic pain, bleeding, infections, cysts, narrowing of the vaginal opening, and partum and postpartum risks. Treatment is mostly symptomatic using analgesics, anti-infectives, neuroleptics, and lubricants. Surgical correction or reconstruction can be tried in some cases.

Structural pathologies of the vulva can include acquired defects (synechia, fusion of labia, stenosis) or congenital anomalies such as agenesis of labia, imperforate hymen, malformations of clitoris, hypospadia of female urethra, hermaphroditism, and female pseudohermaphroditism. Treatment is mostly surgical.

Diagnosis

Correct diagnosis of vulvar diseases involves experience both in gynecology and dermatology (Table 105.5). Anamnesis of the disease, age, social and ethnic background, sexual habits, and medication use is important as well as history of gynecologic and dermatologic pathologies. Vulvovaginal inspection shall be followed by full-body examination, paying special attention to the perineum, lower abdomen, axilla, oral mucosae, scalp, and lymph nodes. Sexual partners or legal representatives of children or teenagers must be consulted or examined. All pruritic lesions of the vulva deserve a very careful examination, because they can be an early sign of malignancy. Different methods of microscopy, culture, PCR, serology, and blood analysis can diagnose most of the causes of vulvar ulcers, erosions, and vulvites. Biopsy and histopathology remain a golden standard in most dermatological diagnosis. Vulvar pigment lesions can be examined with dermatoscopy and laser confocal microscopy. Hormonal and genetic investigations are necessary in endocrine and structural pathologies. Women with hirsutism shall be tested for polycystic ovary syndrome, androgen-secreting tumors, adrenal hyperplasia, Cushing syndrome, and thyroid function. Ultrasonography, MRI, 3D fusion images of SPECT, and CT scans have become popular, noninvasive methods to diagnose cysts, urethral and periurethral pathologies in females, and sentinel lymph nodes.

Table 105.5 Diagnostic methods in vulvar diseases

Method	Indication
Microscopy	Herpes, syphilis, donovanosis, ulcus molle
Culture	Bacterial, fungal, viral infections
Patch test, prick	Allergic vulvitis, vulvar edema
Dermatoscopy	Pigmented vulvar lesions, scabies, pediculosis
Colposcopy	VIN, squamous cell carcinoma
Confocal microscopy	Similar to dermoscopy
Histology and immunohistochemistry	Vulvar melanoma, VIN, SCC, any other unknown clinical condition
Pain assessment tests	Vulvodynia
Blood and hormonal analysis	Autoimmunity, infections, hirsutism
Ultrasound, MRI, CT scan	Cysts, abscesses
PCR	Bacterial, fungal, viral infections
Acetic acid	VIN, SCC

General Principles of Treatment

Local treatment options include antibacterial solutions, creams and ointments, hydrotherapy, corticosteroids, estrogens, and testosterone-containing creams (Table 105.6). Antimicrobial treatment for infectious vulvar ulcers or vulvovaginitis is well established internationally in many guidelines. Noninfectious and non-oncologic ulcers or vulvar inflammations are treated with corticosteroids and other immunosuppressives. Although ultrapotent and potent topical corticosteroids remain standard treatment options for vulvar lichens, calcineurin inhibitors are as effective but with better safety profile. Topical calcineurin inhibitors can also be used for psoriasis inversa, contact dermatitis, seborrheic dermatitis, and vitiligo. Amitriptyline vaginal cream is another advancement in vulvo-

Table 105.6 Local treatments in vulvar diseases

Drug/formulation/dosage	Indication
1. *Antifungals*	
1.1. Nystatin, 100,000 U vaginal tablet, 2–6× a day or in severe cases every 1–2 h till complete healing and then additional 8–10 days	Candida vulvitis, intertrigo
1.2. Ketoconazole, 2 % cream, 2× daily for 2–4 weeks	Candida, dermatophytes, seborrheic dermatitis
1.3. Econazole nitrate, 1 % cream, 1–2× a day for 2–4 weeks	
1.4. Miconazole nitrate, 2 % cream, 7 days; vaginal applicator, 1× daily at night: 100 mg for 7 days, 200 mg for 3 days, 1,200 mg single dose	
1.5. Butoconazole, 2 % cream, 7 days; 2 % sustained release cream 5 g, 1 day	
1.6. Terconazole, 0.4 % cream, intravaginally 1× daily for 7 days; 0.8 % cream or 80 mg vaginal suppositories, intravaginally 1× daily for 3 days	
1.7. Tioconazole, 6.5 % ointment, intravaginally at night, single dose	
1.8. Ciclopirox olamine, 0.77 % cream, 2× daily for 4 weeks	
2. *Antibacterials*	
2.1. Tetracycline, 3 % ointment, 1–3 daily, 5–10 days	Bacterial vulvar infections, ulcers
2.2. Meclocycline, 1 % cream, 1–2× daily, 5–10 days	
2.3. Fusidic acid, 2 % cream/ointment, 1–3× daily, 5–10 days	
2.4. Metronidazole, 5 % vaginal cream, 1× daily intravaginally for 6 days	
2.5. Clindamycin, 2 % vaginal cream, 1× daily intravaginally for 3 days	
2.6. Mupirocin, 2 % ointment, 1–3× daily, 5–10 days	
2.7. Silver sulfadiazine, 1 % cream, 1–2× daily till healing	Wounds, burns
3. *Hormones*	
3.1. Estriol, 0.05 % vaginal cream, intravaginally 1× daily 1 week, then 2× weekly	Atrophy, dry vagina, pruritus vulvae, dyspareunia, vaginal stenosis, lichen sclerosus
3.2. Estradiol, 0.01 % vaginal cream, 2–3× daily on vulvae	
3.3. Conjugated estrogens, vaginal cream, intravaginally continuously (21 days on, then 7 days off) or cyclically (2× weekly)	
3.4. Testosterone propionate, 2 % cream/ointment/gel, 2× daily for 3–4 months; not more than 50 g in the first 2 months and not more than 10–25 g in the next 2 months	
4. *Antiseptics/astringents*	
4.1. Aluminum acetate, 5 % solution	Microbial vulvitis
4.2. Burow's solution, 5 % aluminum acetate diluted in water (1:20–1:40)	
4.3. Tannic acid, 2 % solution	
4.4. Boric acid, 1 % solution	
4.5. Ichthammol, 2 % solution	
4.6. Potassium permanganate, 1: 10,000 solution	
4.7. Hydrogen peroxide, 1–3 % solution	
4.8. Povidone-iodine, 4 %, 5 %, 10 % solutions;10 % ointment; 2.5 % dry powder spray	
4.9. Silver nitrate, 0.5 %, 1 %, 10 % solutions	
5. *Anti-parasite*	
5.1. Permethrin, 5 % cream, over whole body (except head) for 12 h	Scabies
5.2. Benzyl benzoate, 10 %/25 % emulsion, 1–3 applications over whole body for 72 h	
5.3. Lindane, 1 % lotion, whole body application (except head); wash off after 8–12 h	
5.4. Permethrin, 1 % cream rinse, apply for 10 min to dry hair, then wash off	Pubic lice
5.5. Lindane, 1 % shampoo, apply for 4 min to dry hair, then wash off	
5.6. Ivermectin, 0.5 % lotion, apply for 10 min to dry hair, then wash off	

Table 105.6 continued

Drug/formulation/dosage	Indication
6. *Antiviral*	
6.1. Aciclovir, 5 % cream, 5× daily for 5–10 days	Genital herpes
6.2. Penciclovir, cream, every 2 h, 4–5 days	
6.3. Podophyllotoxin, 5 mg/1 ml solution, 2× a day for 3 consecutive days; maximum – 4 weeks	Genital HPV infection
6.4. Imiquimod, 5 % cream, 3× a week; maximum – 16 weeks	
7. *Antineoplastic*	
7.1. Imiquimod, 5 % cream, 3× a week; maximum – 16 weeks	Basal cell carcinoma, usual-type VIN
7.2. Fluorouracil, 5 % cream, 1–2× daily; maximum – 12 weeks	
8. *Esthetic*	
8.1. Botulinum toxin type A, solution of 50/100/200/500 U in vials, 25–200 U per treatment or individually matched doses	Vulvodynia
8.2. Fillers – Hyaluronic acid, solution 20 mg/ml in vials, 0.5–6 ml per treatment	
9. *Anesthetic*	
9.1. Lidocaine, 2 % gel, 1 fingertip unit (0.5 g) 1× daily	Pruritus vulvae, vulvodynia
9.2. Lidocaine (25 mg)/prilocaine (25 mg), 5 % cream, 1 fingertip unit (0.5 g) 1× daily	

dynia treatment to decrease systemic drug use (Table 105.6 and 105.7).

Vulvar surgery helps to solve not just purely surgical or oncological problems but is used in chronic inflammatory diseases, vulvar lichens, and vulvodynia as well. Benign lesions are usually treated with simple incision, drainage, marsupialization, ablative and vascular laser, radiofrequency, cryosurgery, esthetic labial surgery and reconstructive vulvar surgery, PDT, and phototherapy. In neoplasia, either wide local excision, hemivulvectomy, or radical vulvectomy with bilateral lymphadenectomy is used. New drugs and treatment against metastatic melanoma and squamous cell carcinoma give hope to the patients and physicians that a 5- to 10-year survival can be achieved in the nearest future. Besides drugs and surgical treatments, psychological support and rehabilitation is important, especially in vulvar cancer, after vulvar injury, mutilation, or radical surgery.

Finally, prevention shall not be forgotten in vulvar diseases. This applies to STI and safe sex behavior, hypoallergenic intimate hygiene and clothing, vaccination against HPV infections, and early recognition of malignancy.

Table 105.7 Systemic and surgical treatments in vulvar diseases

Medication/device	Specification	Indication
Antibiotics	Azithromycin Erythromycin Clindamycin Penicillins Cephalosporins	Bacterial ulcers and vulvitides, vulvar furuncle, abscess, secondary infected wounds
Antifungals	Fluconazole, itraconazole, ketoconazole	Vulvovaginal candidiasis
Antivirals	Acyclovir, famciclovir, valacyclovir	Genital herpes, vulvar herpes zoster
Retinoids		
Immunosuppresives	Corticosteroids, azathioprine, methotrexate, thalidomide	Autoimmune bullous diseases, atopic dermatitis, psoriasis, vulvar lichens
Biologics	1. Anti-TNF, anti-IL-12/ anti-IL-23p40 2. c-KIT inhibitors 3. EGFR tyrosine kinase inhibitors	1. Psoriasis, autoimmune bullous diseases 2. Metastatic vulvar melanoma 3. Metastatic squamous cell carcinoma
Cryotherapy	Cryogun, cryoprobe, cryo-application	HPV infection, seborrheic keratosis, VIN
PDT		
Phototherapy	UVB, UVA, PUVA, Re-PUVA	Psoriasis, lichen sclerosus
Ablative laser surgery	CO_2, erbium:YAG	VIN, Bartholin's/Skene's abscess
Vascular lasers	Nd-YAG, KTP, PDL	Hemangioma, venous lake
Pigment lasers	Q-switched Nd-YAG, alexandrite	
Radiofrequency	Surgical	Similar to ablative lasers
Surgery	1. Incisional/excisional surgery 2. Skinning vulvectomy 3. Wide local excision 4. Hemivulvectomy 5. Radical "en bloc" vulvectomy 6. Lymphadenectomy – superficial inguinal or inguinofemoral 7. Esthetic vulvar surgery	1. Bartholin's/Skene's abscess 2. Vulvar intraepithelial neoplasia 3. Vulvar intraepithelial neoplasia 4. Vulvar cancer 5. Advanced vulvar cancer 6. Vulvar cancer 7. Vulvar mutilations, scarring, stenosis

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Warts: Cutaneous and Anogenital

106

Antonios Kanelleas and Electra Nicolaidou

Key Points

- Cutaneous and anogenital warts are caused by human papillomaviruses (HPVs), a large group of more than 120 genotypes that infect the epithelia of the skin and/or mucosa.
- Cutaneous warts are very common especially in young children. They can resolve spontaneously.
- Anogenital warts are listed among the sexually transmitted infections. They are highly prevalent in both sexes and are typically caused by HPV 6 and 11.
- Persistence of cervical infection with a high-risk HPV type represents the single most important factor for the development of cervical pathology, including cervical carcinoma.
- Immunosuppressed patients are at a higher risk of developing persistent HPV infection.
- No definitive, etiological treatment for HPV infection exists. Available treatments locally destroy infected tissue. Eradication of virus is not possible up to now.
- Highly effective prophylactic vaccines are licensed for the prevention of type-specific HPV infection.

Definition and Epidemiology

Cutaneous and anogenital warts are the clinical manifestations of an infection with human papillomaviruses (HPVs). Up to date there are more than 120 different HPV types that have been fully characterized. Both conditions are very common and can affect all age groups. A subset of HPV (most often types 16, 18, 26, 31, 33, 35, 39, 39, 45, 51–53, 56, 58, 59, 62, 66, 68, 73, 82) has been designated as high-risk types. They have been implicated in the pathogenesis of cervical cancer and its precursor lesions, of malignancies at the anogenital area and the upper aerodigestive tract, and, rarely, of squamous cell carcinoma of the digit. In the case of immunosuppression, HPV infection can persist, increasing the risk of developing anogenital malignancies.

Cutaneous warts can affect any part of the skin but mainly the fingers, the soles, and the face. They are more prevalent in childhood, ranking as one of the three most common dermatoses in children, with an overall prevalence of 20 % in schoolchildren. The majority will regress spontaneously within a year or 2 from the initial infection. Reinfection with the same type of HPV virus is uncommon after complete clearance.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_106, © Springer-Verlag Berlin Heidelberg 2015

Transmission occurs via direct skin-to-skin contact or indirectly through contaminated surfaces and objects (e.g., swimming pools, towels, etc.). Minor abrasions and breaks of skin's integrity are usually needed to expose basal keratinocytes to HPV. Autoinoculation of the virus is also a major factor of viral spreading.

Anogenital warts are one of the most common sexually transmitted infections (STIs) in the adolescent and adult population. They are uncommon in prepubertal children, and although vertical transmission has been described, the possibility of sexual abuse needs to be excluded when they are diagnosed in that age group. The prevalence of cervical HPV infection varies greatly between different countries and age groups and ranges from 20 to 45 %. Similar rates are described in men. The impact of genital HPV infection to public health is alarmingly high, both in terms of number of visits to doctors and fiscally. It is estimated that the annual cost in the USA is over $6 billion, making it the second most costly STI after HIV.

Transmission occurs mainly by intimate contact (skin to skin or mucosa to mucosa) with individuals who manifest clinical or subclinical lesions. Circumcision seems to be protective in carrying and transmitting HPV infections. Risk factors include first sexual intercourse at an early age, frequency of intercourse and multiplicity of sex partners, partner's number of sexual partners, and concomitant sexually transmitted diseases.

Most anogenital HPV infections will eventually resolve by themselves in a period that may extend from months to years. Recurrences are common, either with or without treatment, especially within the first year. The median duration of high-risk type infection in women is reported to be around 8 months. Persistent cervical infection is observed in 30 % after the first year and in 9 % after the second year. Persistence of cervical infection with a high-risk HPV type represents the single most important factor for the development of cervical pathology, including cervical carcinoma. Altogether, HPV types 16, 18, 31, and 45 constitute for more than 80 % of the cervical cancers worldwide. Routine cytology screening tests with the Pap smear are suggested by international authorities as a major preventive measure of cervical carcinoma.

Immunosuppression, e.g., due to HIV or in organ transplant patients, appears to change the natural course of HPV-related oncogenesis. HPV infections are more frequent, persistent, and more likely to progress to intraepithelial neoplasias in immunosuppressed patients.

Basic Concepts of Pathogenesis

Cutaneous and anogenital warts represent hyperproliferative growths of terminally differentiated keratinocytes of the skin and mucous membranes infected by HPV. Papillomaviruses are nonenveloped, double-stranded DNA viruses, approximately 55 nm in diameter. The capsid is a spherical, icosahedral coat composed of two virally encoded proteins: L1 and L2. It surrounds the viral DNA, thus protecting it from degradation and also enabling adhesion to target cells. It is not surrounded by any lipoprotein envelope, being stable and resistant to environmental stress such as heat, detergents, and desiccation. HPV DNA does not encode any of the known polymerases, kinases, or proteases that are currently used as targets of anti-herpes and anti-HIV drugs.

HPV is highly host specific and no cross infection with other animal papillomaviruses has been reported. The HPV proliferative cycle is completed only in fully differentiated squamous epithelia. The infection starts when the virus finds a way to enter the active, proliferating basal epithelial cells, usually through an abrasion or trauma. As the infected basal cells divide, some of them migrate away from the basal layer toward the surface and others remain on site, acting as a long-standing reservoir of viral DNA. Viral shedding acts as immediate way of viral transmission. Depending on the capacity and activity of basal cells infected, the infection will prove itself to be either transient or persistent. An immune response by the host is mounted, mainly a cell-mediated one. Langerhans cells and infiltrating lymphocytes target and recognize even low levels of viral proteins expressed in the basal and Malpighian layers. There is no viremic phase;

therefore a systemic immune response is avoided. However, approximately 60 % of patients with anogenital lesions develop low titer-specific antibodies, which tend to last even after clearance.

The natural history of HPV infection is either spontaneous regression or in some cases progression to premalignant and malignant lesions. As mentioned before, different types have different oncogenic potential. HPV types 16 and 18 are linked to cervical carcinoma via increased expression of E6 and E7 genes. The current model of multistage carcinogenesis requires a time lag of several decades after initial infection combined with an accumulation of genetic mutations due to environmental or other factors. HPV types 5 and 8 are frequently detected in squamous cell carcinomas in patients with epidermodysplasia verruciformis (EV). Most cases of EV are sporadic but about 25 % of cases have been reported to display autosomal or X-linked recessive inheritance. Two types of lesions are observed, one resembling plane warts and another similar to pityriasis versicolor. Malignant transformation of at least one lesion occurs in more than 50 % of patients.

Clinical Presentation

Clinical features present in various forms depending on the type of HPV, the affected site, and the immune status of the host. We distinguish between cutaneous and mucosal types of HPV; however there are exceptions to this virus tropism.

Common warts (verruca vulgaris) appear in various sizes as firm, hyperkeratotic, rough papules that can form large masses by confluence. They are due mainly to HPV 2. They may occur anywhere on the skin but preferably on dorsum of hands and fingers and around or beneath the nails *(periungual warts)*. Children under 12 years of age are frequently affected. Common warts are usually asymptomatic but may be tender. About 95 % will clear spontaneously within 4 years. It seems that clearance is slower in adults. Malignant transformation is extremely rare but has been reported in immunosuppressed hosts.

Plantar warts (verruca plana) are caused by HPV 1, 2, 4, 27, and 57. They first appear as small, grainy papules and soon evolve into a well-defined, rounded lesion with keratotic surface. Most of the plantar warts develop under pressure points such as the heel or the heads of the metatarsal bones. Mosaic warts are formed by the confluence of closely grouped small-size warts. The epithelial ridges of the plantar skin are not continued over the wart surface. After paring down the surface, small black dots are revealed, which represent the thrombosed capillaries. Pain during walking is common but varies in intensity. Pressure over plantar warts produces pain. Duration of lesions is very variable. Children have a better prognosis compared to adults. Mosaic warts, however, can be extremely difficult to treat. Distinction from corns, calluses, and punctate keratoderma needs to be made.

Plane warts (flat warts) are due mainly to HPV 3 and 10. They are small, 1–5 mm in diameter, round or polygonal, smooth, and flat papules. They can be skin colored or pigmented. The face, dorsum of hands, and shins are sites of predilection. Linear arrangement of contiguous warts is a characteristic sign. Regression is possible and usually associated with inflammation (pruritus, erythema, edema, depigmented halo around the wart). Resolution is completed within a month.

Filiform and digitate warts occur mainly in males. They appear on the face, nostrils, and neck. They can be clustered or irregularly distributed.

Anogenital warts are common in both sexes and are caused mainly by HPV 6 and 11. They are often asymptomatic but may cause discomfort. The typical lesion is soft, pink, elongated, and sometimes filiform, pedunculated, or cauliflower-like (condyloma). Flat papular lesions can also be observed. Lesions can be solitary or multiple and vary in size from 1 to 2 mm up to several cm. They affect mucosal surfaces and keratinized skin. Typical sites of predilection are the glans penis (Fig. 106.1), the corona, and frenulum in men and labia minora (Fig. 106.2) and anus in women. These sites represent areas of greater coital friction. Other areas include the

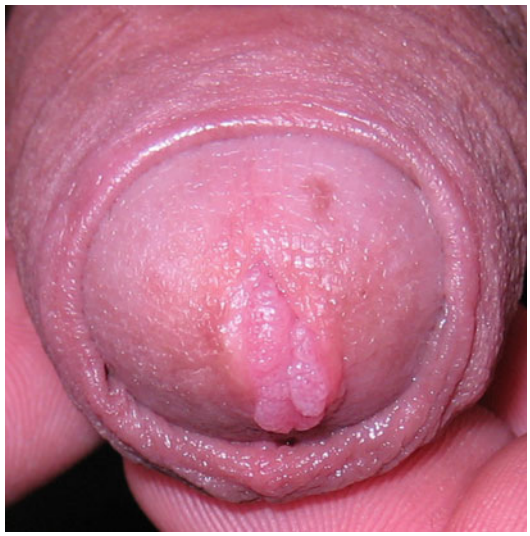

Fig. 106.1 Genital wart on penis (urethra)

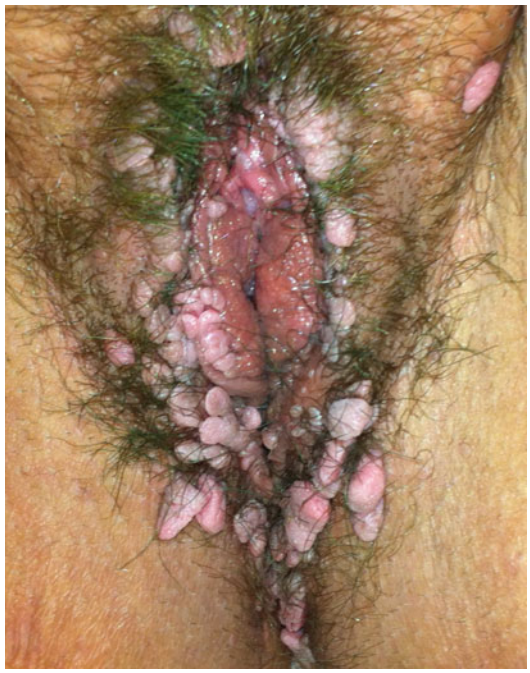

Fig. 106.2 Multiple anogenital warts on vulva, perineum

perineum, the penis shaft, the pubic area, labia majora, inguinal folds, and scrotum. Duration of lesions varies from a few weeks to many years. Recurrences are expected in about 25 % of cases, with an interim period ranging from 2 months to more than 20 years. Viral DNA can be found in clinically and histologically healthy skin adjacent to lesions. This finding probably correlates with recurrences after clinical cure. The development of large masses, induration, pain, and discharge raises the suspicion of malignant change (including Buschke-Löwenstein tumor) and warrants immediate biopsy.

Diagnosis

Diagnosis is usually made on clinical terms. The acetic acid test can be a useful tool, but it is not widely used because of its low sensitivity and specificity. Application of 5 % acetic acid results in characteristic whitening of the suspected lesion within 5–10 min of the application. Atypical lesions may need to be biopsied to histologically confirm the diagnosis. Histological findings are variable, reflecting the great number of clinical presentations of HPV-related lesions. A common pattern in epithelial cells is the presence of cytoplasmic vacuoles isolating the pyknotic nucleus from the cytoplasmic membrane. These cells with this characteristic vacuolization as termed as koilocytes (hollow cells). The presence of koilocytosis is a useful feature which distinguishes verrucae from other types of papillomas. Other methods available for the laboratory diagnosis of HPV infection include: detection of virus particles by electron microscope, immunohistochemistry or immunocytochemistry using type-common or type-specific antibodies, DNA hybridization on tissue extracts or in situ, and PCR for HPV DNA. The last two assays allow HPV typing and are useful in identifying oncogenic types. Serological assays are not used because of low antibody titers and variable intervals between infection and seroconversion.

Anogenital warts warrant further investigation such as colposcopy and Pap smear; orthosigmoidoscopy, if found perianally; and screening for other common sexually transmitted diseases (STDs).

Differential Diagnosis

Common warts may resemble seborrheic keratoses, actinic keratoses, acrokeratosis verruciformis, acrochordons, and keratoacanthoma. Even amelanotic melanoma can imitate a long-standing, resistant to treatment periungual wart. Suspicion should rise if erosions and pigmentation are present. Lichen planus may resemble flat warts. Both can present themselves in a linear way. However, lichen planus is distinguished by the whitish net-like pattern (Wickham's striae).

Plantar warts must be differentiated from clavi (corns). The misdiagnosis is usual. A verruca typically presents black dots and punctate hemorrhage after paring it down. In clavus, pain can be induced if pressure is applied vertically on the center of the lesion, while in verrucae pain also appears when pressure is applied sideways at the borders of the lesion. Punctate porokeratosis, poroma, and hyperhidrotic pitting can also mimic plantar warts. In immunosuppressed patients, warts can appear in large number and in unusual sites and can resemble molluscum contagiosum lesions. The latter are dome shaped with a characteristic central umbilication.

Differential diagnoses for anogenital warts include seborrheic keratoses, lichen planus, melanocytic nevus, syphilitic condylomata lata, pearly penile papules, and vestibular papillomatosis. The latter two entities represent normal anatomic variants in men and women, respectively. Pearly penile papules consist of several rows of miniature papules, 1–2 mm, along the coronal sulcus. Vestibular papillomas are tiny projections of regular shape at the introitus vulvae and the labia minora. Syphilis serology obviously is needed to exclude *T. pallidum* infection. Sebaceous glands of the prepuce and labia majora can appear as white-gray to yellow small papules and sometimes are misdiagnosed as genital warts. Bowenoid papulosis consists of red-brown papules or confluent whitish plaques that may be difficult to differentiate from benign condylomas. It usually affects male patients and most of the time a biopsy is needed to establish a diagnosis. Finally, one should always have in mind the possibility that a recalcitrant to treatment, long-standing lesion may be a premalignant or malignant lesion. Vulvar, penile, and anal intraepithelial neoplasias and squamous cell carcinoma are entities that are included in this category. HPV 16, 18, 31, and 33 are the types frequently implicated in their pathogenesis.

General Principles of Treatment

Up to date no definitive and etiological treatment has been found for cutaneous and genital warts. Our approach is limited to tissue destructive therapies in order to stop viral shedding from the infected sites. None of these methods eradicate HPV. Let it be noted that where treatment trials have been placebo controlled, a 30 % response rate has been observed in the placebo group. Depending on the site and the extent of the lesions, we choose from a wide array of available options. First-line treatments are usually the topical ones, moving then to more aggressive treatments. For anogenital warts in particular, first-episode patients should be offered screening for other STDs. Also, they should be encouraged to notify their partner(s).

Cutaneous Warts

Several combinations of keratolytic and caustic agents are commercially available. Salicylic acid 12–26 % either alone or in combination with lactic acid has been used successfully over the last years. Mono- and trichloroacetic acid, silver nitrate 10 % solution, cantharidin, phenol, formic acid, pyruvic acid, 5 % glycolic acid, formaldehyde soaks, and glutaraldehyde solution are other options. All these agents need to be carefully administered with clear instructions by the physician. Possible side effects include irritation of the surrounding skin. Less common topical treatments have been tried with varied results such as sensitization with diphencyprone, intralesional

therapy with DNA inhibitors such as bleomycin and 5-fluorouracil, immunomodulatory therapy with imiquimod, photodynamic therapy with topical 5-aminolevulinic acid and white light irradiation, and sodium salicylate 2 % iontophoresis. All common and less common topical treatments are listed in Table 106.1.

More aggressive techniques that are doctor administered and result in topical tissue destruction include: cryotherapy (with liquid nitrogen), curettage and cautery, surgical excision, laser, and intense pulsed light.

Cryotherapy with the use of liquid nitrogen is one of the most widely used treatments for cutaneous warts. It is easy, quick, and effective. The wart is frozen with a 2 mm surrounding halo for approximately 5–10 s. Hyperkeratotic warts need to be pared down before cryotherapy. Sometimes, two freeze-thaw cycles per session are administered. The treatments are repeated every 2–3 weeks. Common side effects include blister formation and transient hypopigmentation. Curettage and cautery is another way of removing the lesion along with electrosurgery to cauterize its base. Scarring is the most significant side effect. Surgical excision is used for removing recalcitrant to treatment warts or when there is diagnostic doubt. Histological confirmation is the most important advantage of this method. When other destructive methods have failed, lasers can be used. Pulsed-dye 585 nm laser, Er:Yag, Q-switched Nd:Yag 532 nm, CO_2, and intense pulsed light are among the ones that have been used. Besides the high treatment cost, they can be painful and may induce disfiguring scarring.

As far as systemic treatments are concerned, oral cimetidine, oral levamisole (anthelmintic drug), oral zinc sulfate, and oral retinoids have been used with moderate results. There are also some anecdotal reports regarding the use of topical cidofovir 1–3 %, vitamin D3 derivatives, hypnotherapy, and a combination of salicylic acid and imiquimod.

Table 106.1 Topical treatment for cutaneous warts at a glance

Common topical treatments	Less common topical treatments
Salicylic acid 12–26 % with or without lactic acid	Formaldehyde soaks
Mono- and trichloroacetic acid	Glutaraldehyde solution
Silver nitrate 10 % solution	Immunotherapy with diphencyprone or with squaric acid dibutylester
	Intralesional bleomycin, zinc sulfate, interferon, or formic acid
	Imiquimod
	5-Fluouracil
	Photodynamic therapy
	Tretinoin
	α-Lactalbumin-oleic acid
	Zinc oxide 20 % ointment
	Duct tape application
	Localized heat therapy

Anogenital Warts

Currently available treatments for anogenital warts are classified into patient-applied and doctor-applied modalities (Table 106.2). Data collected and analyzed confirm that only surgical therapies have a primary clearance rate approaching 100 % and that recurrences can occur after all therapies. The recurrence rate, including new lesions at previously treated or other sites, could reach 30 % or even more. All therapies are associated with local irritation reactions, such as burning, erythema, erosions, and pain.

Table 106.2 Treatments for anogenital warts at a glance

Patient-applied treatments	Doctor-applied treatments
Podophyllotoxin (0.15 % cream or 0.5 % solution)	Cryotherapy
Imiquimod 5 % cream	Trichloroacetic acid (TCA) 80–90 %
Sinecatechin 15 % ointment (in the USA, not in Europe)	Surgery: electrosurgery, curettage and cautery, scissors excision, laser, excision under general anesthesia
	Podophyllin 20–25 % resin (in the USA, not in Europe)

Patient-applied modalities include podophyllotoxin, imiquimod, and sinecatechin. *Podophyllotoxin* (0.15 % cream or 0.5 % solution) is an antimitotic drug that is inexpensive, easy to use by the patient, and safe. Each treatment cycle consists of twice daily application for 3 days, followed by 4 days of rest. This cycle can be repeated if necessary for up to 4 weeks. Use of solution is more convenient for penile warts; the cream can be used for vulvar and anal warts. Clearance rates of 36–83 % have been reported. Meatal warts and warts on keratinized skin can often prove refractory. Recurrence rates of 6–100 % have been reported. It is contraindicated during pregnancy. Podophyllin resin 20–25 %, although available in the USA as doctor-applied treatment, is not generally recommended in Europe due to its mutagenic potential, severe systemic toxicity, and moderate efficacy.

Imiquimod is a topically active immunomodulator that stimulates production of interferon alpha and similar cytokines, necessary to mount an immune response to the warts. Its effects are mediated through agonistic activity toward toll-like receptors (TLR) 7 and 8. Consecutively, nuclear factor-kappa B (NF-κB) is activated which leads to the induction of pro-inflammatory cytokines, chemokines, and other mediators. Antigen-presenting cells and other components of innate immunity are activated, and eventually, a profound T-helper (Th1)-weighted antitumor cellular immune response is mounted. Moreover, independent of TLR-7 and TLR-8, imiquimod causes receptor-independent reduction of adenylyl cyclase activity. Finally, imiquimod induces apoptosis of tumor cells at higher concentrations. It is supplied as a package of 12 individual sachets containing 5 % cream. It is applied three times weekly at bedtime and it is washed off the following morning. Treatment continues until clearance or for a maximum up to 16 weeks. Our impression is, based on clinical experience, that it is more effective on mucosal surfaces and perianally. Any local reactions can be managed by a temporary cessation of treatment for a few days or by reducing the frequency of application. Rare systemic reactions (fever, lymphadenopathy, flu-like syndrome) have also been reported. Clearance rates have been reported between 35 % and 75 %, being higher in women and in the perianal area. Relatively low recurrence rates (6–26 %), comparing to other treatments, have been reported. Animal studies have not revealed any teratogenicity; however its safety during pregnancy has not been established.

Sinecatechin 15 % ointment is a green tea extract with an active product of catechins. It is available in the USA but not in Europe; it should be applied three times daily for no longer than 16 weeks. It should not be washed off after use. No data are available regarding its safety and efficacy compared to other treatments. It should not be used during pregnancy.

Doctor-administered therapies include cryotherapy, trichloroacetic acid (TCA), and surgery.

Cryotherapy is a widely used modality which destroys warts by ice-induced cytolysis. It can be delivered either by "open" or "closed" systems, i.e., with a spray gun device (liquid nitrogen) or a cryoprobe (nitrous oxide or carbon dioxide). The lesion and a surrounding halo of healthy skin are frozen for up to 15 s. One or two freeze-thaw cycles can be administered per session. Cryotherapy is performed at 1–2 weekly intervals. Local reactions include blistering, pain, and transient hypopigmentation. It is a simple, inexpensive technique, safe during pregnancy. Its clearance rates depend on compliance to the administration protocol and can vary between 44 % and 75 %. Recurrence rates are 21–42 % 1–3 months after clearance.

Trichloroacetic acid (TCA) 80–90 % solution is a caustic agent that destroys warts by chemical coagulation of proteins. Although widely used, it has not been investigated properly. It is applied sparingly on the wart either by a cotton tip or an applicator, on a weekly basis. It is most suitable for small, keratinized anogenital warts. It is corrosive and may cause scarring. Resolution rates of 56–81 % with recurrence rates of 36 % have been reported. It is safe during pregnancy.

A variety of *surgical treatments* is available including electrosurgery, curettage and cautery, shave excision, scissor excision, and laser therapy. Their main advantage is the elimination of the warts at a single visit. Routine use of local

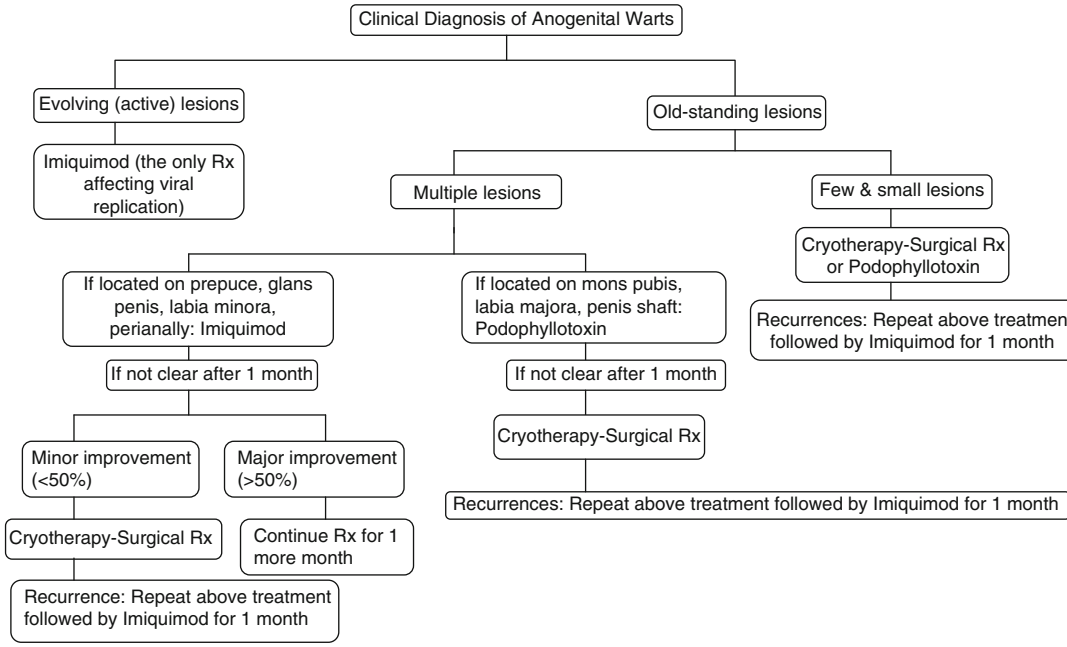

Fig. 106.3 Treatment algorithm for anogenital warts

anesthetic is recommended. Lidocaine 2 % either with or without adrenaline is the most commonly used one. Because most of the warts are exophytic, the resulting wound extends into the upper dermis. If performed carefully and care is taken to control the depth, surgical treatments leave satisfactory cosmetic results. Hemostasis can be achieved by electrocautery or chemical styptics (silver nitrate). Suturing is usually not necessary. Carbon dioxide and YAG lasers destroy warts by emitting very high power densities delivered to small tissue volumes. Fumes from laser treatment and electrocautery contain contagious particles and adequate measures to prevent virus spreading should be used (masks, smoke evacuator). For bulky and extensive warts, anal and intra-anal warts, and significant lesions in children, surgical removal under general anesthesia is indicated.

All treatments have shortcomings; therefore several combination protocols have been used by clinicians. Data evaluating these combinations are limited and further investigation is needed. The same applies for treatments that are generally not recommended due to lack of sufficient data, such as topical or intralesional interferon.

It is obvious that treatment decisions are made based on site, number and extent of lesions, and patients' preferences and needs. A suggested treatment algorithm that is followed by the authors is illustrated in Fig. 106.3.

Prevention

Anogenital warts' spreading is associated with sexual behavior, increased number of partners, and lack of condom use. It is believed that anogenital warts are more common in smokers. Although there is no robust evidence that smoking cessation improves the outcome of treatment or affects recurrence rates, there is a strong rationale from both an individual and a public health promotion point of view for advising smoking cessation. Regular use of condoms reduces but does not eliminate the possibility of viral infection. Nowadays, two HPV vaccines based on virus-like particles are commercially available: a

quadrivalent vaccine against HPV 6, 11, 16, and 18 (Gardasil; Merck) and a bivalent against HPV 16 and 18 (Cervarix; GlaxoSmithKline). There are studies showing near-complete protection (over 90 %) against vaccine-type HPV-associated anogenital warts, low-grade and high-grade intraepithelial dysplasias, and cervical cancer for at least 5 years. Vaccination consists of three intramuscular injections preferably within a period of 6 months according to the following schedule: 0, 2, and 6 months for Gardasil and 0, 1, and 6 months for Cervarix. If flexibility in the vaccination schedule is necessary, it must be noted that the minimum interval period for both vaccines between first and second dose should be no less than 1 month. Also, the third dose should be between 5 and 12 months after the first dose for Cervarix and at least 3 months after the second dose for Gardasil. The need for a booster dose has not been established. Both vaccines are indicated for young girls above 9 years old and for females up to 26 years of age, who did not receive or complete the vaccine series when they were younger. The quadrivalent vaccine can also be used in males 9–26 years old. National vaccination programs vary worldwide. Obviously, these vaccines are most effective when all doses are administered before onset of sexual contacts. The goal is a global vaccination scheme for children and adolescents, so as to establish herd immunity and finally virus elimination.

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Xanthomas

107

Dimitrios Sotiriadis and Aikaterini Patsatsi

Key Points

- In all cases of xanthomas, a thorough detection of a lipid disorder is of great significance.
- Among the different clinical types of xanthomas, eruptive xanthomas, as well as tuberous and tendinous xanthomas, are associated with an underlying hyperlipidemia, which must be detected.
- When the type of an underlying lipid disorder is identified, proper treatment serves in the clinical remission and the prevention of atherosclerosis and pancreatitis.
- Xanthelasmas are mostly found in normolipemic patients and their treatment is based on surgical procedures or destructive modalities.

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Definition

Xanthomas are lesions characterized by the accumulation of lipid-rich macrophages, the foam cells. They may develop in the setting of an altered systemic lipid metabolism.

Basic Concepts of Pathogenesis

Xanthomas have been associated with disorders of lipoprotein metabolism, despite the fact that only a minority of individuals with such disorders develop xanthomas.

A high plasma concentration of lipids leads to the permeation of lipoproteins through the walls of dermal capillaries. The lipid is then taken up by dermal macrophages, which evolve into foam cells.

More than one clinical type of xanthomas may be present in a particular lipoprotein disorder (Table 107.1).

Clinical Presentation

Xanthomas present clinically as yellow or yellow-brown papules, nodules, or plaques.

The amount of lipid present and the depth of accumulated foam cells define the color of lesions. There are distinct clinical forms of

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_107, © Springer-Verlag Berlin Heidelberg 2015

Table 107.1 Types of xanthomas and associated type of hyperlipidemia

Eruptive xanthomas	**Planar xanthomas (palmar, intertriginous)**
Primary systemic hyperlipidemia	*Primary systemic hyperlipidemia*
Familial lipoprotein lipase deficiency (type I)	Familial hypercholesterolemia (type II)
	Familial dysbetalipoproteinemia (type III)
Apolipoprotein C-II deficiency (type I)	*Other primary dyslipidemias*
Familial hypertriglyceridemia (type IV)	Apolipoprotein A-I deficiency
Familial combined hypertriglyceridemia (type V)	Dysproteinemias
Secondary hyperlipidemia	*Special considerations*
	Biliary obstruction
Tuberous xanthomas	**Xanthelasmas**
Primary systemic hyperlipidemia	*Idiopathic – non-hyperlipidemia associated*
	Primary systemic hyperlipidemia
Familial hypercholesterolemia (type IIa, type IIb)	Familial hypercholesterolemia (type II)
Familial dysbetalipoproteinemia (type III)	Familial dysbetalipoproteinemia (type III)
Other primary dyslipidemias	*Secondary hyperlipidemia*
Sitosterolemia	*Other primary dyslipidemias*
Special considerations	Apolipoprotein A-I deficiency
Biliary obstruction	Dysproteinemias
Secondary hyperlipidemia	*Special considerations*
	Biliary obstruction
Tendinous xanthomas	
Primary systemic hyperlipidemia	
Familial hypercholesterolemia (type II)	
Familial defective apo-B100 (type II)	
Familial dysbetalipoproteinemia (type III)	
Other primary dyslipidemias	
Cerebrotendinous xanthomatosis	
Sitosterolemia	
Secondary hyperlipidemia	

xanthomas, with different clinical morphology, sites of predilection, and mode of development:

- Eruptive xanthomas
- Tuberous xanthomas
- Tendinous xanthomas
- Plane xanthomas

Eruptive Xanthomas

Eruptive xanthomas are small, yellow papules, 1–4 mm of size, with a peripheral erythematous halo. They erupt in crops over pressure points and over the extensor surfaces of the arms, legs, and buttocks (Fig. 107.1).

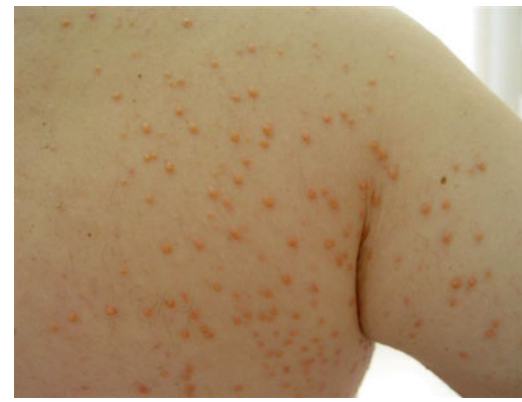

Fig. 107.1 Eruptive Xanthomas

Eruptive xanthomas are a characteristic skin manifestation in patients with familial lipoprotein lipase deficiency which leads to a massive accumulation of chylomicrons in the plasma and

a severe elevation of plasma triglyceride levels (type I pattern, according to Frederickson's classification of familial hyperlipidemia). This hyperlipidemia is extremely rare and may present in early childhood with acute pancreatitis. Apolipoprotein C-II deficiency is another form of type I hyperlipidemia, in patients with genetic defects of the apolipoprotein C-II gene, associated with the eruptive presentation of xanthomas.

This type of xanthomas rarely presents in patients with familial hypertriglyceridemia, leading to the accumulation of VLDL and to severe elevations of plasma triglyceride levels (type IV) or in patients with the combined form of hypertriglyceridemia (type V).

Tuberous and Tendinous Xanthomas

Tuberous xanthomas present as yellow or red nodules located on the extensor surfaces of the extremities, palms, and buttocks. Their initial presentation is that of soft, small, papules, resembling eruptive xanthomas. In the course of time, they enlarge and become firm but they do not attach to underlying structures like tendinous xanthomas.

Tendinous Xanthomas

Arise in tendons, ligaments, and fascia as deep, nontender, firm nodules of various sizes that move with the affected tendon. They are usually 1 cm or larger in size and are most frequently located on the Achilles tendons and the extensor tendons of the hands, elbows, and knees.

Tuberous or tendinous xanthomas may present in patients with familial LDL receptor deficiency and familial defective apoprotein B-100 defects, leading to the accumulation of LDL and elevation of plasma cholesterol levels (type II pattern of hyperlipidemia). These patients have severe atherosclerosis. They may also present in patients with familial dysbetalipoproteinemia (type III) or with sitosterolemia.

Tuberous xanthomas may develop in patients with familial combined hyperlipoproteinemia, leading to the accumulation of both LDL and VLDL, with variable elevations of both triglyceride levels and cholesterol levels in the plasma (type IIb pattern of hyperlipidemia).

Tendinous xanthomas may be found in patients with cerebrotendinous xanthomatosis.

Plane Xanthomas

Plane xanthomas present as soft yellow macules and slightly elevated papules and plaques located anywhere on the body, with a predilection for surgical or acne scars.

This clinical type may present in patients with familial hypercholesterolemia (type II), with familial dysbetalipoproteinemia, leading to the accumulation of LDL (beta-VLDL) and an increase in both triglyceride levels and cholesterol levels in the plasma (type III), with apolipoprotein A-1 deficiency, with dysproteinemias or with biliary obstruction.

Depending on their location, plane xanthomas are further subdivided into xanthelasmas, intertriginous xanthomas, palmar xanthomas, and diffuse (generalized) plane xanthomas.

The most common type, *xanthelasma palpebrarum (XP)*, occurs on the eyelids (Fig. 107.2). Patients with this type of xanthomas are mostly normolipemic. Xanthelasmas may present in patients with type II or type III pattern of hyperlipidemia, as well as in patients with apolipoprotein A-1 deficiency, with dysproteinemias, with biliary obstruction, or with secondary hyperlipidemias.

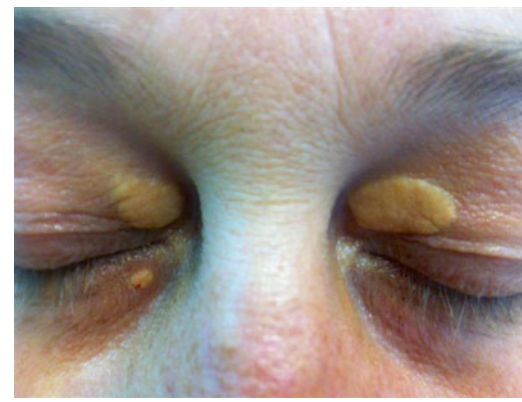

Fig. 107.2 Xanthelasma Palpebrarum

Intertriginous xanthomas present at the intertriginous areas and are pathognomonic of homozygous (type II) familial hypercholesterolemia.

Palmar xanthomas are yellow to orange, flat, linear lesions in the creases of the palms and fingers. They are sometimes subtle, requiring proper lighting in order to be recognized. They are most commonly seen with type III hyperlipidemia.

Diffuse (generalized) plane xanthomas present as macular, yellowish discoloration or plaques, involving particularly the trunk and neck. There is a significant association with lymphoreticular neoplasms and not with lipemic disorders.

Differential Diagnosis

- Lichen amyloidosis
- Disseminated granuloma annulare
- Necrobiotic xanthogranuloma
- Erythema elevatum diutinum
- Necrobiosis lipoidica
- Sarcoidosis

General Principles of Treatment

The most important principle in the treatment of xanthomas is to first detect the presence or not of an underlying hyperlipidemia. Treatment of the underlying disease aims not to improve the aesthetic outcome but to reduce the risk of atherosclerosis associated with lipoprotein disorders.

Eruptive xanthomas usually respond within weeks after initiation of systemic treatment, tuberous xanthomas resolve after months, while tendinous xanthomas take years to resolve or may persist indefinitely.

Xanthomas are very often, but not always, associated with underlying hyperlipidemia.

Treatment of hyperlipidemia consists of diet and lipid-lowering drugs, e.g., statins, bile acid-binding resins, fibrates, and nicotinic acid. Although there are only few well-documented studies to establish the therapeutic efficacy of these agents, eruptive and tuberous xanthomas usually resolve within weeks or months after treatment initiation (Table 107.2). Local surgical or destructive approaches are used mainly for xanthelasmas (Table 107.3).

Table 107.2 Treatment of xanthomas (summary)

Xanthomas (non-xanthelasmas) – treatment options
Diet
Drugs
Nicotinic acid
Bile acid-binding resins
HMG-CoA reductase inhibitors
Fibric acid derivatives
Ezetimibe
Combination of lipid-lowering agents
LDL apheresis

Table 107.3 Treatment of xanthelasmas (summary)

Xanthelasmas – treatment options
Surgical excision
Micrographic surgery
TCA
BCA
Cryosurgery
Electrodesiccation
Lasers (ablative – nonablative)
Diet (?)
Lipid-lowering agents (?)

Diet Therapy

Although diet remains the first step to reduce hyperlipidemia, several studies have reported only modest cholesterol-lowering benefits, generally in the range of a 5–10 % decrease in LDL cholesterol levels. Some patients, however, will have remarkable reduction, up to 25 %, in LDL cholesterol, on diet therapy. In any case, the results of diet should be assessed at least after 4 weeks.

Decreasing total caloric intake and body weight are very important and make a significant impact on lipid levels.

Diet should be very low in total fat or in saturated fats and high in poly- and nonsaturated fats.

There are several nutritional processes to diet therapy. "Mediterranean diet" is a very famous strategy, which maintains total fat at approximately 35–40 % of total calories but replaces saturated fat with nonsaturated ones, such as that found in olive oils. Unfortunately this diet is less likely to reduce HDL cholesterol and to lead to weight loss.

Low-fat, high-carbohydrate diet may result in reduction in HDL cholesterol and dietary changes may also decrease lipid levels in blood. Soluble fiber, garlic, vitamin C, soy protein, and plant sterols may result in reduction of LDL cholesterol. In addition, diet rich in antioxidant vitamins, such as found in fruits and vegetables may also be helpful.

Finally, diet therapy is the most effective management for all types of chylomicronemia.

Systemic Treatments

Several lipid-lowering agents have been proposed for primary hypercholesterolemia treatment, including niacin (nicotinic acid), bile acid-binding resins, HMG-CoA reductase inhibitors, and fibric acid derivatives. In general, the therapeutic goal is approached slowly, following up for side effects and being supportive to diet or other, non-drug therapies.

Nicotinic Acid (Niacin)

Nicotinic acid acts probably through decrease of the hepatic synthesis of VLDL with secondary reduction in LDL and increase in HDL cholesterol levels. This agent will also reduce triglycerides by half, will significantly lower lipoprotein-a levels, and will also increase plasma homocysteine levels. However, because of the need of high doses of nicotinic acid (~3–4.5 g/day) for its hypolipidemic effects, only 50–60 % of patients are able to take full doses due to the increased incidence of side effects.

Flushing, nausea, skin dryness, acanthosis nigricans-like eruption, urticaria, and hyperpigmentation are common side effects. Exacerbation of gout or peptic ulcers may occur. Although nicotinic acid may increase blood sugar in some patients, recent data have shown that it may be administered to diabetics.

Bile Acid: Binding Resins (Cholestyramine, Colestipol)

The resins cholestyramine and colestipol have the advantage of being not absorbed and they work by binding bile acids in the intestinal tube, causing reduction of their enterohepatic circulation. The result of this action is the increase of liver bile acids production, using hepatic cholesterol to do so. Thus, hepatic LDL receptor activity increases with decrease in plasma LDL levels. It has been observed that in some patients, treated with these agents, triglyceride level tends to increase slightly. Therefore, bile acid-binding resins should be used with caution in those with high levels of triglycerides.

Cholestyramine may be most effective in children with inherited hyperlipidemia, in young women of childbearing age, and during pregnancy – but it is contraindicated in type I hyperlipoproteinemia. However, patients – especially children – do not comply, due to the side effects of these drugs, including gastrointestinal symptoms, nausea, gas, and taste disturbance. The dose of cholestyramine is 12–36 g/day (in divided doses) and of colestipol is 20 % higher.

HMG-CoA Reductase Inhibitors (Statins)

These drugs act by inhibiting 3-hydroxy-3-methylglutaryl CoA reductase, the enzyme that facilitates the intracellular cholesterol biosynthesis, with a consequent upregulation of hepatic LDL receptor expression and increased clearance of the LDL from the circulation. Statins are the most effective drugs that reduce cholesterol levels. They have also a moderate action to increase LDL and a slight action to decrease triglyceride levels. Statins have proven to be effective in patients with heterozygous FH and familial defective apolipoprotein B-100 and in patients with secondary dyslipidemias. Atorvastatin (10–80 mg/day), lovastatin, pravastatin (10–40 mg/day), simvastatin (5–40 mg/day), rosuvastatin, and fluvastatin, usually given once a day in the evening, may be used alone or in combination

with other agents such as cholestyramine. In severe cases the combination therapy with statins and LDL apheresis has been particularly effective.

The major side effects of statins are myopathy and hepatotoxicity but they are rare; higher doses cause more side effects. Coadministration of drugs such as fibric acids, erythromycin, or cyclosporine increases the risk of myopathy. Females of childbearing age should be informed about the teratogenicity of statins.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Clofibrate)

Fibrates' main effect is to reduce the synthesis and increase the breakdown of VLDL particles, with secondary effects on LDL (reduce about 10–15 %), triglyceride (reduce about 40 %), and HDL (raise about 15–20 %) levels. These agents are the treatment of choice of severe hypertriglyceridemia and of type III hyperlipoproteinemia. The usual doses, given in the morning, are gemfibrozil (600–1,200 mg/day), fenofibrate (150 mg/day), and bezafibrate (400 mg/day).

Side effects include hepatitis, chololithiasis, myopathy, and increase serum levels of creatinine. The incidence of hepatitis and myopathy may be higher among patients who are also taking other lipid-lowering agents (e.g., the combination of gemfibrozil and statins increases the risk of myopathy).

Ezetimibe

It is the newer lipid-lowering drug that reduces total and LDL cholesterol levels.

It works by inhibition of the intestinal lipid transporter Niemann-Pick C1-like protein. Ezetimibe reduces LDL cholesterol about 15–20 % when used as monotherapy and can further reduce LDL levels in combination with statins. It is generally well tolerated and is the drug of choice in sitosterolemia treatment.

LDL Apheresis

This treatment has been indicated for the most severe cases of hypercholesterolemia. Immunoabsorption, dextran sulfate absorption (DSAL), and heparin-induced extracorporeal LDL precipitate are the most common methods of LDL apheresis.

This therapeutic approach may be applied every 1–2 weeks and can be combined with statins or with other hypolipidemic drugs and suitable diet.

Topical Treatment Approaches

Surgical procedures or destructive modalities are mainly used for xanthelasma palpebrarum treatment. Although XPs are not strictly considered to be treated, patients very often seek removal for aesthetic reasons.

There are many methods available, e.g., microsurgical techniques, blepharoplasty, electrodesiccation, cryosurgery, chemical cauterization (TCA, BCA), and lasers, each with its advantages and disadvantages.

Electrodesiccation and cryosurgery were used mainly in the past for small, stable, and isolated XP, but the cosmetic results of those modalities are generally not acceptable enough.

Surgery is the classical method of treatment for xanthelasma removal. Microsurgical techniques provide excellent results, especially for small XPs. Unfortunately there is a high risk rate (30–40 %) of recurrences, and therefore, patients do not opt gladly this method.

Surgical excision is also indicated for a few cases of tuberous xanthomas.

Trichloroacetic acid (TCA) in different concentrations has been used as tissue cauterant since 1926.

In a recent, well-documented paper, Haque and Ramesh evaluated various strengths of TCA (50, 70, 100 %) in XP lesions. The lesions were categorized according to size and clinical form (flat, papular, or papulonodular). The authors conclude that the selected concentration of TCA for short use is proportional to the clinical severity. Each lesion should be treated for about 1–2 min until the development of frosting. TCA 100 % is recommended for papulonodular XP, TCA 70 % for flat plaques, and TCA 50 % for macular XP.

In any case, according to the current available literature, TCA 70 % seems to be a simple and effective method which achieves a higher rate of patients' satisfaction, despite the fact that TCA 95 % has an overall higher clearance rate.

Main problems of TCA application are determination of the sufficient quantity of the solution that should be applied, the potential need of reapplication and the appropriate time for this action, and, of course, the possibility of side effects.

Most common side effects associated with TCA application include hypo- and hyperpigmentation, while atrophy, scarring, and ectropion are rare and occur usually with higher concentrations (95–100 %).

Use of bichloroacetic acid (BCA) is relatively restricted and seems to be less effective, compared to TCA.

Ablative laser surgery for treating XPs was introduced more than 30 years ago.

Carbon dioxide (CO2) laser, Erbium:ND-YAG laser, Argon laser, and KTP laser are popular options and the results seem satisfactory. Main disadvantage of this option is the induction of pain, and thus, some form of anesthesia is required. Moreover, patients are unable to work for several days.

Nonablative laser (pulsed dye laser) therapy promises good clearance rates in approximately two thirds of the lesions, usually without local anesthesia or major side effects.

Hypo- and hyperpigmentation in about 5–15 % of patients are the most common complications of laser therapy, while persistent erythema, scars, or ectropion rarely occurs. Care must be taken always to protect the eyes.

Combined ablative and nonablative laser surgery may be recommended for the treatment of tuberous lesions. It is very important to emphasize that the risk of recurrence is estimated to be about 40 % and remains almost the same in comparison with the surgical removal. In addition, the wavelength, pulse duration, number of passes, and number of sessions may vary.

In conclusion, management of XPs is difficult, mainly because of the strong possibility of recurrences, regardless of the mode of selected modality.

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Part II

Methods

Acne Scar Treatment

108

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Key Points

- Acne is a chronic inflammatory disease of the pilosebaceous follicles that can leave temporary or permanent scars in a high percentage of patients.
- Techniques at the physician's disposal for the treatment of acne scars are continually increasing.
- Several treatments are now available: from peeling to cryotherapy, fillers, autologous fat implants, lasers, dermabrasion, microdermabrasion, microsurgery, compressive medication, and steroid infiltration.
- The choice of the treatment depends on the type of the scar; their shape, depth, and dimension; the presence of acne active lesions; and personal choices.

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Definition and Epidemiology

Acne is a chronic inflammatory disease of the pilosebaceous follicles characteristically but not exclusively affecting adolescents, having a 35–90 % prevalence in young people between the ages of 14 and 19, generally resolving spontaneously after age 20 in men and age 25 in women. However, in some cases, usually in women, acne can persist through adulthood. The occurrence of scars, more or less pronounced, in patients with previous acne is >80 % of patients. About 5 % of patients present with a severe form of acne, and especially in these cases, acne can result in permanent scars that can be highly disfiguring and conditioning for the patient, causing serious social discomfort and decreased self-esteem.

Typology of Scars

Acne scars can be atrophic, hypertrophic, or keloid. They can vary in shape, depth, and dimension and often coexist in the same patient. The scars also can be associated with skin discoloration (hypo- or hyperpigmentation).

Atrophic Scars

These scars are typically depressed, differing in form and dimension; they can be wide and

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_108, © Springer-Verlag Berlin Heidelberg 2015

shallow (boxcar scars) or narrow and deep (ice-pick scars). When the subcutaneous tissue is severely damaged, they can form tunnels or wide retractions that significantly alter the contours of the face.

- Boxcar scars: these usually are large and superficial. The best treatments in these cases are fillers, peeling, and fractionated CO_2 laser.
- Ice-pick scars: these have a pointed aspect, half walls, extending vertically and deeply (>2 mm). The upper or superior opening is usually wider than the infundibulum. This type of scarring can be treated with punch surgery, ablative fractionated CO_2 laser, and autologous fat grafts.
- Subcutaneous tunnel and scar contractures: these strongly alter the contours of the face. In these cases, surgical excision and aesthetic reparation give more satisfactory solutions.

Elevated Scars

- Hypertrophic scars: these are nodular, with an irregular surface; they can be treated with steroid injections.
- Keloid scars: fortunately, these are quite rare because they are extremely difficult to treat. The rate of unsuccessful treatment is high because often the treated lesions recur or worsen. The best treatments in these cases are steroid injections, compressive medication, or cryotherapy.

General Principles of Treatment

Techniques at the physician's disposal for the treatment of acne scars are continually increasing. All scars can be treated successfully if one is familiar with the various techniques available, the limits, and the indications for each of them. Often the same patient has diverse types of acne scars; therefore, it is fundamental for the physician to know the different therapeutic possibilities and to integrate the various techniques.

Selection of Patients

First and foremost, it is necessary to distinguish the patients with active acne lesions from the patients with scars from preexisting acne. The patients with acne in the active phase may present comedones, papules, pustules, and scarred lesions. In this phase, surgical correction is not particularly indicated; it is instead advisable to treat the acne lesions in the active phase in order to prevent or at least minimize future scarring. Instead, it is possible to surgically treat patients with scars from previous acne.

Treatment of Acne Scars

Minor Surgical Treatment

Peeling

The purpose of peeling is to encourage epidermic exfoliation through the use of chemical agents; these are preferably indicated in the treatment of superficial atrophic scars (boxcar scars). One may employ various types of acids separately or in combination; however, for severe scarring, deep peeling is necessary, as with phenol or trichloroacetic acid (TCA). The skin is cleaned with alcohol after which the acid is applied with a swab. To alleviate post-peeling burning and pain, one may apply ice packs or cold water. Phenol, generally used at 50 % according to the formula backer, can cause liver, kidney, or cardiac damage if absorbed in excessive quantities; further, it can cause postinflammatory hyperpigmentation, especially in subjects with dark skin. TCA peels are safer since they are free of systemic side effects; they can be used at various concentrations according to the desired results to be obtained.

- TCA 20 %: it causes a very superficial exfoliation; thus, it is not very effective for deep scars.
- TCA 35 %: it is used for small and superficial scars as it is a medium-depth peel. After the treatment, the patient is not bandaged but must avoid sun exposure for 3 months using the

highest level sunscreen to reduce the risk of postinflammatory hyperpigmentation.

- TCA 50 %: it is indicated for large and superficial scars. During the first week post-treatment, the patients must be bandaged so the use of TCA has been progressively replaced by equally effective and less disabling techniques (i.e., CO_2 fractionated laser). This peeling causes deep exfoliation with the formation of scabs that detach and expose the epidermis rosea below.
- 50 % is the maximum concentration used; at higher concentration levels, there is a risk of causing atrophic scars and postinflammatory hypo-/hyperpigmentation. However, a new variant of peeling with TCA is the CROSS (chemical reconstruction of skin scars) technique that uses focal applications of TCA at elevated levels of concentration (65–100 %) on the small ice-pick scars; if not done with caution, the risk of creating discoloration or atrophy remains high.

Compressive Medication

External compression using silicone sheets or occlusive dressings can be used to treat recent keloid scars (<6 months). This consists in the application of these dressings to the scars without excessive pressure for 12–20 h, then removed, washed with soap, and reapplied. This type of treatment is also useful for surgically corrected keloid scars to prevent recurrence. The occlusive dressing is not recommended on areas with hair because it can cause folliculitis. The silicone sheets should be replaced every 1–2 weeks, the occlusive bandages every 1–2 months.

Steroidal Infiltration

Localized infiltration of steroids (usually triamcinolone acetonide) is a valid therapeutic alternative for the treatment of hypertrophic or keloid scars, especially when the scars are recent. The steroid works by interfering with the mechanism of scar formation, making it regress. Generally, triamcinolone acetonide 40 mg comes diluted in 3–4 ml of saline solution. Even with this technique, it is preferable to proceed gradually to reduce the risk of inducing cutaneous atrophy. Systemic absorption of the steroid is minimal; therefore, it is extremely rare to observe systemic side effects such as hirsutism, striae distensae, or Cushing's syndrome.

Cryotherapy

This is quite an obsolete technique once used to treat keloid scars. Following infiltrative anesthesia with lidocaine 1–2 %, the freezing of the keloid is carried out with liquid nitrogen. Often more than one session is necessary, 4–6 weeks apart; however, it is preferable to proceed gradually because, especially in patients with a dark complexion, overly aggressive cryotherapy may destroy the melanocytes, leaving behind marked hypopigmentation. Generally, after the treatment, a necrotic crust will form that heals within 2–3 weeks.

Fillers

These are natural or synthetic substances that are injected into depressed scars to fill them from the bottom upward (Fig. 108.1). Fillers are particularly indicated for shallow atrophic scars, although not particularly indicated for ice-pick scars. These fillers may consist of:

- Calcium hydroxyapatite is an optimal polymer for this type of defect as it acts as a support and stimulus for collagen growth, thus having a deep and long-term filling effect (up to 2 years).
- Polylactic acid is a very good filler for correcting acne scars as it not only fills but also stimulates dermal fibroblasts, obtaining a long-lasting effect (up to 2 years).
- Autologous fat (see the following caption).
- Hyaluronic acid is rapidly reabsorbed into the body; therefore, it is not the most recommended product to correct this type of defect.
- Collagen, a material biocompatible with cutaneous tissue, can be used with moderate

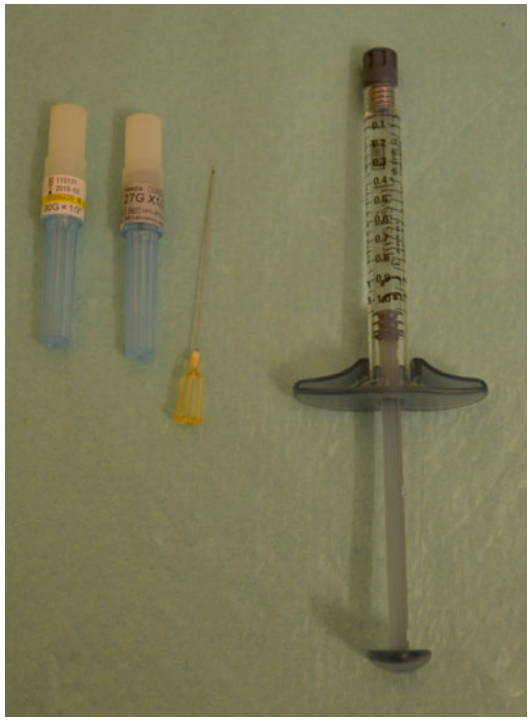


Fig. 108.1 A common filler, new microneedles, and cannulae

success and also has been progressively replaced by products with reduced allergenic potential.

All the materials listed above can be considered safe enough, although transient side effects such as lividity, erythema, or formulation of nodules/granulomas cannot be excluded. Fillers with silicone are now banned in most countries because this synthetic material has generated many cases of granulomatous reactions and improper migration from the point of infiltration.

Autologous Fat Implants

This is used to correct large scars; it is economic and completely biocompatible, does not provoke allergic reactions, and lasts from several months to several years, although the actual duration can be unpredictable. Several factors are indicated in the survival of long-term fat: the patient's age, the site from which the fat is taken, and the technique of processing and implanting. The technique involves the removal of fat from a donor site, preferably under tumescent anesthesia, and subsequent purification by washing, to preserve the vitality of the adipocytes, finally placing the implant immediately, under local anesthesia. All steps involving manipulation of adipocytes are conducted via Luer-Lok syringes to prevent exposure to air and the risk of oxidation. In unfavorable conditions, the graft can be lost after 4 weeks, while in other cases the correction lasts for years.

We can summarize three surgical steps:

Harvesting: the selected anatomical donor region is anesthetized with Klein solution; the necessary amount of adipose tissue is removed by means of invasive microcannulae with a maximum diameter of 1.5 mm connected to 10 cc Luer-Lok syringes (Fig. 108.2).

Purification: multiple methods are used. We prefer washing with saline solution in LL syringe in order to reduce contact with oxygen and related oxidation of adipocytes, for a total of about ten washes (Fig. 108.3).

Implant: adipose tissue presents as bright yellow, using 1.5 mm diameter cannulae for the implantation, and is implanted in the hypodermis at the base of the scars (Fig. 108.4).

The technique is effective, reproducible, minimally invasive, and free of significant complications as it does not require general anesthesia or sedation, and the improvements in the cutaneous quality are always guaranteed (even in the absence of lasting and satisfactory volumetric changes) thanks to the "staminalization" of the fibrous subcutis typical of acne.

CO_2 Laser-Erbium

The advent of laser surgery has created a true revolution in the treatment and resurfacing of acne scars. The two lasers most used are the

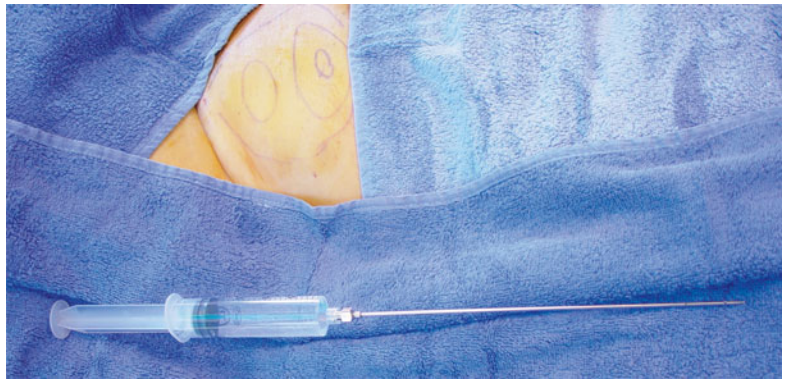


Fig. 108.2 Tumescent anesthesia with syringe and multihole cannula for infiltration

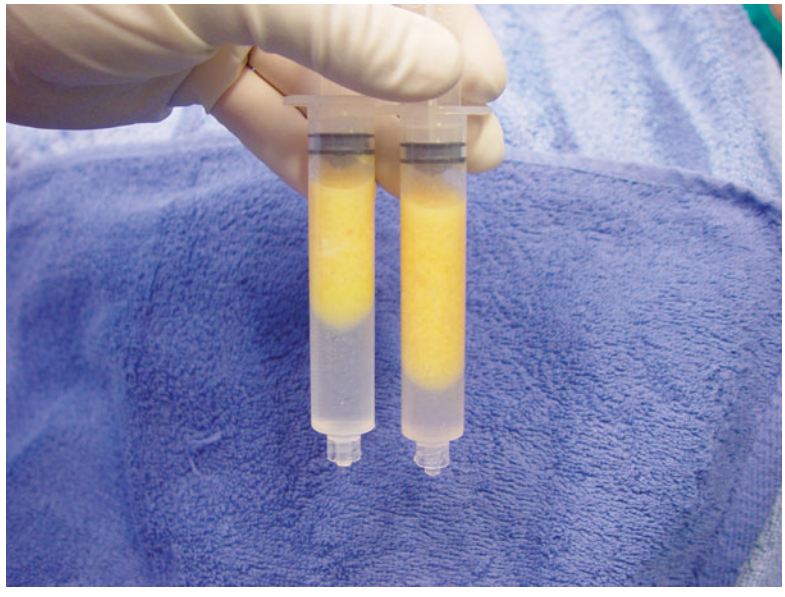


Fig. 108.3 Fat's decanting in FS

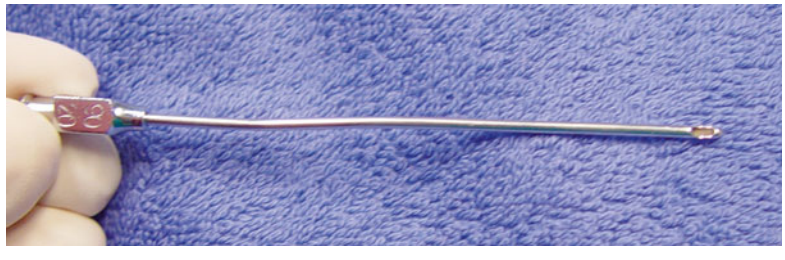


Fig. 108.4 Cannula for implant

CO_2 and the Er:YAG. With these lasers, it is possible to evaporate with precision small areas of cutaneous tissue removing only the most superficial layers. The non-fractionated ablative technique was gradually replaced by the fractional modality that exploits the principle of fractional photothermolysis producing microscopic vertical columns of thermal damage separated between them by healthy tissue. Fractionation has notably reduced post-treatment irritation (erythema, swelling) and the risk of side effects such as hyperpigmentation. Fractionation, in turn, can be utilized in the ablative modality that determines various degrees of cutaneous vaporization stimulating healing with the formation of new collagen and elastin or in the non-ablative modality that does not vaporize but heats the skin and thus is better tolerated by the patient. Generally, the ablative technique causes an erythema of variable duration that lasts between 3 and 14 days (1–3 days for non-ablative), and the risk of postinflammatory hyperpigmentation lasts about a month (15 days with non-ablative). The major indications for using the fractionated technique are atrophic scars, while for ice-pick scars surgical excision is preferred, a few weeks following resurfacing. This technique has also proved moderately useful for hypertrophic scars and hyperpigmentation. The laser setting depends on the depth of the scars, generally using only the erbium laser for the more superficial scars, and using the CO_2 alone or in combination with the erbium for medium to deep scarring. The technique, non-fractionated and non-ablative, is decidedly less effective, and its use is limited to very mild acne scars.

Dermabrasion-Microdermabrasion

Dermabrasion is a technique, now obsolete, known since the First World War, that consists of removing with wire brushes or abrasive diamonds the epidermis and the superficial dermis, leaving behind noticeable scars. Furthermore, this technique is contraindicated in subjects with dark skin, black skin, and olive skin which raise the risk of hyperpigmentation. Microdermabrasion is a variant of its predecessor that uses less traumatic instruments; however, it is an extremely operator-dependent procedure, and other techniques have shown greater efficacy and safety.

Treatment of Discoloration

Postinflammatory hyperpigmentation of scars can be treated with bleaching preparations (e.g., undecylenoyl phenylalanine or diacetyl boldine), light skin peeling, or pigmentary laser. Scars with persistent erythema can be treated with a vascular laser (e.g., dye laser) or pulse light. Hypopigmented scars are more difficult to treat although non-ablative fractionated laser has proved quite useful in these situations.

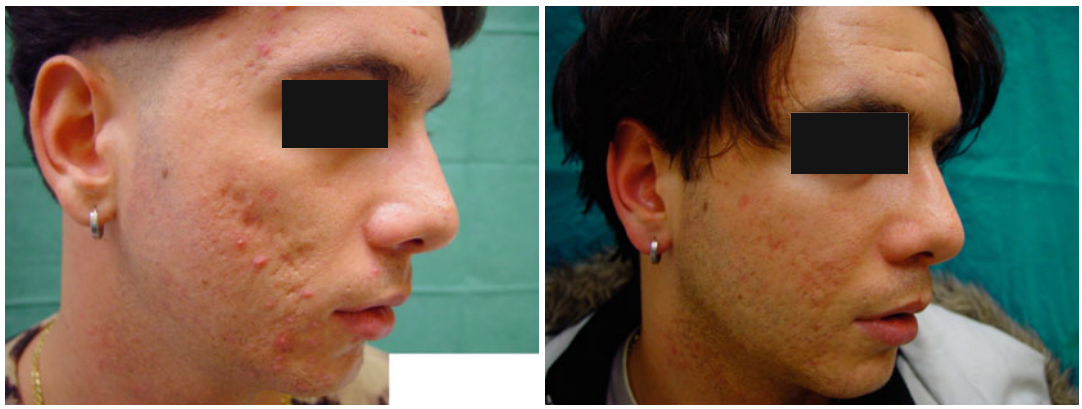
Microsurgery

When performed by experienced personnel, this remains one of the best treatments, using two techniques:

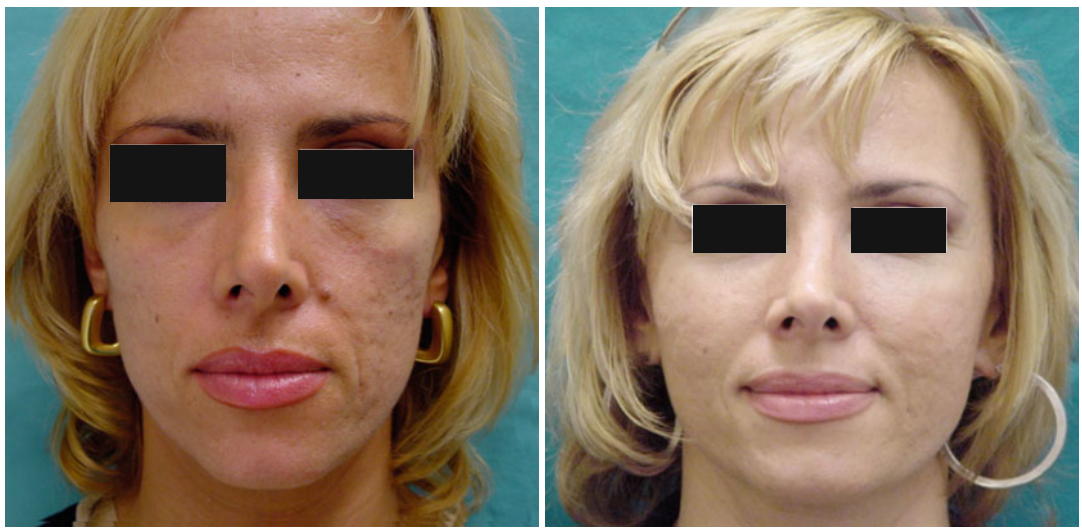
- Punch microsurgery: punches from 0.5 to 2 mm are used, depending on the size of the scars. After local anesthesia, the scars are carried away, and the full-thickness tissue loss is repaired with absorbable 5-0, 6-0 sutures, intradermal nonabsorbable nylon 6-0 sutures, or external 7-0 sutures with nylon. Ideal for treating small ice-pick scars.
- Cold blade microsurgery: classic surgery with local anesthesia and a No. 15 blade. Usually used for extensive scarring and elongated scars for which it is not possible to use punch surgery. Suturing is the same as aforementioned.

Cases

Patient 1: box scars of the face treated with microsurgery and lipofilling, followed by CO_2 laser treatment



Patient 2: acne scars treated with microsurgery (plus nevus) and lipofilling, followed by erbium lasers treatment



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Biopsy

109

Eckart Haneke

Key Points

- Histopathology is the most important method in dermatology and requires good biopsy specimens for diagnosis.
- In most European countries, biopsies are daily routine procedures for virtually all dermatologists.
- Poor biopsy specimens hinder the diagnostic process and there are many pitfalls in performing biopsies.

Indications for Biopsy

Each piece of tissue that is removed should be examined histopathologically. However, multiple benign lesions such as acrochordons, seborrhoeic keratoses or mollusca contagiosa may not require histopathology though one representative lesion should be sent for histopathologic examination. The extent of a biopsy is governed by the suspected clinical diagnosis: whereas benign lesions may be partially or sequentially removed, a diagnostic therapeutic excisional biopsy is indicated for malignant lesions such as melanoma.

The most important reasons for biopsy are:

- To make or confirm the diagnosis
- Tumour grading and staging
- Follow-up
- Scientific documentation

Biopsies can be divided according to the

- Instrument used for biopsy
- Depth of biopsy
- Tissue biopsied

Biopsy Techniques

Punch Biopsy

The punch is a cylindrical knife that cuts into the tissue while rotating it on its longitudinal axis with some downward pressure. Disposable punches are commonly used because they are usually sharper and less traumatizing. Punch diameters range from 1 to 8 mm with those of 4 and 6 mm being most often used for diagnostic purposes. They are held vertically on the skin surface and the tissue cylinder is cut out with turning motions under slight pressure. The tissue is then gently lifted, either with a forceps or the tip of an injection needle that has been bent to

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_109, © Springer-Verlag Berlin Heidelberg 2015

90°, and it is cut at the level of the subcutaneous fat. Extreme caution is necessary not to squeeze the tissue specimen as this will give rise to hourglass deformation of the tissue cylinder with crush artefacts of inflammatory and often also neoplastic cells rendering the biopsy more or less useless.

Punch biopsies are not adequate for lesion of or extending into the fat tissue or for bullous lesions as the blister roof will inevitably be sheared off. They are also not indicated when architectural features are necessary components of the lesion. Small punch biopsies may be left for second-intention healing whereas those of 4 mm and more are usually sutured. Monofil suture material, 5-0 or 6-0, gives good cosmetic results. A modified cross-stitch technique with the stitches over the skin running parallel ensures excellent defect closure.

Scalpel Biopsy

The scalpel is the universal instrument for any type of biopsy and virtually all tissues. Most diagnostic biopsies are performed as fusiform or elliptical excisions of tissue. Although many different types of scalpel blades are available, the pointed #11 blade usually gives the best results, especially for smaller biopsies. Its sharp tip is vertically stabbed into the skin and the desired biopsy is sectioned with either a straight cut through the entire skin down to the subcutaneous fat or with gently stabbing motions, carefully avoiding 'carving' motions. Depending on the type of lesion, the biopsy should either include the entire lesion, a representative portion of it from one end to the other, or the margin with both the centre of the lesion and normal surrounding skin. A small drawing showing the lesion, the biopsy and how it is supposed to be cut in the laboratory should accompany the biopsy so that the histopathology lab can see how the biopsy was performed and how it has to be sectioned in order to yield adequate sections for histological diagnosis.

The biopsy defect is usually closed with simple interrupted stitches, 5-0 for most localizations, 6-0 for the face, 7-0 for the eyelids and 4-0 for the scalp, trunk and extremities. Buried sutures using monofil absorbable material give the best cosmetic result. For particularly delicate locations, the suture should be secured with suture strips. Tissue glue is adequate for narrow defects that can be closed without tension. However, scar dehiscence remains a common problem, particularly on the back. Tiny dog-ears may develop when the length-to-width ratio was too small; they are particularly disturbing on convex surfaces in the face.

Electrical Scalpel and Laser Biopsies

Classical electrosurgery with kHz alternating current gives huge margins of heat destruction that are not suitable for histological examination. However, both radiofrequency at around 3.8 MHz and CO_2 laser are much less tissue damaging and may be used in highly vascularized areas. They have the advantage of leaving an almost bloodless field due to the heat generated by these devices. The disadvantages are heat artefacts of the margins of the biopsy specimens and prolonged healing with inferior cosmesis of the biopsy scar.

The suture technique depends on the site, size and depth of the wound, but in many cases, small wounds are left for second-intention healing.

Curette Biopsy

Even though the curette is useful to remove superficial lesions, it is too coarse an instrument for almost all diagnostic biopsies. It yields tissue debris that no longer allows the architecture of the lesion to be evaluated. However, an alternative is the sharp ring scalpel, which allows strips of tissue to be cut superficially from the skin without severe tissue damage.

The resulting defect is left for second-intention healing. Use of a hemostyptic solution or electrocautery to stop the bleeding etches or burns the wound base and excessively prolongs the healing time; often a whitish scar is the result. Application of a thick padded dressing with plenty of ointment to adsorb the blood and avoid sticking to

the wound is therefore recommended. This can be removed after 24 h and only an antibiotic ointment is applied several times a day. It should be continued for several days in order to avoid drying out of the wound. Healing is twice to three times faster with moist wound healing.

Depth of Biopsy

Tangential (Shave) Biopsy

This very superficial biopsy is a simple, inexpensive and time-honouring procedure. It should only be used for very superficial lesions involving the epidermis and papillary dermis. The lesion is slightly raised, either by gently pinching the skin around it or by injecting a sufficient volume of local anaesthetic under it. A #23 scalpel, or for very small lesion #15, is pressed flat on the neighbouring skin and the lesion superficially biopsied or excised with back-and-forth sawing movements parallel to the skin surface. Depending on the size of the scalpel blade, relatively large superficial biopsies can be taken resembling split-thickness skin grafts. The thin specimen is transferred with the scalpel blade upside down onto wet gauze and gently spread. A small piece of filter paper is then pressed on it where it sticks. The perfectly spread specimen is immersed into 4 % formalin solution for fixation. For embedding and sectioning, the specimen is laid between two foam sheets and brought into the cassette.

The wound is left for second-intention healing. We do not favour haemostasis as this delays wound healing.

Tangential biopsies are ideal for seborrhoeic keratoses, actinic keratoses and other lesions sitting on the skin or only affecting the epidermis and papillary dermis. They are not adequate for most inflammatory lesions or those extending into the hair follicles and for most tumours.

Full-Thickness Skin Biopsy

In most instances, a full-thickness skin biopsy including the epidermis, papillary and reticular dermis and superficial subcutaneous fat is the best option. It is indicated for virtually all dermatoses including inflammatory, autoimmune bullous disorders and most skin tumours. The universally useful instrument for these biopsies is the scalpel. Biopsies can be taken from everywhere and in all depth levels needed, including fat, fascia, muscle and other structures. A scalpel biopsy is usually fusiform and does not have to have a wide transverse diameter; rather, when indicating on the report sheet that the biopsy specimen has to be cut lengthwise, a narrow but longer biopsy gives even more information. Marking the specimen can help the laboratory in the orientation of the specimen.

Biopsies of subcutaneous tissue may be taken for the diagnosis of lesions in the hypodermis; whether or not overlying dermis and epidermis are included depends on the specific problem. However, inflammatory diagnoses always require the overlying skin.

Tissue for Biopsy

Scalp

Scalp biopsies are frequently taken for diagnostic purposes. For the diagnosis of alopecias, two punches may be taken resulting in a figure-of-eight defect: One of the punch specimens is cut horizontally at different levels, the other one vertically. Care has to be taken to orient the punch along the axis of the hair follicle. The margins of the figure-of-eight-shaped defect are moved parallel to each other so that a tongue-in-groove picture results. Two stitches keep the wound together yielding a lazy S scar line.

Ear

A biopsy including the cartilage is indicated for the diagnosis of relapsing polychondritis and pseudocysts of the helix. Local anaesthesia is performed in the retroauricular fold and a narrow spindle with underlying cartilage is taken from the back of the pinna. The skin is closed with a running suture without touching the cartilage.

Cartilage only is taken for the treatment of chondrodermatitis nodularis helicis as a subcutaneous chondrectomy via a short incision of the helix margin along its posterior aspect.

Vermilion of the Lip

Vermilion biopsies are indicated for precancers and carcinomas as well as for rare isolated labial involvement of psoriasis and other dermatoses. An incisional biopsy should always be a narrow spindle oriented perpendicular to the mouth opening. Benign and precancerous lesions do not require inclusion of the orbicularis oris muscle, which is, however, necessary for suspected labial carcinoma.

Oral Mucosa

Biopsies of the labial and buccal mucosa are as easy to perform as skin biopsies. However, the common infiltration local anaesthesia causes an instream of plasma into the epithelium with vacuolization of keratinocytes, crescentic deformation of their nuclei as well as intra- and intercellular deposition of immunoglobulins and other proteins. For suspected immunodermatoses, a regional block of the mental or infraorbital nerve should be used if possible. Suture is performed either intramucosally or with soft threads.

Both the hard palate and the attached gingiva are rarely biopsied. The biopsy should be small as suture is usually not possible; the wound may be sealed with dental silicone paste.

Biopsies of the dorsum of the tongue involve both the epithelium and the lingual musculature. A narrow spindle of tissue is excised and the wound sutured without tying the knot too tight.

Minor salivary gland biopsy is a valuable adjunct for the diagnosis of Sjögren's syndrome. After mental block anaesthesia, a 2 cm incision is made between the vermilion and the fornix inferior opposite the second incisor. The wound is gently spread exposing the peppercorn-sized greyish-glossy labial glands. These are separated from the underlying submucosa using blunt-tipped curved scissors. Six to eight glands should be collected. Infiltrates of more than 50 lymphocytes are typical, but epithelial islands are rare in minor salivary glands.

Axilla and Other Apocrine Regions

Inflammatory and tumourous lesions may occur. Biopsy site and size are chosen according to the suspected lesion. Since these are intertriginous regions with maceration due to eccrine sweat and often heavy bacterial and fungal colonization, airtight dressing must be avoided and dry sterile ones reapplied every 24–48 h.

Breast and Nipple

Punch and scalpel biopsies are commonly oriented along the relaxed skin tension lines, but those of the nipple always in radial manner. A vasoconstrictor added to the local anaesthetic agent causes the nipple to contract and is therefore not recommended. A layered suture with fine material is used to prevent scar dehiscence and the patient is asked to wear a tight-fitting sports bra for the next days.

Penis and Scrotum

The glans penis often presents plaque-like red lesions; the differential diagnosis of which can be difficult. Superficial infiltration anaesthesia elevates the lesion and allows for easier separation of the superficial glans skin from the subepithelial connective tissue. The defect is sutured with fine simple stitches.

Prepuce and penile shaft are biopsied like any other skin region.

Biopsies of scrotal lesion should include the epidermis, dermis and tunica dartos. This is a layer very rich in smooth muscle bundles extremely sensitive to pressure from tying a knot tightly.

Vulva

The labia minora are similar to scrotal skin. However, biopsies for suspected malignancies must reach into deeper tissue. A superficial biopsy is not sufficient for the exact diagnosis of Paget's disease.

Lesions of the labia minora are biopsied by removing a full-thickness wedge of tissue and a two-layered suture is used for repair.

Palms and Soles

Both inflammatory and neoplastic lesions occur. For small lesions, a 3–4 mm punch is ideal. If possible the handedness of the patient is respected: e.g. the left palm is chosen for right-handers.

Biopsies for the sole of the foot have to be kept as small as possible. A punch is ideal. Local anaesthesia is commonly very painful and infiltration may have to be started from the side of the foot. The subcutaneous tissue with its elastic cushion function is unique in the human body. Even though the skin appears to be resilient, sutures tend to cut through due to the stress and strain from walking and running.

Nails

Histopathology is the gold standard for the diagnosis of nail diseases. This requires, however, an optimal biopsy. The nail forms a functional unit with the tip of the digit and the distal interphalangeal joint and is made up of four different components: matrix and nail bed, the proximal and two lateral nail folds, the hyponychium and the cuticle, and the nail plate. Understanding the physiology and biology of nail growth is essential for a good nail biopsy.

Lesions of the nail folds are biopsied according to their size and orientation; if Bowen's disease is suspected, a very superficial biopsy is adequate to make the diagnosis. Digital recurrent herpes simplex can be diagnosed from a Tzanck smear or a blister roof biopsy. Pemphigus of the nail usually hides as suppurative chronic paronychia and may be diagnosed by a Tzanck test. For the diagnosis of autoimmune collagen diseases, a crescentic biopsy of the free margin of the proximal nail fold was recommended. For more tissue, a wedge of the proximal nail fold with its base at the free margin may be performed. Nail bed lesions can be biopsied with a 3 or 4 mm punch; whether or not the overlying nail plate is removed prior to biopsy depends on the condition. Usually the nail plate will shear off anyhow so it can be removed facilitating the biopsy procedure. If a scalpel biopsy is taken from the nail bed, the long axis of the spindle must be oriented longitudinally along the direction of the unique nail bed rete ridges. In contrast, a deep matrix biopsy must be oriented in transverse direction in order to prevent longitudinal post-biopsy scar, which would result in a split nail. A matrix punch biopsy must not be wider than 3 mm at maximum.

For the diagnosis of longitudinal melanonychia, a tangential biopsy technique was developed that avoids the risk of post-biopsy nail dystrophy. The proximal nail fold is cut at its both sides, separated from the underlying nail plate and reflected. The nail plate is then gently separated from the matrix at one side, cut transversely between the proximal and middle third just 3 mm beyond the pigmented streak and opened in a trap-door manner exposing the origin of the longitudinal melanonychia. A very shallow incision is carried out around the lesion with an adequate safety margin, usually 3 mm, sometimes more, and the scalpel blade is pressed on the matrix parallel to cut the lesion out tangentially by sawing back-and-forth motions. The thin slice of matrix is laid on wet gauze, transferred to filter paper and immersed into formalin. The nail plate is laid back and fixed with a stitch, and the proximal nail fold is laid back and also fixed with stitches or suture strips. Healing is without nail dystrophy as the biopsy leaves the morphogenetic onychodermis behind allowing for complete restitution of the matrix.

Muscle

Muscle biopsies are performed in dermatology for the diagnosis of dermatomyositis. The most

commonly affected muscle is the triceps. Local anaesthesia is performed for the skin by infiltration of the subcutaneous tissue. The muscle is not directly injected. An incision is made through skin, fat and fascia. Two bites of a suture are made with a sufficiently big needle in a distance of 1.5–2 cm and gently tied. The muscle is carefully isolated between the sutures using blunt-tipped scissors and cut beyond the sutures so that the muscle tissue can be lifted out without touching it with a forceps. It is of utmost importance not to squeeze or otherwise traumatize the tissue as skeletal muscle cells are extremely sensitive. Depending on the preferences of the laboratory, the fixative is chosen; some authors stretch the specimen out by pinning the sutures on a small plate of cork or cardboard.

Artery

Arteritis temporalis is the classical indication for an arterial biopsy in dermatology; it may even be curative in the sense that it prevents extension of the disease. The artery is usually palpable as a hard string. The skin is incised over it; the artery dissected with enough periarterial tissue around it, ligated on both sides of the artery biopsy; and the interior part is taken for histopathology. Sometimes there is a diffuse erythematous swelling not permitting the artery to be palpated. Then a deep biopsy is taken at its supposed localization; as the artery is occluded, there is no risk of excessive bleeding.

Occasionally, a venous biopsy is taken. Again, the vein is ligated proximally and distally and then a 1 cm long piece is biopsied.

Nerve

The classical nerve biopsy site is the sural nerve. This is infrequently done in dermatology as many skin biopsies contain enough nerves to make the diagnosis of some disorders. Sural nerve biopsy is an invasive procedure performed in the operating room, and it carries potential risks such as pain and permanent sensory loss distal to the biopsy site. In fact, punch biopsies of the skin are recommended for the diagnosis of neuropathies by neuropathologists. The density of small fibres can be measured easily in skin sections immunostained with antibodies against markers expressed by peripheral nerve fibres, such as protein gene product 9.5, microtubules and neuropeptides.

Testicle

In some countries, andrology and male fertility diagnostics are part of dermatology. Although spermiogrammes give a lot of information, azoospermia, such as in the Sertoli cell-only syndrome, requires confirmation by a testicular biopsy. The scrotum is anaesthetized next to the raphe scroti and an incision is made through the scrotal skin, then the other deeper layers which are individualized and clamped as they will have to be sutured individually. The testicle is identified by its smooth and shining surface. A small spindle is taken, about 10–15 mm long, 5 mm wide and 10 mm deep. The tissue is very fragile and has to be handled with utmost care. Fixation is with Carnoy's or other solutions allowing better tissue conservation and details than formalin. The testicle is sutured with catgut as the other deeper layers, and a skin sutured completes the procedure. The patient gets a light dressing and a suspensory; the testicles are laid on a small cushion for about 24 h.

Conclusion

Biopsies are indispensable procedures in dermatology. Most techniques are easy to perform and yield a wealth of information not matched with any other technique. Histopathology, immunofluorescence, immunohistochemistry, cultures and polymerase chain reaction from biopsy material as well as many other sophisticated techniques allow most diagnoses to be made with certainty.

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Botulinum Toxin in Aesthetic Medicine

110

Barbara Boone and Koen De Boulle

Key Points

- Thanks to its proven efficacy and favourable safety profile, the injection of botulinum toxin (BT) is rapidly gaining popularity in the field of aesthetic medicine.
- Although BT is FDA approved only for the treatment of vertical glabellar lines, hyperkinetic facial lines and primary axillary hyperhidrosis, off-label use in the approach of dynamic wrinkling and sculpting of the face is widespread.
- There are different BT products on the market each with their specific characteristics.
- A thorough history and clinical examination should be performed before treatment in order to identify contraindications and to adjust the patient's expectations which are sometimes too high.
- The patient should be well informed about possible risks and side effects.
- A correct treatment procedure demands a thorough knowledge of the product used, human anatomy and the injection technique. Despite this knowledge one should always be aware of possible complications and have the know-how to handle them.
- This review aims at giving a better insight in the responsible use of BT as a minimal invasive technique in aesthetic medicine.

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General Principles

During the eighteenth century, consumption of improperly preserved or stored meat and blood sausages gave rise to botulism with general muscle paralysis and many deaths in Germany. Justinus Kerner was the first to link these cases to the presence of a toxin or poison in the sausages in anaerobic conditions. He concluded that the toxin acts on the motor nerves and the autonomic nervous system and that it is strong and lethal even in small doses.

On December 14, 1885, a large outbreak of botulism occurred in Ellezelles (Belgium) after the meal of pickled and smoked ham during a funeral ceremony. Different guests noticed symptoms as mydriasis, diplopia, dysphagia and dysarthria followed by increased muscle paralysis. Three persons died. Emile Pierre Marie Van

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_110, © Springer-Verlag Berlin Heidelberg 2015

Ermengem, Professor of Microbiology at the Ghent University, isolated an unknown bacterium in the ham and the corpses of the victims and called it *Bacillus botulinus* (botulinus = intestine, sausage).

During the first decades of the 1900s, it was discovered that seven different strains of *Bacillus botulinus* exist. They each produce their specific neurotoxin serotype (A, B, C1, D, E, F, and G). In 1949 Burgen discovered that BT blocked the release of acetylcholine at neuromuscular junctions.

During World Wars I and II, BT was known as a potential lethal biological weapon.

In 1946 Schantz produced the first batch of toxin which was the basis for the later clinical production. During the 1970s, Alan Scott, an ophthalmologist from San Francisco, used BT serotype A in the treatment of strabismus and blepharospasm. In 1989 BT, as manufactured by Schantz, was approved by the FDA in the use of strabismus, hemifacial spasm and blepharospasm. Later, the FDA has approved other BT drugs and of a broader range of BT treatment indications.

In 1992 Carruthers JD and Carruthers JA published the first reports regarding improvement of glabellar frown lines in patients treated with BT because of blepharospasm. Since 2002 BT is FDA approved for the treatment of these glabellar frown lines.

In 1994 Khalaf Bushara showed BT to inhibit sweat production. In 2004 the FDA approved BT in the treatment of idiopathic axillary hyperhidrosis.

Currently clinical indications for BT are still expanding and the off-label use of the drug is widespread.

Mechanisms of Action: Pathophysiology and Pharmacokinetics

BT is synthesised by the bacterium *Clostridium botulinum*. There are seven different serotypes (A, B, C1, D, E, F, and G). Only serotype A and B are used for clinical implications because their effect lasts longer in comparison to the other serotypes. BT is a very lethal substance with an LD_{50} (= lethal dose, dose causing death in 50 % of a mouse population after intraperitoneal injection) ranging between 0.1 and 1 ng/kg body weight.

The neurotoxin is initially synthesised as a precursor protein and consists of one chain with a molecular weight of 150 kDa. Then the protein undergoes post-translational, activating changes. Specific proteolytic activity, also called 'nicking', causes the formation of a light (50 kDa) and a heavy (100 kDa) chain which are interconnected by a strongly conserved disulphide bridge. This neurotoxin is non-covalently bound to non-toxic haemagglutinins, which impart stability and thereby prevent degradation. Also these non-toxic proteins would potentiate the biological activity of the neurotoxin.

BT exerts its effect via inhibition of exocytosis of the neurotransmitter acetylcholine at the cholinergic nerve ends. Under normal circumstances, release of acetylcholine in the synaptic cleft causes activation of the target cells amongst which the striated and smooth muscle cells as the eccrine sweat glands. Striated muscles are innervated by cholinergic neuromotoric nerves, whereas eccrine sweat glands (involved in the process of hyperhidrosis) are innervated by post-ganglionic cholinergic sympathetic nerves.

Acetylcholine is present in vesicles at the cholinergic nerve terminals. Fusion of the vesicles with the cellular membrane of the nerve terminal is achieved via three different SNARE (soluble N-ethylmaleimide-sensitivity factor attachment receptor) proteins and causes the release of acetylcholine.

BT diffuses through systemic circulation towards the presynaptic membrane. There the heavy chain portion of the molecule binds to the cell membrane of the motor nerve via an unidentified high-affinity acceptor molecule. Internalisation of the toxin occurs as the protein passes through the cell membrane of the motor nerve and into its cytoplasm through endocytosis. By high acidity in the endosome, the toxin undergoes conformational changes causing translocation of the light chain towards the cytosol. The light chain with its very strong zinc-dependent

endopeptidase activity then binds with high specificity to three different SNARE protein complexes. BT serotype A and E cleave the synaptic vesicle protein SV2 of SNAP-25 (synaptosomal-associated protein of 25 kDa); BT serotype B, D, F and G cleave synaptotagmin I and II of VAMP (vesicle-associated membrane protein); and BT serotype C cleaves both syntaxins as SNAP-25. This cleavage procedure enables vesicles containing acetylcholine to attach to the cell membrane.

Recently it has been observed that BT not only inhibits the release of acetylcholine but also influences the release of other neurotransmitters as noradrenaline, dopamine, serotonin, ATP and glutamate.

The clinical effect of BT starts 2–3 days after injection and reaches its maximal point at 5–6 weeks. This effect is only temporary. Previous nerve-impulse activity is restored over the course of several months. This phase consists of nerve sprouting and reestablishment of the original nerve connection. The duration of the effect of BT is not determined by its molecular target (cleaved SNARE proteins are degraded with a half-life of 1–2 days) but by its intrinsic proteolytic activity. This activity differs between the different BT serotypes. Serotype A has the longest duration of action. During nerve sprouting, new nerve endings emerge and connect to the neuromuscular junction after the original nerve ending is blocked. Eventually the new nerve sprouts retract and the original nerve ending regains its function. Clinical findings suggest the process of nerve sprouting would not take place at the level of the eccrine sweat glands, since the effect goes up to 6–12 months. An additional difference between both target organs is the fact that BT causes muscles to atrophy, whereas eccrine sweat glands do not undergo structural changes. This observation explains why the interval of administration can be extended when treating muscles but not when treating eccrine sweat glands.

Classical kinetic and distribution studies cannot be performed with BT since the applied dosages are extremely low and the molecule is quickly and irreversibly bound to the cholinergic nerve endings. Allergan has performed distribution studies in animals with Botox® and Vistabel®. They show a slow muscular diffusion of ^{125}I- BT serotype A, followed by a rapid systemic metabolisation and urinary excretion. Radioactivity is bound to large protein molecules at the injection site, whereas it is bound to small protein molecules in the plasma. Sixty percent of the radioactivity is excreted within 24 h. The toxin is probably metabolised by proteases and the molecular components are recycled by the classical metabolic pathways.

In conclusion BT is not expected to be present in the peripheral blood at measurable levels following intramuscular or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects as muscle weakness in patients without other neuromuscular dysfunction. However, subclinical systemic effects have been shown by single-fibre electromyography after intramuscular doses of BT appropriate to produce clinically observable local muscle weakness.

Pharmacology of BT

Several BT products are widely available. They differ in composition, serotype, concentration, toxin complex size, molecular weight, target protein, biological activity, risk of antigenicity, pH, storage, indication of use and geographic distribution. The most commonly used BT products for facial aesthetics are Botox®, Dysport® (Azzalure®) and Xeomin® (Bocouture®). Other BT products are available in select geographic regions: Korean Neuronox® is approved for cosmetic indications in different countries, as is the Chinese Lanzhou BT, in South America and some other countries under the name Prosigne®. New BT drugs are under development at Tokushima University (Japan) (PureTox®) and at the Mentor Corporation (USA) (see Table 110.1).

Some of the clinically relevant properties of the different commercially available BT products are commented below.

Table 110.1 Different BT drugs

	Onabotulinum	Abobotulinum	Incobotulinum	Botulinum toxin	Botulinum toxin	Botulinum toxin	Rimabotulinum
Brand	Botox®	Dysport®	Xeomin®	Hengli®	Neuronox®	PureTox®	Myobloc®
	BotoxCosmetic®	Reloxin®	Bocouture®	Lantox®	Meditoxin®		Neurobloc®
	Vistabel®	Azzalure®		Redux®	Botulift®		
	Vistabex®			CBTX A®			
				Prosigne®			
Manufacturer	Allergan, Inc. (USA)	Ipsen, Inc. (UK)	Merz Pharmaceuticals (Germany)	Lanzhou Institute of Biologic Products (China)	Medy-Tox, Inc. (South Korea)	Mentor Corporation (USA)	Solstice Neurosciences, Inc.; Eisai Co., Ltd. (USA)
		Medicis, Inc. (USA)					
Approval							
Countries	Worldwide	>65 countries (Europe, US)	Europe, USA, Mexico, Argentina, South Korea	>10 countries China, Brazil, South Korea	Korea, India, South America		USA, Europe
Indications	Blepharospasm	Blepharospasm	Blepharospasm	Blepharospasm	Blepharospasm	Phase 3:	Cervical dystonia
	Cervical dystonia	Cervical dystonia	Cervical dystonia	Cervical dystonia	Cosmetic indications	Glabellar frown lines	
	Focal spasticity	Focal spasticity	Glabellar frown lines	Glabellar frown lines		Phase 1:	
	Glabellar frown lines	Glabellar frown lines		Hyperhidrosis		Cervical dystonia	
	Hyperkinetic/upper facial lines	Hyperhidrosis					
	Hyperhidrosis						
	Migraine						
	Urinary incontinence						
Pharmaceutical Form	Vacuum-dried powder	Freeze-dried lyophilised powder	Freeze-dried lyophilised powder	Lyophilised powder	Powder		Solution
Molecular composition	BNT + NTP	BNT + NTP	BNT	BNT +NTP		BNT	BNT + NTP
Molecular weight	900 kDa	500–900 kDa	150 kDa			150 kDa	700 kDa

Toxin serotype	A	A	A	A	A	A	B
Clostridial strain	Hall A	Ipsen strain	Hall A	Hall A	Hall A	Hall A	Bean B
Excipient	HSA 0.5 mg	HSA 0.125 mg	HSA 1 mg	Gelatin 5 mg			HSA 0.5 mg/mL
	NaCl 0.9 mg	Lactose 2.5 mg	Sucrose 4.7 mg	Dextran 25 mg			Disodium succinate 0.01 M, NaCl 0.1 M, HCl 0.01 M, H_2O
	Buffer system	Buffer system	Buffer system	Sucrose 25 mg			
Target SNARE	SNAP-25	SNAP-25	SNAP-25	SNAP-25	SNAP-25	SNAP-25	VAMP
pH	7.4	7.4	7.4				5.6
Storage (before opening)							
Duration	36 months	24 months	36 months				24 months
Temperature	<8 °C	<8 °C	<25 °C				<8 °C
Biological activity (per vial)	50–100 MU-A	50–500 MU-I	50–100 MU-M				10–25–100 kMU-E
Clinical conversion ratio to onabotulinum	1:1	1:3	1:1 (?)			1:1.5	1:40
Total protein/100 MU	5.0 ng	0.87 ng	0.44 ng				
Total BNT/100 MU (proportion of total protein)	0.73 ng	0.65 ng	0.44 ng				
	(15 %)	(75 %)	(100 %)				
Specific biological activity (MU)	137 MU-A/ng BNT	154 MU-I/ng BNT	227 MU-M/ng BNT				
Specific biological activity (equivalent MU)	60 MU-EV/ng BNT	100 MU-EV/ng BNT	167 MU-EV/ng BNT				5 MU-EV/ng BNT

BNT botulinum neurotoxin (150 kDa), *NTP* non-toxic protein, *HSA* human serum albumin, *M* molar
MU-A Mouse Unit according to Allergan mouse lethality testing, *MU-I* Mouse Unit according to Ipsen mouse lethality testing, *MU-M* Mouse Unit according to Merz mouse lethality testing, *MU-E* Mouse Unit according to Solstice mouse lethality testing, *MU-EV* equivalent Mouse Unit (approximate and only for the effect on motor neurons, 1 MU-EV = 1 MU-A = 1 MU-M = 3 MU-I = 40 MU-E)

Molecular Composition

BT drugs consist of the BT component and excipients. Excipients include lactose, sucrose, gelatine, dextran or serum albumin for stabilisation purposes and buffer systems for pH calibration.

The BT component is formed by botulinum neurotoxin (BNT) and by non-toxic proteins also known as complexing proteins. BNT consists of a heavy amino acid chain with a molecular weight of 100 kDa and a light amino acid chain with a molecular weight of 50 kDa. Both chains are interconnected by a single disulphide bridge. The non-toxic proteins are divided according to the presence or absence of haemagglutinating properties.

BNT and complexing proteins form BT with a molecular weight of 450 kDa. Two BT molecules associate to a dimer with a molecular weight of 900 kDa. In incobotulinum (Xeomin®/ Bocouture®) and PureTox®, the complexing proteins could be removed during the manufacturing process so that the products contain isolated monomeric BNT only. These differences in molecular weight lead towards a different range of spread of the toxin in the tissue after injection. Botox® is the largest BT molecule with a low risk of migration beyond the target tissue and a highly predictable result as a consequence. On the other hand, 'pure' neurotoxin would have a lower risk of immunogenicity (see below).

The use of different excipients in different BT products also has clinical implications. Due to a low pH, injection with rimabotulinum is painful. The Chinese Hengli® BT contains bovine gelatine, leading to a higher risk of the development of allergic reactions and spongiform encephalopathy.

Serotype

Only BT serotype A and B are used for therapeutic purposes. As for the cosmetic indications, BT serotype B is not approved and thus used to a much lesser degree than serotype A. There are some major differences between both serotypes. The target molecules of serotype A and B are SNAP-25 and VAMP respectively. Serotype A has a longer duration of action than serotype B. Serotype A exerts a stronger effect on the skeletal muscles than serotype B. The risk of systemic spread with autonomic side effects is much larger with serotype B compared to serotype A.

Biological Activity, Antigenicity and Immunological Quality

The biological activity of BT is given in mouse units (MU). One mouse unit describes the amount of BT which would kill 50 % of a BT-intoxicated mouse population (= lethal dose 50 or LD_{50}). Although mouse units are defined by international convention, the activity assays used by the manufacturers are performed differently so that the activity labelling of the different BT drugs cannot be compared directly. One mouse unit of onabotulinum is equivalent to approximately 3 MU of abobotulinum. The activity of onabotulinum and incobotulinum would be identical; however recent research suggests the activity of onabotulinum to be higher. The potency labelling of different BT serotypes can also not be compared directly. The motor effect of onabotulinum and rimabotulinum seem to be comparable on a 1:40 ratio. For treatment of autonomic disorders, this conversion ratio is different since BT serotype B has relatively stronger autonomic and relatively weaker motor effect as compared to BT serotype A. A new assessment modality for onabotulinum toxin, the cell-based potency assay (CBPA), reduces the need for animal testing substantially (by 95 % over next 3 years) and has been applauded by animal rights advocacy groups. CBPA for onabotulinum toxin uses a specific cell line that can evaluate all four phases of botulinum toxin action: binding, internalisation, translocation and SNAP-25 cleavage. This method is sensitive to measure the complex mechanism of action in very small quantities of neurotoxin and has been successfully cross-validated with the LD50 assay. Also this is suitable for use in a high-capacity and in a highly quality-controlled environment. In 2011 this assessment method has been approved by the FDA for the USA, Canada and Switzerland and

has at the same moment been filed with the relevant health authorities in the European Union.

Since BT drugs are foreign proteins, the human immune system may respond to them with the formation of antibodies. These antibodies can be directed against the 150 kDa neurotoxin, the non-toxic complexing proteins or both. Antibodies against the non-toxic proteins are described in 40–60 % of treated patients. They do not influence the neurotoxin activity and are referred to as non-neutralising antibodies. However, when antibodies are formed against the neurotoxin itself, they block its pharmacological effect, and they are termed neutralising or blocking antibodies.

The risk of antibody formation is proportional to the amount of antigen presented to the immune system. The total amount of bacterial protein and neurotoxin content in 100 MU onabotulinum, abobotulinum and incobotulinum is 5 ng, 0.87 ng and 0.44 ng respectively. By means of sensitive ELISA technique, it was found that 100 MU of onabotulinum, abobotulinum and incobotulinum contain 0.73 ng (15 % of total protein content), 0.65 ng (75 % of total protein content) and 0.44 ng (100 % of total protein content) of neurotoxin, respectively. Although the formation of non-neutralising antibodies would not lead to therapeutic failure, the presence of complexing proteins potentially increases the immunogenic risk of neutralising antibody formation. Therefore, it has been proposed that reducing the foreign protein load of BT by removal of the complexing proteins would help to reduce the formation of neutralising antibodies, without affecting therapeutic efficacy. The use of purified neurotoxin preparations (e.g. incobotulinum) could potentially reduce the rate of secondary treatment failure.

Based on the data mentioned above, calculations show the highest specific neurotoxin activity in incobotulinum (227 MU/ng) followed by abobotulinum (154 MU/ng) and onabotulinum (137 MU/ng). As incobotulinum and onabotulinum would have the same biological activity, these findings suggest that some of the 150 kDa neurotoxin is likely to be inactive. When BT is manufactured and stored, conformational changes can inactivate it. This additional amount of inactivated neurotoxin or 'toxoid' may increase the production of neutralising antibodies and the risk of therapeutic failure. Besides the process of inactivation, also the presence of non-activated or 'unnicked' neurotoxin influences antibody formation. Before BT exerts its function, it must be activated or 'nicked' to form the dichain moiety (light chain linked to a heavy chain by a disulphide bond). Some of the serotypes (e.g. A and F) are inherently activated and nicked by proteases endogenous to the bacterial strain by which they are produced, whereas others (e.g. B and E) are activated by exogenous proteases like trypsin after secretion by *Clostridium botulinum*. BT serotype A is recovered from cultures more than 95 % nicked. Therapeutic BT preparations are often subjected to a step designed to increase the percentage of nicked neurotoxin during the production process, since unnicked neurotoxin increases the risk of formation of neutralising antibodies. Moreover unnicked neurotoxin may also compete with nicked neurotoxin for binding sites, resulting in a reduced clinical effect.

The amount of inactive BNT determines the immunological quality of a BT drug. When the immunological quality is high, the amount of inactive BNT is low, the biological activity is high and the antigenicity is low. When the immunological quality is low, the drug has low biological activity, resulting in high antigenicity. The relationship between biological activity (MU) and the amount of BNT (ng) is called the specific biological activity which serves as a parameter for the immunological quality of BT drugs. As shown in Table 110.1, the specific biological activity varies substantially between different therapeutic preparations.

Indications and Other Uses

BT is a strong therapeutic agent with various indications. In 1989 Botox® was FDA approved for the treatment of strabismus, blepharospasm and hemifacial spasm. Afterwards FDA approval was obtained for different BT drugs and the following indications: treatment of

persistent muscle spasms in neck and shoulders, persistent muscle spasms in the wrist and hand of patients who have suffered a stroke, foot deformity in children of 2 years or older caused by persistent muscle spasms in the legs due to cerebral palsy, leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis, chronic migraine, glabellar frown lines and hyperkinetic facial lines and excessive sweating of the armpits. Moreover, its off-label use in the treatment of hyperfunctional larynx, temporomandibular disorders (bruxism), gastrointestinal disorders (chronic anal fissure, achalasia), tremors and tics, sialorrhoea and benign prostate hypertrophy is widespread (see Table 110.1).

Today Botox®/Vistabel® is approved for the treatment of glabellar frown lines and hyperkinetic facial or upper facial lines in 76 and 19 countries respectively. Dysport®/Azzalure®/Reloxin® and Xeomin®/Bocouture® are approved for glabellar frown lines in 42 and 14 countries respectively. As for cosmetic indications, BT is also used for brow lifting, treatment of brow ptosis, bunny lines, perioral wrinkling, marionette lines, gingival smile, mental crease, dimpled chin, platysmal bands, reducing columellar show, reducing lateral oblique forehead lines (formerly called sleeping lines) and mandibular contouring.

Contraindications

Patients treated with BT should be selected carefully. During the intake consultation, the following issues should be addressed.

Allergies

Patients with a known hypersensitivity to BT or any of the other ingredients of BT drug (e.g. albumin) should not be treated. Patients with a known bee and wasp venom allergy have a higher risk of the development of neutralising antibodies against BT with a therapeutic failure as a consequence.

Neuromuscular Disorders

Caution is required when using BT in patients with pre-existing pareses as in amyotrophic lateral sclerosis, myopathies and motor polyneuropathies or in patients with impaired neuromuscular transmission, such as myasthenia gravis and Lambert–Eaton syndrome, since this can potentiate muscle weakness. Moreover the risk of developing clinically significant systemic side effect as dysphagia and breathing problems is higher in this patient population.

Medication

Medicines influencing the cholinergic signalling process can alter the effect of BT. Different antibiotics (aminoglycoside, spectinomycin, lincosamide, polymyxin), anticholinesterases, neuromuscular inhibitors (succinylcholine, tubocurarine derivates, muscle relaxants), kinin and magnesium sulphate potentiate the effect of BT with a theoretically increased risk of pareses as a consequence. Whether these interactions are relevant in a therapeutic situation remains open.

4-Aminoquinolines (chloroquine) diminish the effect of BT.

Pregnancy and Breastfeeding

No data are available concerning the effects of the use of BT in humans on fertility or foetal development. Animal studies suggest reproductive toxicity. The use of BT during pregnancy is contraindicated as a precautionary measure until further experience is gained. It is not known whether BT is excreted in human milk or whether it has any effect on the infant's nervous system. Therefore it is advised not to treat during lactation.

Infection and Inflammation

Infectious (e.g. herpes, impetigo, tinea) or inflammatory (e.g. eczema, psoriasis, acne) diseases at the injection site should be adequately treated before injecting BT.

Bleeding Diathesis

The risk of ecchymoses, haematomas and bleeding is higher in patients with an elevated bleeding tendency due to illness (e.g. thrombocytopenia, haemophilia) or medication (anticoagulants and antiaggregants).

Breathing and Swallowing Problems

High-dose BT can induce diffuse muscle weakness with breathing and swallowing problems as a consequence. Therefore, one should be careful when treating patients with known breathing (e.g. asthma, COPD) or swallowing difficulties.

Side Effects

The occurrence of side effects of BT is dependent on the dose administered, the treatment location and the product that has been used. An abundance of evidence has found the approved formulations of BT medicines to be exceedingly safe, particularly at the very low doses used for facial aesthetics. Most importantly, when used for aesthetic indications, all adverse events that do occur are reversible, with no long-term sequelae. *Reactions at the injection site* (pain, erythematous papule, haematoma, crust) and *headache* can occur during the first hours after injection and are considered to be caused by the injection technique rather than by the toxin. Limited *muscle weakness and ptosis* can be observed 1 week after treatment with a spontaneous recovery after 2–4 weeks. This side effect is caused by diffusion of the product to the adjacent muscles. Since onabotulinum has a larger molecular structure than abobotulinum and incobotulinum, the risk on diffusion is lower. Ptosis of the upper eyelid is a known side effect after treatment of dynamic forehead wrinkles with BT and results from migration of the toxin to the levator palpebrae superioris muscle. A therapy recommended to treat ptosis from administration of BT is the use of apraclonidine 0.5 %, which is an alpha2-adrenergic agonist causing Müller muscles to contract, quickly elevating the upper eyelid 1–3 mm. Analogously, muscle weakness in the upper arm can occur after injection of BT because of axillary hyperhidrosis. Another similar phenomenon is the development of dysphagia following BT injections in the sternocleidomastoid muscle in the treatment of cervical dystonia, causing diffusion of the toxin to the oesophagus muscles with swallowing problems as a consequence.

When treating primary axillary hyperhidrosis, *compensatory sweating* beyond the axillary region is reported in 4.5 % of patients within 1 month after treatment. No anatomical distribution pattern can be observed. In 30 % of affected patients, the problem spontaneously disappears within 4 months.

Allergic reactions as urticaria, serum sickness or anaphylaxis after treatment with BT are extremely rare.

Systemic adverse effects are adverse effects in tissues distant from the injection site and based upon BT transport within the blood circulation. These effects only occur when very high doses of BT are administered.

Systemic side effects can be motoric and/or autonomic. High doses of BT serotype A mainly cause motor adverse effects (dysphonia, dysarthria, breathing difficulties, dysphagia), whereas high doses (4,000 MU) of BT serotype B in addition can give rise to autonomic adverse effects (xerostomia, xerophthalmia, accommodation difficulties, irritation of nasal or genital mucosae, urinary incontinence, constipation).

Once systemic symptoms are observed, hospitalisation of the patient is required. Indeed systemic affection can be slowly progressive and very persistent. Meticulous supportive care is necessary. A rising pCO_2 signals alveolar hypoventilation and requires endotracheal intubation to maintain airway patency. Administration of antitoxin is advised; however this antitoxin cannot affect BT polypeptides that have already entered cells. Functional recovery may take several weeks to months and occurs once the neurotoxin is excreted or metabolised.

Although BT can produce indirect *central nerve system* effects, direct ones beyond the alpha

motorneuron have not been described after intramuscular injection. BT remains predominantly concentrated at the presynaptic nerve ending of the neuromuscular junction. Only a small portion is transported centripetally by retrograde axonal transport. This transport is so slow that BT is inactivated by the time it reaches the central nervous system. Retrograde transsynaptic passage of active BT in the central nervous system has not been described. Affection of the central nerve system via transport through the blood–brain barrier is excluded due to BT's molecular size.

However, BT can exert an indirect effect on the central nervous system by modulating the sensory input with secondary reorganisation of the intracortical exciting and inhibiting motor neurons. This effect can explain the effectiveness of BT in the treatment of chronic pain syndromes as migraine.

As mentioned above, the development of *neutralising antibodies* against BNT can lead towards *therapeutic failure*. This risk is facilitated by administration of high doses of BT per treatment session and the presence of non-toxic complexing proteins and non-active neurotoxin. Also exogenous factors as lectins (agglutinin, phytohaemagglutinin, concanavalin, cholera toxin, wasp venom) can stimulate the immune response against BNT.

Studies show the antigenic epitopes of BNT to be localised at the H_c fragment of the heavy chain of the molecule. The antigenic epitopes are analogous in the different BNT serotypes. If neutralising antibody production is suspected because the clinical effects of botulinum toxin decline, biochemical and/or functional tests can be employed to detect antibodies against BNT.

Attempts to overcome the effects of antibody-induced treatment failure have limited success. Once neutralising antibodies are present one BNT serotype, switching to another is unlikely to produce a clinical response because immunoresistance to the second serotype will develop swiftly. The antigenic epitopes of BNT are highly conserved with cross reactivity as a consequence. Also administration of massive doses of BT cannot overcome antibody-induced treatment failure as it exacerbates the problem because the antibody response will increase when the antigen dose is increased. Several studies show anti-BNT antibody titres to decline during time. However, with reintroduction of the toxin, the immune system is activated again, leading to the formation of new antibodies. Thus a temporary pause in the administration of BT injections to overcome the problem of antibody formation is not useful. Depletion of anti-neurotoxin antibodies by means of plasmapheresis and administration of intravenous immunoglobulins or immunosuppressant drugs is mentioned sporadically with variable results.

Since the approach of the presence of neutralising antibodies is difficult, prevention of the formation of these antibodies should be emphasised. It is important to keep the BT dose per treatment as low as possible and to make the interval between different treatment sessions as long as possible. Treatment with BT serotype B more often leads to the formation of neutralising antibodies than treatment with BT serotype A. This could be explained by the large administration doses of BT serotype B and by the fact that BT serotype B preparations contain up to 25 % non-activated BNT with a lower immunological quality and a higher immunogenic capacity as a consequence.

Fortunately the problem of therapeutic failure due to the presence of neutralising antibodies rarely occurs in the treatment with BT for aesthetic indications, since the doses and administration frequency are low. In addition it has been shown that the presence of neutralising antibodies not always leads to a diminishing clinical effect.

Most BT preparations contain human serum albumin. This is a derivate of human blood. Theoretically *transmission of known and unknown pathogens* cannot be excluded. In order to prevent infections, donors are carefully selected and screened for infectious markers. In addition BT preparations undergo several production steps in order to inactivate and eliminate viruses. Until now no reports on viral transmission after treatment with albumin-containing medications produced following the specifications of the European Pharmacopoeia have been reported.

Clinical Practice

Aesthetic Counselling and Considerations

A thorough anamnesis and clinical investigation should be performed before treatment with BT.

An accurate medical history can uncover potential contraindications for treatment. Prior to treatment, the procedure, its potential complications and the large variability of effects among patients must be explained to the patient. In-depth questioning of the patients must be conducted to clarify patient's treatment goals. The patient should be well informed about the temporary effect of the treatment. Also it should be explained that wrinkling is due not only to muscle activity but also to a loss of elasticity and volume and to the influence of gravity. Since BT only causes relaxation of the muscles, sometimes it is not sufficient in the treatment of wrinkling and should be combined with other anti-ageing techniques such as fillers and peels. Patients who present with severe, deep wrinkles may have unrealistic expectations as to the outcome of BT treatment. Clinicians can help avert dissatisfaction by setting overall aesthetic goals with patients, developing an overall treatment plan and establishing realistic expectations for the outcome.

It is mandatory to take photographs of the face at rest and in contraction prior to the first injection and preferably at each injection session. It is advisable to schedule a 2-week follow-up appointment especially for first-time patients who need to be photographed and evaluated.

In many countries it is mandatory to obtain a written informed consent from the patient and to clearly mention all the given clinical and product information in the patient's medical file.

Aesthetic planning involves understanding and assessing the patient's desires and preferences in the context of an overall treatment plan. The evolving emphasis on facial shaping and enhancement argues against treating any one area in isolation, without regard to its effect on other areas.

Prior to BT treatment of axillary primary hyperhidrosis, a Minor starch-iodine sweat test should be performed. An iodine solution is applied to the skin and allowed to air-dry. Once dry, the area is dusted with potato flour. Then sweating is encouraged. When sweat reaches the surface of the skin, the starch and iodine combine, causing a colour change from yellow to dark blue, allowing sweat production to be actively visualised. Although the treatment area usually locates at the hairy zone of the axilla, a sweat test should be performed to discover ectopic areas of sweat glands and also to trace differences in sweating intensity so that the distribution of BT injection volumes can be adapted to the intensity of sweating.

Pre- and Post-procedural Considerations

All available BT serotype A drugs are supplied in a vial containing powder. Different available BT drugs have different storage conditions. Ona- and abobotulinum should be stored at low temperature, whereas incobotulinum can be stored at room temperature, which might be an advantage (see Table 110.1). Reconstitution of the drug should be performed with 0.9 % non-preserved saline. The dilution differs according to the BT drugs used and the number of units to be injected. Preserved saline can also be used to reconstitute the vial. The presence of benzyl alcohol renders the injections almost pain free due to its anaesthetic properties known since 1946. Benzyl alcohol works through an increase in cell membrane lipid fluidity. One should only be aware in fragrance-sensitive patients for potential cross-allergic reactions, with flares of contact dermatitis.

It is recommended to avoid agitation and foam during reconstitution since there would be a risk of loss of BT biological activity. When reconstituting incobotulinum, the vial should softly be turned around to avoid the toxin to adhere to the glass wall due to the absence of complexing proteins.

Before injection the solution should be carefully inspected: only a clear, colourless solution without floating particles can be injected.

Reconstituted vials should be used within 4 h after reconstitution. Clinical experience and published data suggest that potency can be maintained for up to 6 weeks with proper storage at 2–8°.

The number of units to be injected depends on the specific region of treatment but also on muscle mass, skin thickness and texture. Muscle mass is influenced by gender and individual variation. Generally the muscles of men are greater in mass and require higher doses of BT. Skin thickness may influence the injection technique and the required doses. In general thicker skin requires higher doses of BT.

Before injection with BT, the treatment area should be thoroughly disinfected with non-alcoholic disinfectants since alcohol inactivates BNT. For the injection, plastic single-use syringes are recommended. A 30-gauge needle is standard, but several practitioners report reduction of pain with the use of a 32-gauge needle. Also the use of ice packs or topical anaesthetic cream can reduce the discomfort associated with the injections.

Patients should be advised to avoid the intake of medications that inhibit clotting such as vitamin E, aspirin and nonsteroidal anti-inflammatory drugs for a period of 10–14 days before treatment.

During BT treatment, patients should be placed in a comfortable position, ideally with their head supported. An upright or slightly reclined position is ideal for cosmetic injections. For the treatment of axillary sweating, patients should lie down with both their arms crossed behind the head.

After BT injections patients should not massage or rub the treatment area and should avoid pressure on the injected zone. Patients should be advised to contract the injected area for approximately 2 h in order to expedite uptake of the toxin. Limiting activity and heat exposure may reduce unwanted diffusion of the toxin; however these recommendations are not based on documented physiological observations or data.

In assessing response to a starting treatment, it is recommended seeing patients at 14 days after treatment. At that time adjustments of dosing or touch-ups can be made. When this assessment is not necessary, the typical interval for retreatment of wrinkles or axillary hyperhidrosis is 3–4 months or 6–12 months respectively.

Specific Treatment Areas, Treatment Regime and Dosage

Different panels of experts have already developed consensual guidelines for treating the ageing face with BT. Here you find a compact overview of the most frequently treated zones and applied techniques. Doses given are for ona- and incobotulinum; approximate dosages for abobotulinum can be determined using a 2.5:1 to 3.0:1 conversion ratio. For more detailed information, we refer to the written consensus recommendations (Carruthers et al. 2004, Raspaldo et al. 2011a, b, Lorenc et al. 2013).

Vertical Glabellar Frown Lines

The musculature of the glabellar complex, responsible for the vertical frown lines, is the most common site for BT injections. Target muscles for treatment are the corrugator supercilii, the procerus and the depressor supercilii which all have the function of brow depression. In order to study the musculature and identify the injection sites, the patient should frown. Usually five to seven injection points are used: one to two points in the centre of the glabella and two points bilaterally at the medial portion of the corrugator supercilii muscle. In order to avoid eyelid and/or brow ptosis, BT should be injected 5–10 mm above the orbital rim and medial of the mid-pupillary line. Injections are given more superficially at the tail of the corrugator or at the subdermal insertion points and somewhat deeper (intramuscularly) at the more medial body of the corrugator muscles based on frown pattern. The recommended total treatment dose of onabotulinum for the glabellar region is 20 MU. However, total doses up to 80 MU have been described, depending of muscular mass (see Fig. 110.1).

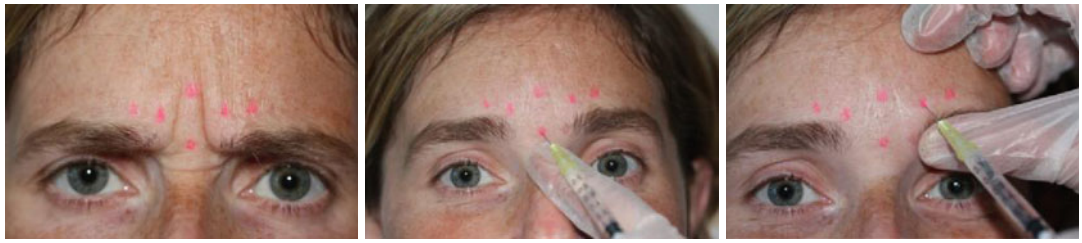

Fig. 110.1 BT treatment of glabellar frown lines

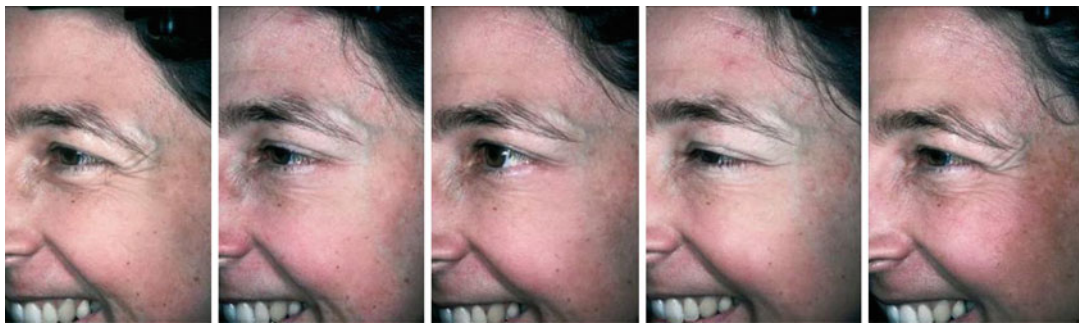

Fig. 110.2 BT in crow's feet: evolution after single treatment over time

Horizontal Forehead Lines

Horizontal forehead lines are caused by the activity of the frontalis muscle, which is the only levator muscle of the upper face elevating the eyebrows and the skin of the forehead. There is a considerable interindividual variation in structural features of the frontalis. This variation plays an important role in the treatment plan. To avoid lowering of the (eye)brows, injections should start 1–2 cm above the orbital rim and inside the segment delimited by the mid-pupillary vertical lines and doses should be low. Usually 1–2 MU onabotulinum per injection point and 8–12 injections sites are advised. The pattern of injection and doses needed will vary depending on the height of the forehead, the volume of the muscle and the placement of the eyebrows at rest. The injections should be given in the hypodermis, avoiding bone contact. It is strongly recommended to associate treatment of the horizontal forehead lines with treatment of the glabellar region in order to obtain a harmonious balance between elevator and depressor muscles. Frontalis muscles can extend laterally and if not treated this can induce a 'Mephisto look'. This peaked brow can be brought down by the injection of 1–2 MU onabotulinum in the lateral temporal part of the frontalis muscle.

Crow's Feet Lines

The wrinkles at the lateral canthus are caused by contraction of the lateral portion of the orbicularis oculi muscle and to a lesser degree the zygomaticus muscles. As with horizontal forehead lines, lower doses are preferable. Typically two to four injection points are required with a starting dose of 6–12 MU onabotulinum per canthus. The injections should be given very superficial with avoidance of hitting one of the many small superficial vessels in the area. They should be kept well laterally, approximately 1–1.5 cm from the orbital rim, and the needle should be oriented away from the orbit. Also injections should stay above the zygomatic arch to avoid lip and cheek ptosis (see Fig. 110.2).

Lower Eyelid

A prominent bulge and wrinkling of the lower eyelid is partially caused by the pretarsal portion of the orbicularis oculi muscle. One intradermal injection at the mid-pupillary line approximately 2 mm inferior to the lid margin with 1–2 units onabotulinum is usually sufficient to reduce the bulge and to widen the palpebral aperture size. Bruising is common in the area and lid ectropion can occur. Injections medial to the mid-pupillary line can weaken the blink reflex and result in dry eyes. Injections lateral to the mid-pupillary line increase the risk for lower lid ectropion. Dry eyes, scleral show and loose lower eyelids should alert the injector the possibility of problems with the treatment of this zone with BT.

Lateral Oblique Forehead Lines

Lateral oblique forehead lines had previously been defined as 'sleeping lines'. There are arguments to support the premise that these lines are not caused by sleeping position but arise instead from the repeated contraction of powerful frontalis and orbicularis oculi muscles and can therefore be successfully treated with onabotulinum toxin A. Each lateral oblique forehead line can be treated by injections medially to this line, in two sites, 2 cm apart, using two units at each site (the lowest point situated 1.5 cm above the orbital bony rim). Two more units need to be injected at a third site, 1 cm lateral to the oblique forehead lines, midway between the hairline and the eyebrow.

Brow Lift

Brow ptosis is common and gives the patient a tired appearance. Most patients desire to have eyebrows that are positioned slightly higher, more arched and more symmetrical.

The position of the eyebrow is affected by a continuous interaction between elevator (frontalis muscle) and depressor (procerus, corrugator, depressor supercilii, internal part of orbicularis) muscles. The depressor muscles should be treated while maintaining the elevator muscle function. Treatment of the glabellar complex as described above can help in raising the medial portion of the eyebrow. In order to raise the external eyebrow, an injection should be given subcutaneously at 4–5 mm of the orbital ridge under the brow tail, directed away from the eyelid. Doses of 2–4 MU onabotulinum per side can be administered. Also the treatment of the crow's feet lines can be helpful.

When treating eyebrow position, appropriate dose adjustments are very important in order to obtain a symmetrical result.

Bunny Lines

Bunny lines are horizontal wrinkles that form across the bridge of the nose and are accentuated with speech, smiling and frowning. They are produced by the transverse portion of the paramedian nasalis muscle and occasionally the levator labii superioris alaeque nasi muscle. Very small doses of onabotulinum are needed, typically 2–5 MU onabotulinum per side. A midline procerus injection of 1–2 MU onabotulinum will address the transversal nasal lines. Injections should be given in the hypodermis and at an oblique angle perpendicular to the nasal vault. Placement is particularly important on the nose as the levator labii superioris alaeque nasi and the levator labii superioris both originate along the medial aspect of the malar prominence. Diffusion of BT towards these muscles can cause drooping of the upper lip.

Reducing Excessive Columellar Show

One can speak of excessive columellar show when exposure of the inner lining of the nostrils is visible for 4 mm or more when looking to the nose laterally in active condition. It is mainly due to the over contraction of one and/or two muscles (levator labii superioris ala nasi and depressor septi nasi). Depending on the relationship of the alar rim and the columella, three forms of the columellar show can be seen: upper, lower and combined.

The medial alar portion of the levator labii superioris ala nasi, also called the levator ala nasi, elevates the wing of the nose and dilates the nostrils which results to retracted alar rim and making it more arched (upper show). The depressor septi nasi primarily pulls the nasal septum downwards and makes it more pronounced (lower

show). The combined show is the combination of both the upper and lower show which is due to the hyperfunction of the two muscles. Excessive use of the muscles mentioned above under physical, emotional stress or unconsciously and repeatedly contracting these muscles lead to a more pronounced upper, lower or combined show. The most common among the three is the upper show.

Excessive columellar show can be corrected by injecting botulinum toxin midway along the levator alae nasi. A dose of 4 U onabotulinum toxin could reduce this unwanted condition for up to 12 weeks.

Perioral Region

Rejuvenation of the mouth can be achieved using small doses of BT. Outcomes are usually maximised when combined with other techniques such as fillers of resurfacing.

Vertical perioral rhytids are caused by the orbicularis oris muscle which is the sphincter muscle of the mouth. Fibres derive partially from other muscles inserted into the lips and from muscles associated with the lips. Because of the complex functions of this region and the interplay of muscles, treatment of the perioral region deserves careful attention. Two to four injections sites should be symmetrically distributed per lip quadrant. Injections can be given just above or slightly away from the vermillion border directly in the folds. Avoid treating the corners of the lip and the midline of the upper lip as this can result in drooling and flattening of the lip respectively. A maximum dose of 1 MU onabotulinum per injection site with a total of 4 MU onabotulinum per lip is advised. Overtreatment should be avoided since this can result in significant dysfunction including difficulty in pursing the lips.

Marionette Lines and Depressor Anguli Oris

Oblique lines radiating downward from the oral commissures, called marionette lines or melomental lines, are partially formed by the hyperactivity of the depressor anguli oris (DAO) at its medial insertion. As corners of the mouth turn downwards with age, it portrays sadness or anger. Weakening the DAO with BT minimises downward pull on the dermal insertions of the muscle and can raise the oral commissures due to the activity of the opposing zygomatic muscles. Injections in the DAO should be given superficially 1 cm above the mandibular border at the intersection of the line passing through the nasalis ala and the corner of the mouth. Higher injections in the DAO at its upper third part are more efficacious but have a high risk of paralysing the depressor labii inferioris. Also treatment of the depressor anguli oris that is too close to the mouth can result in unwanted injection of other muscles and produce oral incompetence, drooling and asymmetrical smile. An average dose of 2 MU onabotulinum per injection point is advised.

Gingival Smile

Excessive display of gingival tissue during smile is an aesthetically unpleasant condition known as ‘gummy’ smile. This is partially related to hyperactivity of the upper lip elevator muscles (levator labii superioris and levator labii superioris alaeque nasi). Different injection techniques with BT have been described. Injections should be given deep and 1 cm above the lower insertion of the nostril. Doses should be low (2 MU onabotulinum per injection site) in order to prevent drooping of the upper lip (see Fig. 110.3).

Chin

A deep mental crease or chin dimpling can be improved by paralysing the mentalis muscle. Only one injection with BT is generally necessary to weaken the muscle, although some experts inject two sites. A total of 5–10 MU onabotulinum can be injected ideally at the inferior and near midline part of the muscle to avoid diffusion to the depressor labii inferioris muscle, causing lower lip incompetence and drooling. Injections should be given deeply and perpendicular to the skin surface. Combined treatment with fillers can improve the aesthetic outcome.

Neck

Vertical neck bands and cords may become very prominent in some individuals. These bands are caused by the platysma, a broad and thin sheet of

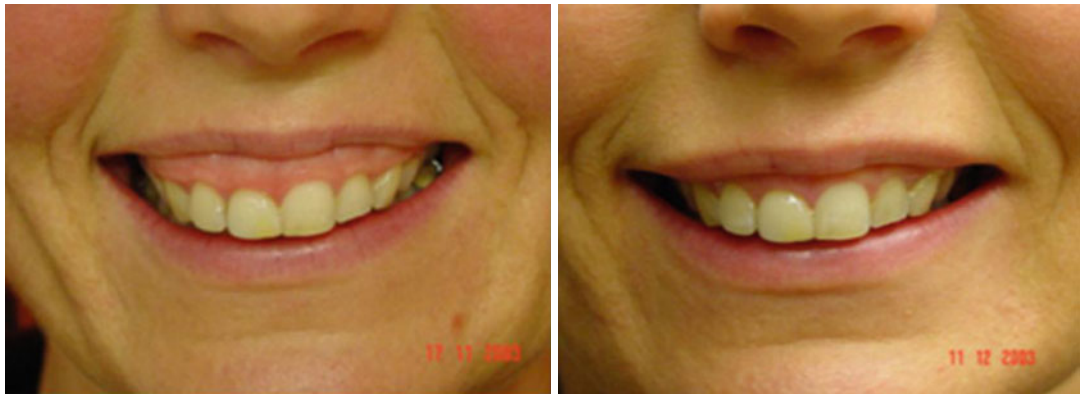

Fig. 110.3 Gummy smile: injection in M. levator labii superioris alaeque nasi

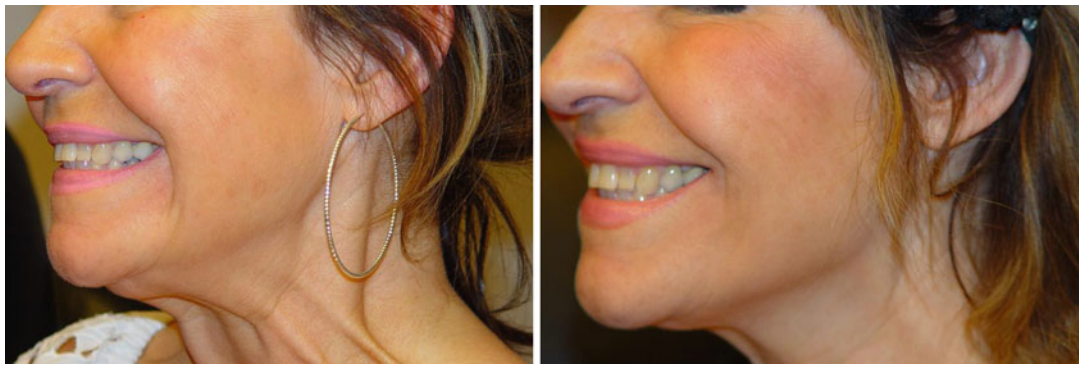

Fig. 110.4 Platysmal bands treated with BT

muscle, originating in the pectoral and deltoid muscles and extending upward, covering the neck's anterolateral aspect. Treatment with BT can only be performed in a strictly selected patient population: patients must have retained a satisfactory skin elasticity in the neck and have only minimal descent of submental fat. It is suggested to inject 2–4 MU onabotulinum every 1–2 cm per band which results in 2–4 injection sites per band (see Fig. 110.4). A maximal dose of 50 MU onabotulinum for the global neck treatment is accepted. It is recommended to grasp the band with the nondominant hand and inject intramuscularly. High doses and deep injections should be avoided since they increase the risk of general neck weakness, dysphagia and dysphonia.

Horizontal neck lines can be treated but are much less responsive than the vertical neck bands.

Mandibular Contouring

A hypertrophic masseter muscle, which is involved in mastication, may lead to a square jaw contour. Injection with BT can reduce muscle hypertrophy leading to a slimmer, oval-shaped lower face. In order to define the injection sites, the borders of the masseter muscle must be determined while the patient is clenching teeth. Two to six injections should be given at 1 cm away from the borders and in the muscle lower half. Also they should be given intramuscular up to bone contact and perpendicular to the skin surface. An average dose of 25–30 MU onabotulinum per masseter muscle should be administered.

Primary Axillary Hyperhidrosis

Primary axillary hyperhidrosis is a common disorder for which treatment is often a therapeutic challenge. When topical treatment with

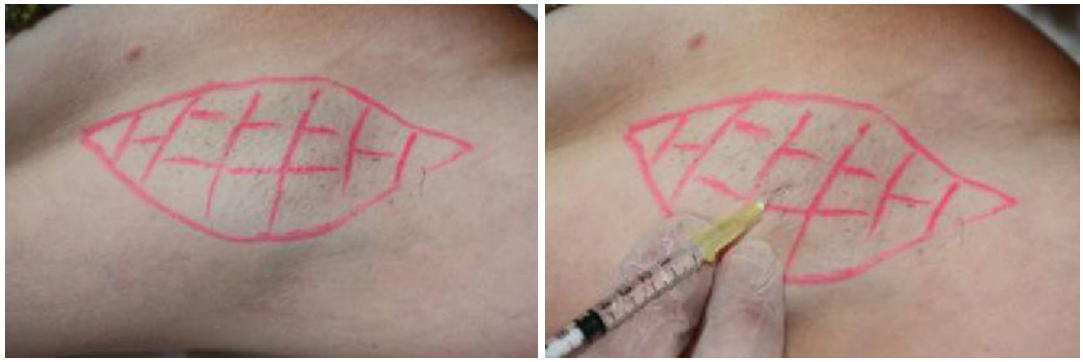

Fig. 110.5 BT treatment of primary axillary hyperhidrosis

aluminium salts does not reduce the sweat secretion, the next step is treatment with BT. After disinfection the sweating area should be demarcated and subdivided in squares of 1–2 cm^2. A vial of 100 MU onabotulinum should be diluted with 4–5 mL 0.9 % non-preserved or preserved saline. Afterwards 3–5 MU onabotulinum is injected intradermally into each square, totalling 50 MU per axilla (see Fig. 110.5). Higher dosing, up to 150 U of onabotulinum toxin, divided over both axillae, might be associated with more intense reduction in hyperhidrosis or longer duration of the hypo- or anhidrotic result.

Recent Development

A major disadvantage of the treatment with botulinum toxin is the administration route. Since many consumers are needle adverse and would prefer a more noninvasive alternative, a targeted alternative may be found in topical BT.

Nanotechnology allows the potential to deliver molecules into the skin which normally do not penetrate the corneal layer. Recently two companies developed topical BT gels. By using nanospheres and absorption enhancers, the toxin is delivered into the skin and can exert its function of inhibiting the release of acetylcholine and thereby blocking the neuromuscular transmission. Studies so far have mainly focussed on treating axillary hyperhidrosis and lateral canthal lines.

Transdermal Corp. (Birmingham, Michigan) has developed CosmeTox®, a topical BT cream based on commercially viable ionic nanoparticle technology. Different studies revealed efficacy, stability and safety of the product. The product is FDA approved in the treatment of facial rhytids and (axillary and palmoplantar) hyperhidrotic conditions.

RT001 (Revance Therapeutics, Newark, California) is another topical BT cream consisting of the combination of 150 kDa BT coupled with a peptidyl macromolecule transport system. Analogously to CosmeTox®, different clinical studies showed the product to be safe and efficacious in the treatment of facial wrinkles and hyperhidrosis.

Possible side effects of topical BT treatment are temporary, involuntary muscle contractions and transient local reactions as tenderness, erythema, eczema and folliculitis. A potential risk of topical BT is misuse. Misapplication could lead to ptosis or facial asymmetry. These limitations will be a source of debate as to under which conditions the topical product can be used and prescribed.

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Capillaroscopy

111

Giorgio Filosa and Rossella De Angelis

Abbreviations

aCL	Anticardiolipin antibodies
DM	Dermatomyositis
NC	Nailfold capillaroscopy
RP	Raynaud's phenomenon
SLE	Systemic lupus erythematosus
SP	Scleroderma pattern
SSc	Systemic sclerosis
UCTD	Undifferentiated connective tissue disease

Key Points

- Capillaroscopy is a 'non-invasive' method of undoubted value in the recognition of morphological and functional abnormalities of the microcirculation at the nailfold skin.
- Nailfold capillaroscopy (NC) should be performed in all fingers.

- In healthy individuals the capillaroscopic pattern is generally characterised by an homogeneity in morphology, diameter, orientation and distribution of the capillaries, which appear as 'inverted U' or 'hairpin', and arranged as a 'comb', with the major axis parallel to the skin surface.
- NC is useful in the study of scleroderma pattern (SP) of the connective tissue diseases. The SP can be observed in more than 90 % of patients with systemic sclerosis (SSc), in about 75 % of patients with dermatomyositis and in over 50 % of patients with mixed connective tissue. Morphological aspects and characteristics of the scleroderma, a microangiopathy, may vary in relation to its evolutionary stage. In the early phases it is mainly characterised by the alteration of normal capillaries with unevenly distributed dilated loops. In the most aggressive forms, the avascular areas and the anarchic newborn capillaries emphasise the architectural disorder that can be considered hallmark of SSc.
- NC measures also variations of capillary dimensions and density ('microvascular remodelling') under treatment, and this could be the potential major clinical application of this technique, for monitoring the response to drug treatment.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_111, © Springer-Verlag Berlin Heidelberg 2015

General Principles

Capillaroscopy is a 'non-invasive' method of undoubted value in the recognition of morphological and functional abnormalities of the microcirculation. Its use dates back to the early twentieth century but remained mostly confined to the experimental until the 1980s. Since then, the clinical applications of capillaroscopy have progressively developed, especially in the field of rheumatology, to become an essential top-level examination in patients with Raynaud's phenomenon and play a key role in the diagnosis and prognosis of systemic sclerosis (SSc).

The 'in vivo' study of the microcirculation is mostly carried out at the nailfold skin, due to the fact that in this district, the major axis of the capillaries runs parallel to the skin surface, while in other areas the capillaries have a perpendicular course to the skin.

Nailfold capillaroscopy can be realised with various optical devices, which may vary from a simple magnifying glass up to a video capillaroscope with optical contact probes. The use of an ophthalmoscope or a dermatoscope is the easiest method for a wide-ranging and direct assessment of the nailfold microcirculation, albeit with low sensitivity to the limited level of magnification (20×). A reflex camera equipped with a good optical kit allows an adequate overview, while a stereomicroscope and a transmitted light microscope (magnifications ranging from 10× to 100×) provide a general observation and a simultaneous analysis of details of the single loops. In recent years, the videocapillaroscopy with optical probes has opened new and original perspectives in the study of microcirculation, for the chance to explore both the nailfold and the entire skin microcirculation. The images of capillaries captured through the probe are shown on a monitor, where the examination is particularly easy for the sharpness and the amplitude of the field of observation. The instrument can be equipped with software that uses algorithms for image storage and allows immediate printing.

Nailfold capillaroscopy should be performed in all fingers, with the lens correctly positioned perpendicularly to the examining surface. The application of a cedar oil drop on the skin allows to get the best conditions of visibility. The survey should be carried out after a period of 'acclimatisation', lasting from few minutes to half an hour, with regard to the difference between outdoor and room temperature.

The main parameters to be analysed in the course of the examination are the skin transparency, the visibility of the subpapillary venous plexus, density and spatial distribution of the loops, the length and diameter of the capillaries and the flow characteristics (Table 111.1).

In healthy individuals the capillaroscopic pattern is generally characterised by a homogeneity

Table 111.1 Capillarosopic nailfold patterns

Primary Raynaud's phenomenon	Normal pattern
Systemic sclerosis	'*Early*' pattern (few enlarged/giant capillaries, few haemorrhages, no evident loss of capillaries), '*active*' (giant capillaries, capillary haemorrhages, mild disorganisation of the capillary network) and '*late*' pattern (enlargement of the capillaries, few or absent giant capillaries and haemorrhages, avascular areas) (Figs. 111.2, 111.3 and 111.4)
Dermatomyositis	Similar to those in patients with SSc and with features of angiogenesis that can represent the dominant characteristic
Mixed connective tissue disease	Wide variability scleroderma pattern predictive of the development of pulmonary hypertension
Undifferentiated connective tissue disease	Most normal
Systemic lupus erythematosus	Tortuosity, loop elongation, enlarged and/or branching loop scleroderma pattern in 5 % of cases
Sjögren's syndrome	Non-specific
Psoriatic arthritis and psoriasis	Non-specific microhaemorrhages and reduction in length ('dwarf loops')

in morphology, diameter, orientation and distribution of the capillaries, which appear as 'inverted U' or 'hairpin', and arranged as a 'comb', with the major axis parallel to the skin surface (Fig. 111.1).

The number of capillaries varies from 9 to 13 per mm, and the morphological and structural features of the nailfold microcirculation tend to remain constant over time. The capillary characteristics and the microvascular network can have a wide interindividual variability, due to many factors such as age, sex, race and occupation. Isolated abnormalities in distribution, morphology and orientation are not uncommon in the healthy subject, and their presence can be related with a wide range of conditions such as manicure, nail biting, microtraumas and manual activities.

Nailfold capillaroscopy is indicated in all those conditions in which it is presumed or there is already existing microangiopathy; furthermore, capillaroscopy may allow a better understanding of the pathophysiological aspects regarding the microvascular involvement in systemic diseases.

Several marked alterations of the main capillaroscopic parameters can be observed in the presence of a microangiopathy, with significant changes in the course, morphology and spatial distribution of the capillary loops, contributing to the disruption of the normal microvessel network.

The 'Scleroderma Pattern'

The wide variety of the changes observed in SSc and in the so-called scleroderma spectrum disorders is well known as the 'scleroderma pattern'. The expressions of the scleroderma microangiopathy are various and mainly characterised by architectural disorder, homogeneous and inhomogeneous ectasia, microhaemorrhages, marked capillary neoformation and reduction in the number of capillaries until the appearance of avascular areas (Fig. 111.2).

The scleroderma pattern can be observed in more than 90 % of patients with SSc, in about 75 % of patients with dermatomyositis, in over 50 % of patients with mixed connective tissue disease and, to a lesser extent, in patients with undifferentiated connective tissue disease (UCTD) and with Sjögren's syndrome.

Morphological aspects and characteristics of the scleroderma microangiopathy may vary in relation to its evolutionary stage. In the early phases it is mainly characterised by the alteration of normal capillaries with unevenly distributed dilated loops. In the most aggressive forms, the avascular areas and the anarchic newborn capillaries emphasise the architectural disorder that can be considered hallmark of SSc.

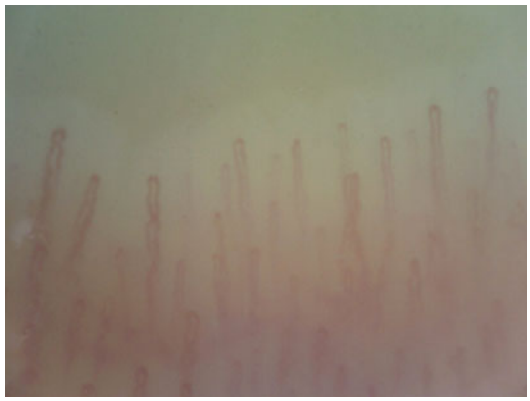

Fig. 111.1 Nailfold capillaroscopy ×200. Healthy subject: hairpin loops arranged as a 'comb' structure

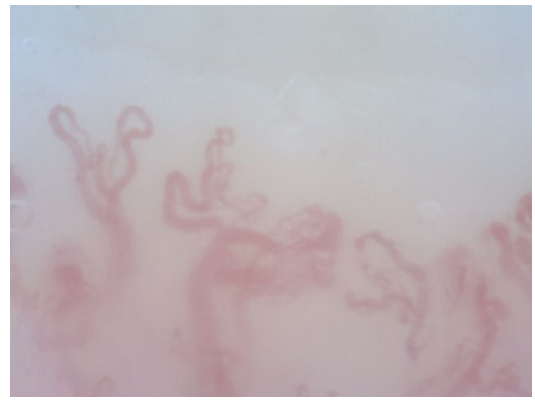

Fig. 111.2 Nailfold capillaroscopy ×200. Systemic sclerosis: architectural derangement with newly formed capillaries

Capillaroscopy in Autoimmune Diseases

Raynaud's Phenomenon

The nailfold capillaroscopy can be considered the method of first use to make a clear distinction between 'primary' and 'secondary' Raynaud's phenomenon (RP).

In a patient with clinically isolated RP, the presence of one or more of the typical abnormalities of the scleroderma microangiopathy (even if limited to a single finger) should be regarded as evidence of a significant secondary nature and justifies the execution of further investigation, such as the research of anti-nuclear antibodies. Moreover, the capillaroscopic findings allow to stratify the risk of a significant evolution towards a 'scleroderma spectrum disorder' over 5 years in patients with isolated RP, using a composite algorithm based on the presence of dilated capillaries, microhaemorrhages and density of capillaries. The association of this type of capillaroscopic abnormalities with a positive 'specific' antinuclear antibody (anti-centromere or anti-topoisomerase I) makes it possible to develop a predictive model able to assess the evolution of RP towards a true SSc.

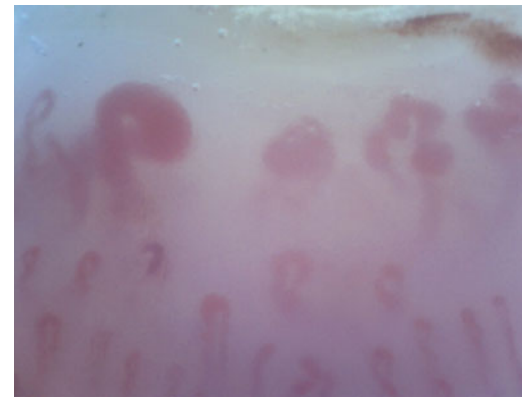

Fig. 111.3 Nailfold capillaroscopy ×200. Systemic sclerosis: extremely dilated loops ('giant capillaries')

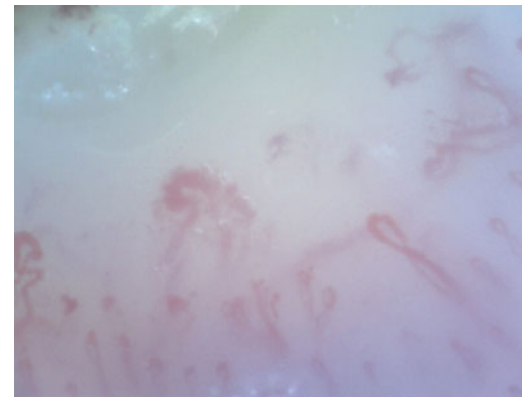

Fig. 111.4 Nailfold capillaroscopy ×200. Systemic sclerosis: loss of capillaries with a marked disorganisation of the capillary bed

Systemic Sclerosis

Capillaroscopy can be regarded as the most valuable technique for detecting the early features of microangiopathy in SSc, with the morphologic changes of the nailfold that have been extensively studied. They include architectural derangement of the nailfold microvascular network, enlarged loops, neovascularisation, loss of capillaries and avascular areas. Such capillary abnormalities can be recognised, even in the early stages of SSc, when clinical features of the disease are limited to RP. A marked increase in capillary size is the most characteristic feature of the nailfold capillary bed in SSc, the shape being largely heterogeneous.

Previous studies on nailfold capillaroscopy had partially graded the vascular damage in SSc, distinguishing two main groups of capillary abnormalities for prognostic purpose, the first characterised by extremely dilated nailfold capillaries with no clear avascular areas ('slow pattern') (Fig. 111.2) and the latter by extensive loss of capillaries with a general disorganisation of the capillary bed ('active pattern') (Figs. 111.3 and 111.4). About 10 years ago, microvascular alterations have been reclassified into three different patterns, including 'early' pattern (few enlarged/giant capillaries, few capillary haemorrhages, no evident loss of capillaries), 'active' pattern (frequent giant capillaries, frequent capillary haemorrhages, mild disorganisation of the capillary network) and 'late' pattern (irregular

enlargement of the capillaries, few or absent giant capillaries and haemorrhages, extensive avascular areas).

In SSc patients a significant association between the severity of the involvement of the skin and internal organs and the capillaroscopic patterns has been found. Patients with extensive avascular areas have an increased risk to develop digital ulcers and to present a more significant skin, pulmonary and cardiac involvement.

Capillaroscopy is also used for prognostic purposes to identify patients with high risk of developing digital ulcers and pulmonary arterial hypertension. In particular, the 'quantitative' analysis of some abnormalities (number of megacapillaries, maximum capillary diameter, total number of capillaries) allows to build a prognostic index with high specificity and sensitivity, able to predict the appearance of digital ulcers.

Dermatomyositis

Dermatomyositis (DM) is distinguished from polymyositis for the substantial involvement of the microcirculation in the skin and muscle and for the relief of capillaroscopy alterations in about two-thirds of the subjects.

In patients with DM capillaroscopic abnormalities may be similar to those that can be found in patients with SSc, with architectural derangement of the nailfold capillary network and features of angiogenesis that, in some cases, can represent the dominant characteristic. In patients with polymyositis without cutaneous involvement, the capillaroscopic pattern usually shows aspects that fall in the normal range.

Patterns characterised by a rapid change of the capillaries' morphology occurring even in a few days were also described.

Mixed Connective Tissue Disease

The nailfold microvascular pattern of mixed connective tissue disease may present a wide variability, ranging from a normal pattern to frankly pathological features. Capillaroscopic alterations typical of the scleroderma pattern are detectable in more than half of patients. The presence of avascular areas is associated with interstitial lung disease, and the finding of a scleroderma pattern seems to be predictive of the development of pulmonary arterial hypertension.

Undifferentiated Connective Tissue Disease

The undifferentiated connective tissue disease (UCTD) is a condition in which there are signs and/or symptoms of a systemic autoimmune disease that do not meet the classification and/or diagnostic criteria of a 'major' connective tissue disease. In most subjects the nailfold capillaroscopic arrangement is normal. In some patients, especially those with RP, it is possible to observe non-specific expressions of microangiopathy, with predominance of tortuous capillaries and homogeneous and inhomogeneous ectasia. In this case, a follow-up seems appropriate in order to identify a possible evolution towards an SSc. Abnormalities of the scleroderma pattern can be observed in association with the simultaneous presence of anti-RNP antibodies and RP.

Systemic Lupus Erythematosus

The main capillaroscopic abnormalities described in systemic lupus erythematosus (SLE) patients include increased tortuosity, loop elongation, enlarged and/or branching loops and increased visibility of the subpapillary venous plexus, although in about 50 % of patients, the capillaroscopic pattern is similar to that of healthy subject. In some cases loops take on a convoluted course, named 'meandering capillaries'. A true scleroderma pattern is observed as significant in a minimum proportion of patients (5 %), when associated with RP and anti-RNP antibodies.

Antiphospholipid syndrome (APS) patients and SLE patients with anticardiolipin antibody (aCL)-positive titres show microvascular alterations, suggesting a direct damage of the vascular endothelium triggered by aCL. Symmetrical

microhaemorrhages at the nailfold were found particularly in patients showing both serum IgG and IgM aCL with marked microvascular damage related to the occurrence of thrombotic manifestation.

Sjögren's Syndrome

In patients with Sjögren's syndrome, capillaroscopic alterations are unusual and, when present, are considered as non-specific. Some authors have observed a reduction in capillary density in the presence of RP or systemic manifestations of the disease. The relief of a scleroderma pattern holds predictive value with respect to a possible evolution towards an 'overlap' with SSc.

Rheumatoid Arthritis

The capillaroscopic framework in patients with rheumatoid arthritis does not show changes characteristic or representative of a microvascular damage. In most cases the capillaroscopic pattern is similar to those of the healthy subject. In some patients it is possible to observe thin and elongated loops together with a strong visibility of the subpapillary venous plexus, valued in the past as a distinctive element of a 'rheumatoid arthritis pattern'. These anomalies are considered non-specific and by some probable expression of a concomitant steroid therapy.

Psoriatic Arthritis and Psoriasis

Capillaroscopy in patients with psoriatic arthritis may reveal a series of abnormalities such as non-specific microhaemorrhages and reduction in length ('dwarf loops'), the latter probably related to a reduction of visibility secondary to hyperkeratosis. Examination of the untreated psoriatic skin shows many uniformly arranged tortuous and dilated capillaries, appearing as bushy, with a highly distinctive pattern. In the perilesional skin, capillary loops show a parallel course with respect to the skin surface and with a lengthened apex directed towards the marginal zone of the lesion. The number of capillary loops per area unit seems to increase in perilesional skin compared to lesional skin. In the normal-appearing skin, the capillary loops become perpendicular to the surface of the skin.

These changes are reversible and may regress with the disappearance of the psoriatic lesions.

Capillaroscopy in Therapy Monitoring

The role of capillaroscopy in therapy monitoring awaits further improvement. Changes described after therapy mainly refer to dynamic studies in which the parameters used were the variations of blood flow and capillary permeability. A single oral administration of 10 mg of nifedipine has demonstrated a prompt antagonist effect on the cold-induced reduction of capillary permeability in patients with SSc (Grassi et al. 1994). Very few studies reported morphological modifications and numerical loop change at nailfold later than vasoactive therapy. A decreased capillary loss was observed after cyclosporine (2.5 mg/kg/day) and intravenous iloprost, during an open, double-arm trial in which 20 SSc patients were randomised to receive treatment with either iloprost alone or in association with low-dose long-term CyA (Filaci et al. 1999). A development of nailfold microvascularisation, characterised by an increase of the loop number and a reduction of avascular areas, was described in four patients with SSc, after a 3-year treatment sequence with iloprost (Faggioli et al. 2006). A significant decrease in avascular areas was observed in 16 % of patients with mixed connective tissue disease after iloprost, throughout a sequential evaluation of 3 years (de Holanda Mafaldo Diógenes et al. 2007). Measure variations of capillary dimensions and density ('microvascular remodelling') could be the potential major clinical application of this technique, for monitoring the response to drug treatment. The development of new computer-based systems, with the visualisation of single loops' picture, may improve the reproducibility,

especially the ability to guarantee examination of the same capillaries at different time points, thus applying this technique to longitudinal studies and clinical trials.

Conclusions

Capillaroscopy is a well-recognised method for the early detection of SSc and related conditions. The diagnosis of SSc should be considered in any patient with RP indicating the typical nailfold capillaroscopic changes included in the 'scleroderma pattern'. Moreover, capillaroscopy shows a predictive value with regard to the more aggressive variants of SSc and is helpful to assess the microvascular involvement in other autoimmune disorder, such as SLE. The 'classic' approach to capillaroscopy is based on the use of optical instruments (macrophotography, stereomicroscopy, dermatoscopy) that guarantees a global evaluation of the entire nailfold area ('widefield capillaroscopy'). Apart from being time-consuming, this procedure limits the realisation of high-quality documentation. The availability of new computer-driven videomicroscopy systems has greatly simplified the acquisition and recording of images of excellent quality, with a computer-based system for image acquisition and measurement. Digital storing of the images, with the consequent option of printing immediately for reports, and/or saving on support may give the possibility to send the images via the Internet for 'telediagnosis' and 'teleconsultation', thus contributing to the spreading of the technique.

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Chemical Peelings

112

Ilaria Ghersetich, Lara Tripo, Alice Garzitto, and Torello M. Lotti

Key Points

- A chemical peeling involves the application of an exfoliating chemical agent on the skin to produce a controlled injury with subsequent removal of superficial lesions within the skin layers.
- Many peelings are available today and produce therapeutic and cosmetic benefits.
- Chemical peelings are commonly used in dermatological practice to treat sun-damaged and sun-related pigmentary dyschromias, postinflammatory hyperpigmentation, melasma, acne, and acne scars.

General Principles

A chemical peeling involves the application of an exfoliating chemical agent on the skin to produce a controlled, partial-thickness injury with subsequent removal of superficial lesions within the skin layers, regeneration of new tissue with improvement of skin texture, and long-lasting therapeutic and cosmetic benefits.

Chemical peelings are commonly used in dermatological practice for the treatment of sun-damaged skin with actinic elastosis, facial wrinkles and actinic keratoses, sun-related pigmentary dyschromias (especially lentigo simplex), postinflammatory hyperpigmentation and melasma, acne and acne scars, warts, and rough oily skin with enlarged pores.

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Classification of Chemical Peeling

On the basis of wound depth, chemical peelings are classified as follows.

Superficial Chemical Peels

They penetrate the epidermis down to the dermal-epidermal interface. Examples of superficial peeling agents are listed in Table 112.1. The peeling agent used is one of the most important determining factors for peeling depth, but many other factors should be considered including length of application, Fitzpatrick skin type, prepeeling treatments, and repeeling. Although the procedure is standardized as much as possible, a "light" peeling agent can sometimes result in a deeper peel.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_112, © Springer-Verlag Berlin Heidelberg 2015

Table 112.1 Superficial chemical peeling agents

Jessner's solution
Glycolic acid 50–70 %
Salicylic acid
Modified Unna's resorcinol paste
Trichloroacetic acid, 10–20 %
Pyruvic acid 40–50 %

Table 112.2 Medium-depth chemical peeling agents

Trichloroacetic acid, 35–50 %
Jessner's solution + TCA 35 %
Glycolic acid 25–70 % + TCA 35 %
Salicylic acid + TCA 35 %
Pyruvic acid 70 %

Medium-Depth Peels

They can be obtained with agents or a combination of agents (Table 112.2) that produce an injury deep down into the upper reticular dermis.

The application of medium-depth peeling agents induces both full-thickness dermal necrosis and partial-thickness dermal necrosis.

Trichloroacetic acid (TCA) alone or in combination with other agents is the mainstay of medium-depth chemical peels.

Combination chemical peels attempt to maximize the therapeutic effects of different agents while minimizing adverse reactions and side effects through decreased concentrations of caustic agents.

In general, a combination chemical peel consists of two wounding agents: the first causes epidermal thinning or necrosis (Jessner's solution (JS) (Table 112.3), glycolic acid (GA), salicylic acid (SA)), while the second (TCA 35 %), which penetrates easily and deeper, accomplishes dermal necrosis.

These peelings are relatively simple and associated with a favorable risk/benefit ratio. However, proper patient selection, with attention to both medical and psychological factors, requires sound experience. The indications for these peelings are both medical and cosmetic conditions. Primary medical conditions include diffuse actinic keratosis, and cosmetic conditions include mild to moderate wrinkles, dyschromias, solar elastosis, solar lentigines, melasma, and postinflammatory hyperpigmentation.

Table 112.3 Jessner's solution

Resorcinol	14 g
Salicylic acid	14 g
Lactic acid (85 %)	14 g
Ethanol (95 %)	100 cm^2

Table 112.4 Baker-Gordon's phenol formula

Phenol USP 88 %	3 mL
Distilled water	2 mL
Septisol soap	8 drops
Croton oil	3 drops

Deep Chemical Peels

These involve the use of chemoexfoliants that penetrate to the mid-reticular dermis. Deep chemical peels entail longer healing times and increase the potential for complications. Baker-Gordon's formula (Table 112.4) is the most commonly used deep chemical peeling agent. Deep phenol peeling can lead to irreversible hypopigmentation because of the melanotoxicity of phenol and, thus, is not advised for dark skin types. Cardiac arrhythmia and hepatorenal toxicity may occur with systemic absorption; therefore this peel must be performed with very slow application in pigmentations and melasma.

Salicylic Acid

SA is an organic aromatic carboxylic acid with a hydroxyl group in position beta. It is a hydrophobic lipophilic phenolic compound. The application of SA 30 % in ethanol can produce detachment of corneal cells, basal cell proliferation, and activation of fibroblasts in the skin. An important advantage of SA over other superficial peeling agents is that it is a safe and efficacious treatment for acne and dyschromias in subjects with skin types V and VI (Fitzpatrick's

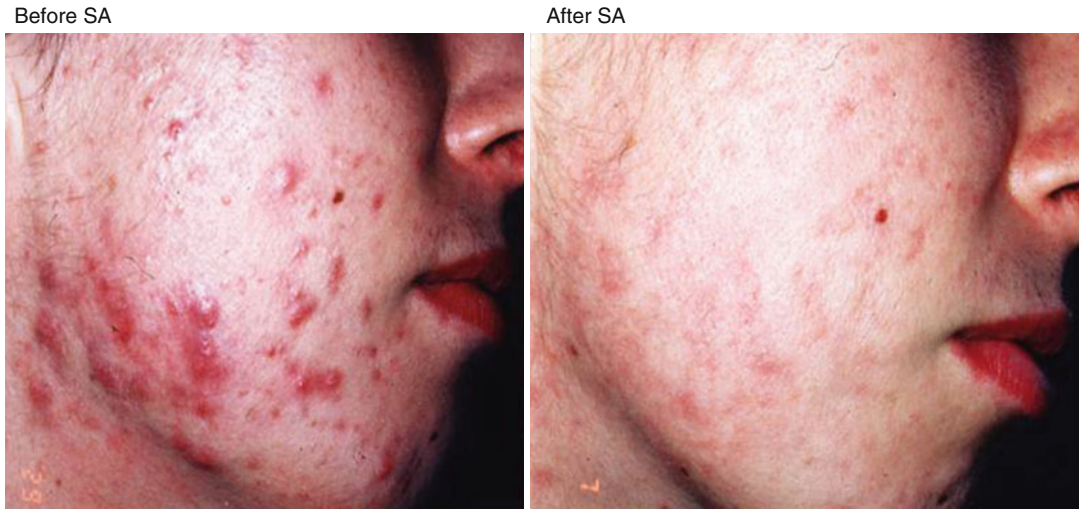

Fig. 112.1 Before and after SA in acne

Table 112.5 Modified Unna's paste

Resorcinol	40 g
Zinc oxide	10 g
Benzoinated axungia	28 g
Ceyssatite	20 g

classification). SA can also be used in combined peelings to achieve thinning of the epidermis that permits better penetration of other caustic agents, such as TCA or pyruvic acid (PA) (Fig. 112.1).

Resorcinol Peeling

Currently the resorcinol formula most often used is modified Unna's paste (Table 112.5). Resorcinol (*m*-dihydroxybenzene) is structurally and chemically related to phenol. It is soluble in water, alcohol, and ether and acts as a potent reducing agent. Application of resorcinol induces a split at the granular cell layer, vasodilatation, increased mitosis of the basal cell layers, fibroblast proliferation, and formation of a thickened dermal band. It also has bactericidal and keratolytic properties.

This type of peeling is quite easy to handle and has a low risk of side effects (temporary hyperpigmentation and occasional contact allergy). It is recommended especially for subjects with acne, including comedogenic acne, and is successful in clearing pigmentary acneic outcomes and very superficial scars. Melasma usually responds favorably too.

Pyruvic Acid

This is an α-keto acid that converts physiologically to lactic acid, and its additional properties make it a particularly effective topical peeling agent.

This very potent acid can be used as a peeling agent, without risks of scarring, in concentration between 40 and 70 % in a well-balanced proportion between water and ethanol.

The application of PA in the abovementioned concentration induced keratinocyte detachment with thinning of the upper layers of the epidermis.

PA penetrates down to the upper papillary dermis and causes dermal–epidermal separation and increased production of collagen, elastic fibers, and glycoproteins.

In addition to its keratolytic and desmoplastic properties, PA has also demonstrated antimicrobial activity.

Thus, PA can be employed as a superficial-medium peeling agent in subjects with inflammatory acne, moderate acne scars, greasy skin, actinic keratosis, and warts.

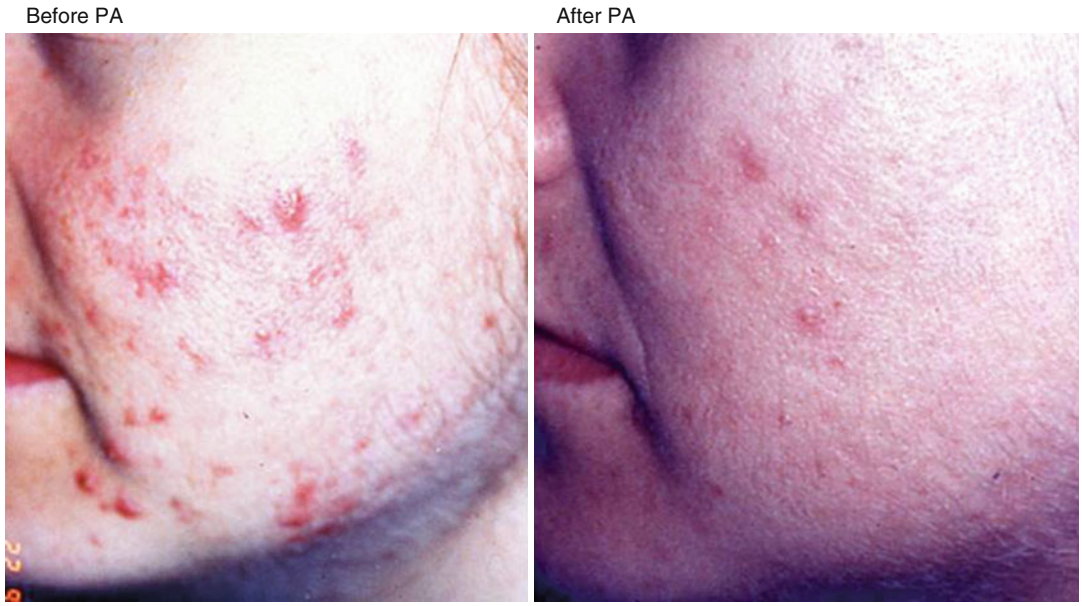

Fig. 112.2 Before and after PA in acne

We have also achieved good results in the treatment of photodamaged skin (fine wrinkles and localized superficial hyperpigmentations – color mismatch) (Fig. 112.2).

Glycolic Acid

GA, an α-hydroxy acid (AHA), has been the most popular peeling agent over the past 10–15 years.

We use solutions of 50–70 % GA made with water or combination of water, alcohol, and propylene glycol.

These solutions are clear, are not sensitive to light, and are highly stable (more than 2 years) but evaporate easily (the bottle must be kept tightly closed).

The application of high concentrations of GA reduces corneocyte cohesion (interacting with ionic bonds on the cellular surface) immediately above the granular layer and induces complete epidermolysis, epidermal and dermal thickening, reversal of basal cell atypia, dispersal of melanin, and increased synthesis of glycosaminoglycans and collagen; it may also improve the quantity and quality of elastic fibers.

Clinically these effects on the epidermis and dermis result in an improvement of skin surface irregularities, dyschromias, minor wrinkles, and moderate acne (Fig. 112.3).

An in vivo preliminary study by our group showed an increase of epidermal Langerhans cells in three subjects treated for 1 month with GA (70 % peeling once a week and daily home therapy with a 10 % lotion). In the same subjects, we also demonstrated an increase in the mRNA of transforming growth factor-β (TGF-β), a cytokine that is critically involved in dermal matrix remodeling.

Interestingly, all these effects occurred without any evident inflammatory outcome. GA also has anti-inflammatory activity combined with antioxidant properties. This strengthens the hypothesis that the mechanism of action of the AHAs and related substances is a specific direct effect on the skin, one that goes beyond the irritating effect.

It is very important to note that the effect of a GA peel depends on the length of time it is left on the skin, and thus, the peel needs to be neutralized with water or sodium bicarbonate with

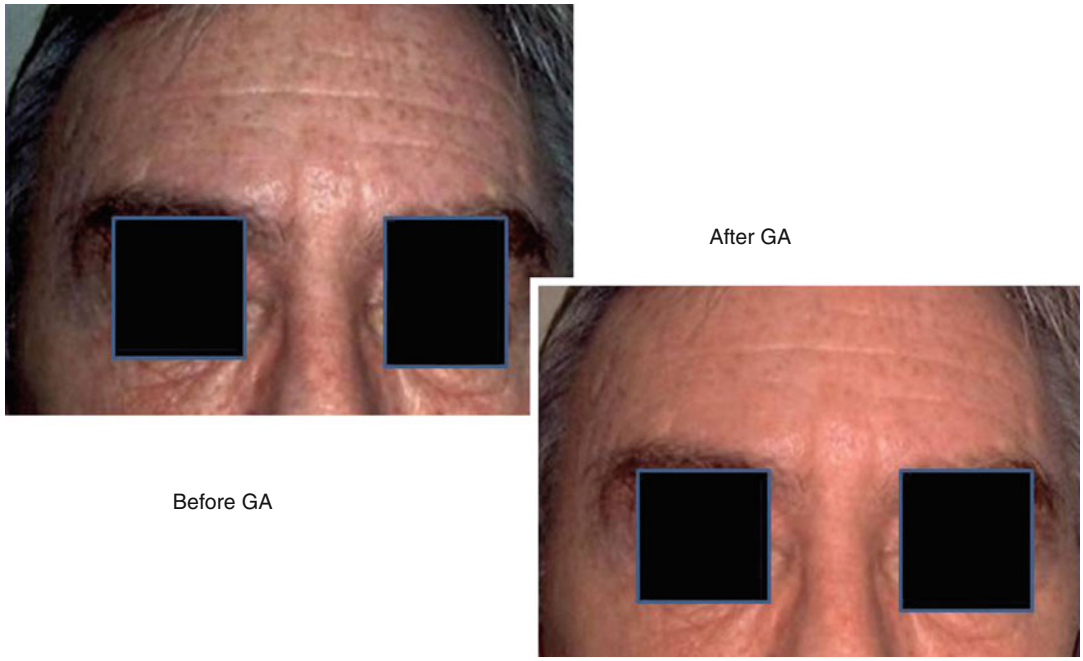

Fig. 112.3 Before and after GA in photoaging

perfect timing to prevent deeper dermal penetration that would lead to variable healing, crusting, and even scarring.

Tretinoin 10 % Mask

This peeling involves the application of a face mask with a high concentration of tretinoin (10 %). After 1 h the cream is removed. The skin becomes reddish on the first to second day, and superficial exfoliation starts on the third to fourth day and lasts approximately 1 week. Only one application per week for four to five sessions is needed, and it is possible to obtain clinical results that are similar to those that could be achieved with a common tretinoin cream used for 5–6 months, without the occurrence of the typical side effects. This mask can be effective in preventing and treating skin aging (whether spontaneous or photoinduced) and hypermelanosis (especially melasma, where it can be used to safely treat also phototype V–VI patients) (Fig. 112.4).

Trichloroacetic Acid

TCA can be used at different concentrations (10–20 % for superficial peels, 30–50 % for medium-depth peels) that lead to different peeling depths. In all cases the peeling is easy to control and predictable because it is neutralized by serum in superficial dermal blood vessels.

This acid is nontoxic systemically. The solution is clear and transparent with no precipitates and is not sensitive to light, and no refrigeration is necessary; it is stable for at least 2–3 weeks.

TCA causes necrosis and exfoliation of normal and actinically damaged cells and also precipitates epidermal proteins. Histological and ultrastructural studies have demonstrated that TCA peeling can renovate epidermal polarity, reducing epidermal intracytoplasmic bodies, increasing the number of fibroblasts, and increasing the deposition of collagen type I. Generally these effects become visible after 1 month of treatment. The main indications for TCA peeling are moderate photoaging with sun elastosis, slight wrinkles, superficial localized hyperpigmentations, and actinic keratoses (Fig. 112.5).

Fig. 112.4 Before and after tretinoin mask in melasma

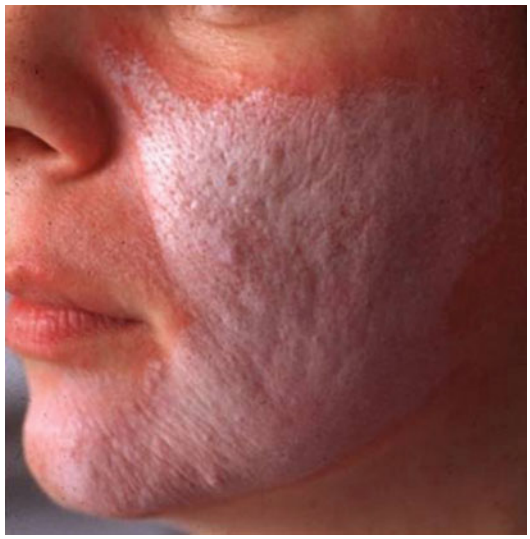

Fig. 112.5 TCA

Clinical Uses of Chemical Peels

The first step in treating a subject with a chemical peel is to determine any possible contraindications for peeling. For instance, a patient with recurrent herpetic lesions on the face may need to either avoid medium and deep chemical peels or require pre-procedural oral antiviral therapy (acyclovir). Before a superficial peel, we do not administer prophylaxis for herpes simplex unless the patient has had herpetic lesions within 2 weeks prior to the chemical peel procedure. Other contraindications (Table 112.6) include oral therapy with retinoids that may alter postpeel healing (it is

Table 112.6 Relative contraindications for chemical peels

Fitzpatrick skin type IV–VI
High degree of photoaging
Daily sun exposure
Past history of superficial X-ray treatment
Present or recent use of oral retinoids
Recent cosmetic surgery
Big smokers
Use of anticoagulants (warfarin)
Chemotherapy
HIV infection
History of recurrent herpes simplex
Hypertrophic scar or keloid formers
Unrealistic expectations

Table 112.7 Major indications for chemical peels

Facial skin rejuvenation
Dyschromias: melasma, postinflammatory hyperpigmentations, lentigo
Acne and acne scars
Greasy skin

best, in our experience, to wait at least 6 months after cessation of the oral retinoid before medium and deep peelings are performed).

As stated above, there are many indications for chemical peels (Table 112.7). Each case requires a specific treatment depending on the severity of the disorder and the characteristics of the patient. Thus, each treatment must be personalized. However, we can propose general guidelines for the major disorders that can be treated with chemical peels.

Postpeel care is similar for all types of chemical peels; in particular all subjects must avoid sun exposure for at least 1 month after superficial peels and 6 months after medium-depth peels, use sunscreens, and apply facial moisturizers daily. After superficial peels subjects can return to social life immediately, using cosmetic camouflage if necessary. For medium and deep peels, a 7–10-day stay at home period is necessary, and the subject must follow a very careful postpeel care procedure (described below).

Facial Rejuvenation

The wrinkles, textural alterations, diffuse dyschromias, yellowing, and mottling characteristics of photodamaged skin can be significantly improved with chemical peels.

Superficial peels are recommended for subjects with early photoaging or those who do not want to experience the temporary discomfort following medium and deep peel treatments.

Before performing any kind of chemical facial peel, it is advisable to treat the subjects for at least 2 weeks with topical applications of tretinoin (0.025 %), bleaching agents (4 % hydroquinone, azelaic acid), and 1 % hydrocortisone to decrease the risk of postinflammatory hyperpigmentation and promote wound healing. Subjects could also apply AHA creams (8–15 % GA) or PA creams for long periods (remembering to interrupt the application for at least 1 week after each chemical peeling); this reduces the thickness of the stratum corneum and helps to maintain the effect of the peeling.

Peeling with 70 % GA is recommended for only mildly photodamaged skin with fine wrinkles. To improve fine wrinkles effectively, the peeling is done in a series of four to six repeated treatments, once every 3–4 weeks. Before each peeling, the skin must be degreased with alcohol or acetone in order to remove surface debris, oils, and portions of the stratum corneum to allow uniform penetration of the peeling agent.

The acid can be applied with a special brush, cotton bud, or gauze. Once the acid has been applied to the whole face (starting from the forehead and then spreading to the cheeks, chin, upper lip, and nose), it is necessary to wait to see if erythema or "frosting" occurs.

Frosting may occur with GA peeling as a spotted pattern indicating epidermolysis, consisting in detachment of the epidermis from the papillary dermis. Generally, the aim of GA peeling is a slight exfoliation (without side effects) to make the skin smoother. The occurrence of "frosting" presents no additional benefit, but rather discomfort for the individual with increased risk of postinflammatory hyperpigmentation and scarring. Therefore, the acid must be neutralized immediately if frosting appears. The length of time of the application varies extremely from one subject to another in an unpredictable manner. It is advisable to observe subjects carefully during applications to build expertise based on personal experience. There is a great difference in manufacturing methods for products from different companies, and it is not advisable to use products you have not tested personally before performing a peeling. The acid must be neutralized with water or sodium bicarbonate to prevent deep dermal penetration, "overpeel." Following the peeling, no cream containing AHA should be applied for 1 week; if the patient does not show signs of irritation, erythema, or abrasion, no specific postpeel care is necessary.

In cases of significant erythema, topical non-halogenated steroids should be prescribed. If overpeel with abrasions occurs, application of an antibiotic ointment is recommended for at least 1 week.

Peeling with PA is suggested for subjects with mild to moderate photoaging with numerous dyschromias and rough skin with dilated pores. If the skin appears particularly thickened, a peeling with SA should be performed 1 week before beginning the series of PA peels in order to induce thinning of the epidermis that permits deeper, more uniform penetration of PA.

Before the application of SA, the skin is degreased with alcohol or acetone. The peel solution is applied with a brush or a cotton-tipped applicator starting from the forehead and progressing down to the cheeks, chin, upper lip, nose, and eyelids.

Subjects experience a stinging and burning sensation that increases progressively and then decreases rapidly when the peeling agent is neutralized with water. A small fan will help the subjects tolerate this discomfort better. The hydroethanolic vehicle volatilizes, leaving a white precipitate of SA on the skin surface.

SA does not need to be neutralized, but a splash of water on the skin stops the burning sensation and the SA precipitate is removed very easily. If the SA is applied in multiple layers and left on the skin for a longer time (>3 min), the skin turns grayish, meaning that frosting has occurred. Frosting is not required in this type of peel.

PA is applied after degreasing the skin with alcohol. Since PA causes very intense burning, we suggest applying it to small areas (forehead, one cheek at a time, chin, nose, and upper lip) and neutralizing each area with sodium bicarbonate before progressing to the next one. It is best to apply PA with a gauze and scrub gently and continuously for about 1 min. When PA vapors are inhaled, they are pungent and irritating to the upper respiratory mucosa so a small fan should be used during the procedure.

To achieve a satisfactory result, four to six peelings are required, to be done once every 3–4 weeks.

Subjects will experience tightening of the skin and desquamation, and only rarely abrasion for a few days immediately after the peeling. Therefore, it is necessary to prescribe a moisturizing cream that should be applied daily.

Some authors also suggest the use of multiple SA peels, at 4-week intervals, for the treatment of moderate photoaging.

This procedure presents several advantages over the other superficial chemical peels. First, the main benefit of SA compared to GA is its predictability.

It is easy to achieve uniform application and there is no worry about timing or overpeeling: also, the peel causes superficial anesthesia (burning ceases rapidly).

This type of peeling causes significantly more desquamation than GA.

In cases of more advanced photoaging, with skin laxity and diffuse dyschromias, peelings with 35 % TCA alone or preceded by the application of JS or 70 % GA are recommended.

The face is cleaned with a gauze pad soaked with acetone, alcohol, or chlorhexidine gluconate until the sebaceous oils have been thoroughly removed. The eyes are protected with sterile ophthalmic ointment, gauze pads, and hypoallergenic tape or goggles.

Oral or intramuscular anxiolytics may be used. Local anesthesia is not required.

A cotton-tipped applicator is moistened with TCA and rolled against the wall of the glass cup to remove excess fluid.

The TCA is applied to the skin area to be treated by firmly rubbing the moistened applicator in a circular or linear fashion, and the substance is allowed to penetrate for a few seconds, after which a further application is made, sometimes followed by a third application. Usually application is started from the forehead and progresses to the cheeks, chin, upper lip, and nose. Once the skin has been treated, it slowly changes color, becoming whitish gray as a result of chemical coagulation of the epidermis (frosting).

The frost appears more rapidly with high concentrations of TCA and may not appear with low concentrations, especially if the skin has not been adequately degreased.

After the acid is applied, a dry gauze pad is used to blot (not wipe) excess TCA.

Neutralization, as used for GA, is not necessary.

TCA stings when it is applied, and the severity depends on the concentration. The pain increases, normally peaking approximately halfway through the procedure.

A handheld fan may be helpful to soothe discomfort.

Often, anatomical facial subunits require different concentrations of TCA, i.e., for the forehead, cheeks, and chin 40 % and for the periorbital regions 18 %.

TCA should not be passed directly over the eyes. When eyelids are treated, particular care must be used to avoid seepage of TCA onto the sclera.

Immediate postoperative care consists of application of an antibiotic ointment, sometimes followed by a hydrogel dressing.

Subjects must be warned to expect various skin changes such as: (a) itching; (b) transitory marked hyperpigmentation, possibly associated with edema; and (c) exfoliation, which is never regularly distributed all over the treated areas but generally starts at the periorbital and perioral areas and ends at the forehead.

It is very important not to remove the skin in this phase to avoid postinflammatory hyperpigmentation. Generally, during the days that follow, the peeling subjects must avoid use of soaps and detergents, apply antibiotic creams or ointments twice a day, and use total sunblock screens; direct sun exposure must be avoided for at least 4–5 months.

In some cases the skin maintains a pinkish color for 2–3 weeks following exfoliation.

A nonhalogenated corticosteroid cream or zinc oxide paste may accelerate return to normal skin color.

The final result of TCA peels can be appreciated 3–4 weeks after the treatment.

The skin will appear tightened, with a general improvement in skin texture, rhytides will be much less evident, and the skin color will be more homogeneous.

For skin rejuvenation it is also possible to use two caustic agents to increase the depth of the peeling while reducing side effects. 70 % GA and 35 % TCA and JS and 35 % TCA are the combined peelings most often performed.

Seventy percent GA is uniformly applied to the cutaneous surface (as formerly described) and then neutralized. Then, 35 % TCA is applied on the same areas.

JS is applied evenly to the skin, after appropriate degreasing with either cotton-tipped applicators or a 2×2 cm gauze, to achieve a light but even frosting.

The frosting achieved with JS is much lighter than that with TCA and produces less discomfort to the patient.

A mild erythema appears with a faint tinge of frost evenly all over the face. JS does not need to be neutralized. At this point the 35 % TCA is applied evenly with a cotton-tipped applicator, and the acid is left on the skin for a few moments until a white frost appears. The peel is then neutralized with water.

Combined peels usually require a longer time for the procedure, approximately 20 min, and this is sometimes unpleasant for the treated patient.

The effects of these combined peels are comparable to that of 50 % TCA, but with lower risk of complications, especially scarring.

Dyschromias

Melasma, postinflammatory hyperpigmentations, and photoinduced dyschromias can be improved with PA, modified Unna's paste, tretinoin 10 % mask, or 35 % TCA peels. We believe that 35 % TCA gives the best results in dyschromias due to photoaging, while PA, tretinoin 10 %, and resorcinol peels are more effective in cases of melasma and postinflammatory hyperpigmentation. However, chemical peels alone are not adequate in such cases. Simultaneous treatment with bleaching agents (4 % hydroquinone, azelaic acid, kojic acid) and lifelong use of sunblock screens is a must for these individuals.

Acne and Acne Scars

There are various peeling options for the treatment of greasy skin and acne.

Greasy skin is characterized by skin thickening and increased sebaceous secretion, giving the face a shiny appearance, especially on the nose and forehead. Superficial chemical peels with SA or PA can significantly improve this unpleasant situation. The same results are obtained with these two kinds of peelings, although SA peels require fewer applications. In particular, two peeling sessions with a 3-week interval are adequate with SA, while at least three sessions are necessary with PA.

The peeling procedures and postpeel care are the same as for facial rejuvenation.

Very satisfying results are obtained using SA and PA in acne patients. These two peeling agents can be used in comedogenic, inflammatory, and nodular acne and papular and pustular rosacea because of their keratolytic and bactericidal properties. Repeated treatments, one peeling every 2–3 weeks for a total of six to eight treatments, are necessary to achieve clinically significant benefits. Also 70 % GA and JS have been reported to be effective for the treatment of facial acne, but in our experience the best results, with minimal discomfort for the subjects and lower risk of complications, are achieved with SA and PA peels. GA and JS should not be used in cases of inflammatory acne.

Moreover, modified Unna's paste is recommended in cases of comedogenic acne and in clearing pigmentary acneic outcomes and very superficial acne scars.

This paste is applied with a spatula to the area to be treated and left on for 1–2 h.

The post-application reaction resembles that of a first-degree burn with further exfoliation of dark brown skin that generally lasts for 7–10 days. Postpeel care includes a 1-week home stay period for cosmetic reasons and the use of antibiotic and moisturizing creams for 10 days and total sunblock screens for at least 2 months. It is advisable to pretreat the patients (as for skin rejuvenation) with topical 0.025 % tretinoin, topical bleaching agents (4 % hydroquinone, azelaic acid), and 1 % hydrocortisone.

In cases of acne scars, only moderate (partial) results are obtained with chemical peels; laser resurfacing is usually recommended. However, some good results can be obtained with 35–50 % TCA peels or combined peels (GA-TCA or JS-TCA).

Complications

Obviously, the deeper the peeling goes, the higher the risk of complications will be. The most frequent complications are listed in Table 112.8. Most of the complications listed occur after phenol peeling; hyperpigmentation is the only true complication that occurs after superficial or medium-depth peel.

Table 112.8 Complications of chemical peels

Pigmentary changes	Hyperpigmentation Hypopigmentation Depigmentation (porcelain) Mixed combination pigmentation Lines of demarcation Nevus accentuation
Scarring	Atrophic Hypertrophic Keloidal
Infections	Streptococcal or staphylococcal folliculitis (acne-like eruptions) *Pseudomonas* infections Toxic shock syndrome Herpes simplex Epstein-Barr virus keratitis
Prolonged erythema or pruritus	
Textural changes	Uneven texture Enlarged pores
Atrophy	
Milia	
Cold sensitivity or cold urticaria	
Cardiac arrhythmias	
Laryngeal edema	
Poor physician/patient relationship	
Allergic reactions	

There is an evident difference in color with clear boundary lines between the exfoliated and the non-treated areas. Generally this is temporary, and uniform skin color will be observed within 1–2 months.

The most feared complication following chemical peels is hyperpigmentation.

This is often due to even minimal sun exposure but may occur without such exposure, especially in dark-skinned subjects (Fitzpatrick IV–V). Hyperpigmentation can be treated with bleaching agents, generally with good results. It sometimes disappears spontaneously after some months. It is more difficult to treat a hypopigmentary outcome caused by destruction of melanocytes. This may be a permanent side effect, and it usually occurs with deep peelings (50 % TCA or phenol).

Infections associated with peelings are very rare, but the frequency of this complication increases with the depth of the peeling and is more pronounced in the case of crusts formation allowing bacterial colonization. The most common pathogens are *Streptococcus* and *Staphylococcus* species. A small percentage of patients manifest *Streptococcus* and *Staphylococcus* infection as folliculitis or acne-like eruptions.

Infections due to *Pseudomonas* are very rare.

A herpes simplex infection may be reactivated by any peeling agent (superficial, medium, or deep).

Suitable local and/or systemic therapy with antibiotics or antiviral drugs provides quick relief and if well timed can prevent scar formation.

Allergic reactions are generally very rare, and most occur after resorcinol peels.

An allergic reaction is often difficult to diagnose since the symptoms may be similar to alteration induced by the peeling itself (erythema and edema).

Identification and therapy of this complication is mandatory, since it drastically increases the likelihood of side effects such as hyperpigmentation and scarring.

Persisting erythema lasting for 2–3 weeks is considered a normal event, especially after medium and deep peels.

Erythema persisting more than 3 weeks may indicate hypertrophic scar formation.

Overpeel after 25% TCA

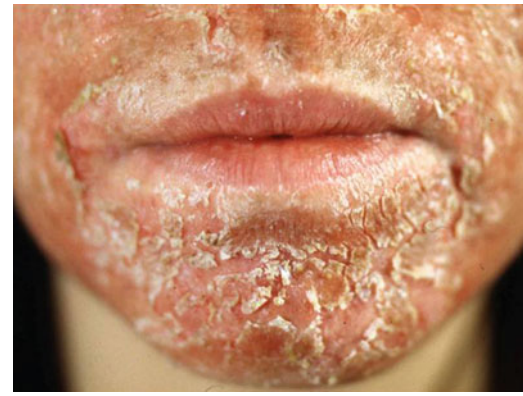

Fig. 112.6 Overpeel after TCA

Scarring is certainly the most dreadful complication.

The risk of scars is greater in subjects who undergo deep peelings or overpeel (Fig. 112.6) with superficial and medium peels, those with a past history of hypertrophic scarring or keloid formation, and those who have recently undergone systemic treatment with isotretinoin or in cases of postpeel infection or allergic reaction.

Different scarring reactions are possible, including flat, hypopigmented, depressed atrophic areas; thickened, elevated areas; and keloid.

The treatment differs according to the type of scar and involves the use of intralesional steroids, Silastic plasters, laser therapy, cryotherapy, and even excision and surgical revision of the scar in the most extreme cases.

Written Informed Consent to Chemical Peeling

Each individual that is going to be treated with a cosmetic procedure that involves a risk of complications should provide signed written, informed consent.

It is appropriate to give the patient a form with written information on side effects and complications, discomfort, and temporary skin changes that may or may not occur.

Figure 112.7 shows a draft form of written informed consent.

The undersigned _____ herewith gives formal consent to the chemical peeling treatment at _____.
The treatment has been explained to me and I have had the opportunity to ask questions.
This procedure will cause a modification in treated area of my face / body which may be unpleasant.
My face will become red and successively pigmented as if sunburnt.
Exfoliation will then start and last about 10 days.
An erythema may persist for 15-20 days. Have been informed that there is a minimum risk of side-effects, such as hyperpigmentation and scarring (very rare).
I agree that photographs of me trated may be taken.
Date_____--
Patient's signature (or patient's parents if < 18 years old)

Fig. 112.7 Informed consent form

Conclusions

Chemical peelings are an efficacious and safe approach to the treatment of some cutaneous problems of aesthetic natures. To avoid any undesired side effects, they should be performed by a specialist and according to a standardized procedure, when possible. Apart from the well-known chemical exfoliating effect, the stimulatory activity of some of the chemical peeling agents (GA and TCA) on fibroblasts has been described in numerous studies. For this reason, the use of these substances in photoaging can be recommended, and there is also a possibility that they can be used in other skin lesions. Further investigation of the exact molecular mechanism inducing fibroblast activation and subsequent collagen synthesis is definitely needed. Several studies document the benefit of combining chemical peeling with topical tretinoin, but comparative studies on the use of topical tretinoin and chemical peeling, mostly with GA, have not yielded fully satisfactory results to date. In any case the most successful chemical peeling agent seems to be TCA that can be used for superficial, medium, and deep peelings. Depth of penetration is easily noted when frosting occurs; neutralization is not needed; and there is no systemic toxicity. The combined use of two substances to peel the skin has proved to be successful. Proper degreasing, use of GA or JS, and 35 % TCA are steps that usually make peelings very effective. The amount of each agent applied governs the intensity and thus the efficacy of the peel. The variables should be adjusted according to the individual skin type and the area of the body being treated. Familiarity with the technique of single or, better, combination peeling, especially in subjects with moderate/severe signs of photodamage, is a prerequisite for expert use of this safe and inexpensive tool for effective chemical resurfacing of the skin.

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Reflectance Confocal Microscopy 113

Caterina Longo and Giovanni Pellacani

Key Points

- Reflectance confocal microscopy (RCM) is a new noninvasive technique that allows to rapidly explore the skin at nearly histologic resolution.
- Since its inception, RCM was applied mainly in the field of melanocytic lesions because melanin is the strongest source of contrast for this method.
- In skin oncology, RCM stands up as an add-on test for the diagnosis of melanoma being capable of improving the specificity of a narrow selected population of dermoscopically equivocal lesions. Despite melanoma diagnosis, it has been applied for the diagnosis of basal cell carcinoma for which this technique reached a very high diagnostic accuracy and for the diagnosis of other nonmelanoma skin cancer. Other fields of application include inflammatory and infectious skin diseases although few studies on large scale are still needed.

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General Principles

The ultimate goal of early melanoma diagnosis is the detection of all melanomas, while minimizing the number of excisions of nevi. To achieve this goal requires the clinician to not only be able to identify specific melanoma features but to also recognize the distinct aspects of nevi. To complicate the matter, several pigmented and nonpigmented lesions are in differential diagnosis with melanoma. Besides melanoma diagnosis, clinicians deal with the overwhelming number of nonmelanoma skin cancer (i.e., basal cell carcinoma) for which a clear-cut diagnosis is warranted as well as a good subtype differentiation to choose the most appropriate treatment.

Dermoscopy is regarded as first-line diagnostic technique, and in 2008 the evidence-based Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand gave the recommendation that training and utilization of dermoscopy are recommended with the highest grade (grade A: body of evidence can be trusted to guide practice) for clinicians routinely examining pigmented skin lesions. However, a small quote of melanoma may turn as featureless on dermoscopy, while some nevi may be regarded as melanomas.

Reflectance confocal microscopy (RCM) is a novel imaging technique that has been proved to improve the specificity for melanoma diagnosis when used as a second-level examination for dermoscopically difficult-to-diagnose lesions.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_113, © Springer-Verlag Berlin Heidelberg 2015

Following its application on skin oncology, RCM has been used in several clinical situations including inflammatory skin diseases, treatment monitoring, and infectious diseases, just to name a few.

In this chapter we provide a summary of the main application of confocal microscopy in clinical practice.

Basic Principles and Instruments

Two confocal microscopes are commercially available. Although the laser light used and the basic principle are the same in both types, they are fundamentally distinct in their approach: one is a full-scale microscope constituted by a large scanning head and the other is a handheld device. The former confocal microscope (VivaScope® 1500, Lucid Inc., Rochester, NY, USA) contains a probe (the head of the microscope) that is attached to the skin by using a disposable plastic window that is in turn taped to a metal ring. A confocal microscope consists of a point source of light, condenser, objective lenses, and a point detector (Australian Cancer Network Melanoma Guidelines, 2008; Skvara et al. 2005). The pinhole collects light emanating only from the in-focus plane. The mechanism of bright contrast in reflectance confocal microscopy is backscattering. In grayscale confocal images, structures that appear bright (white) have components with high refractive index compared with their surroundings and are similar in size to the wavelength of light. Backscattering is primarily governed by the structures' refractive index compared to the surrounding medium. Highly reflective skin components include melanin, collagen, and keratin. The confocal scanning produces high-resolution black and white horizontal images (0.5×0.5 mm) with a lateral resolution of 1.0 μm and axial resolution of 3–5 μm. A sequence of full-resolution individual images at a given depth is acquired and "stitched" together to create a mosaic ranging in size from 2×2 to 8×8 mm. A vertical VivaStack® can be imaged. It consists of single high-resolution images acquired from the top skin surface up to 200 μm, corresponding to the papillary dermis, to obtain a sort of "optic biopsy."

The handheld RCM has been recently introduced on the market (VivaScope® 3000). This version is a smaller, flexible device that is quite useful in difficult-to-access areas. Unlike the 1500 version, it has a manual control for laser power on the probe, imaging depth, and capture, but it does not allow scanning of a large field of view, needed, for example, to analyze the architecture of tumors. The application of handheld device is for surgical pre-mapping or when multiple site imaging is requested.

Melanocytic Tumors

Nevi

The realm of common acquired nevi includes a variety of clinically different nevi. Traditionally, they are classified based on histopathologic criteria in junctional, compound, and intradermal nevi. Although this classification does not encompass the clinical variability of these lesions, it offers a good understanding of the confocal findings according to different skin depths. Moreover, a perfect correlation between dermoscopy and confocal substrates is helpful to interpret the histopathologic substrate.

Junctional nevi usually do not represent a clinical challenge since dermoscopy shows a regular pigmented network ranging in color from light brown to dark brown or orange hue. Confocal microscopy shows the presence of a regular honeycomb pattern and ringed junctional architecture due to the alternation of hyporeflective dermal papillae surrounded by bright polygonal cells. Few junctional nests can be present at time and they enlarge the interpapillary space. In compound nevi presenting a mixed dermoscopic pattern, it is frequent to observe the presence of several junctional nests that generate a "meshwork pattern." When a blue color is present upon dermoscopy, RCM images highlight the presence of plump bright cells corresponding to melanophages, usually seen into the dermal papilla close to a tiny canalicular vessel. The intradermal nevi with a predominant dermal component usually show a regular epidermis and the presence of

large aggregates of roundish monomorphous cells ("clod" pattern) when the nested population is superficially located. In case of a deep dermal component, the limited laser depth penetration hampers the visualization of the melanocytic proliferation.

Besides the stereotypical dermoscopic and confocal aspects of these lesions, some nevi can be challenging either from a clinical point of view or histopathologic ones. Several terms have been coined to refer to these lesions such as "dysplastic" or "atypical" nevi although a precise correlation between the clinical "atypical" aspects and the "atypical" histologic appearance has not found yet. Recently, the exact correlations between the histopathologic findings in the so-called dysplastic nevi and the confocal findings such as the bridging of the nests and the inflammatory infiltrate have been defined. However, a clear-cut distinction from severe atypical nevi and incipient melanoma is not always feasible, and it is strongly operator dependent either for pathologist or clinicians. In the presence of flat, reticular lesions, digital monitoring with short- and long-term follow-up represents the best strategy to avoid the excision of benign nevi and to not miss melanoma that do not fulfill all dermoscopic and confocal criteria to be classified as such at baseline.

Another difficult scenario is represented by the morphologic universe of Spitz tumors. Spitz/Reed nevi represent a family of lesions that show a variety of clinical and dermoscopic aspect, histologic features, and biologic attitudes.

A good correlation between histopathology and confocal microscopy is reached for the pagetoid spread that can be readily detected by the RCM as well as for the presence of a sharp lateral demarcation and spindled cells. Other parameters include the presence of junctional and dermal nests, parakeratosis, transepidermal melanin elimination, and inflammatory infiltrate rich in melanophages. No structures referable to Kamino bodies were observed on RCM. However, a deep assessment of cytologic and architectural changes is not possible by means of RCM, and thus, the management of Spitz tumors relies on the integration of clinical information and dermoscopic aspects.

Besides common nevi, Spitz nevi, and atypical nevi, another category consists of the so-called special nevi. They include a variety of different nevi such as recurrent nevi, Meyerson's nevi, and uncommon histopathological variants such as balloon cell nevus, just to name a few. Recurrent nevi are benign lesions that may regrow after partial excision (shaving) or trauma, but they can be challenging in case of unknown histological diagnosis of the primary tumor. Recurrent nevi do not exhibit prominent pagetoid or lateral spread of melanocytes and atypical nests at the junction, whereas recurrent melanomas were typified by the presence of classical RCM diagnostic criteria.

Although the diagnosis of Meyerson's nevus is usually rendered on a clinical ground, RCM can be used for cases with subclinical and not clear-cut dermoscopic criteria. In these cases, RCM allows the visualization of spongiotic vesicles in vivo, as round to ovoidal dark spaces, visible in the superficial layers of the epidermis around a typical melanocytic nevus.

Balloon cell nevus is a rare variant of nevus that is characterized by the presence of multiple aggregated white to yellow globular structures on dermoscopy. RCM reveals the presence of melanocytes within the nests with a vacuolized cytoplasm, visible as shiny grayish areas surrounding a dark nucleus.

Melanoma

The role of RCM for the diagnosis of melanoma and its characterization in different subtype has been demonstrated over the past decades.

Distinctive RCM criteria for melanoma diagnosis have been identified and validated.

The most relevant criteria include the presence of pagetoid spread, cytologic atypia at the DEJ, nonspecific architecture (nonedged papillae), melanocytes infiltrating dermal papillae, and atypical nesting including several nest types in particular sheetlike structures and cerebriform nests (Fig. 113.1). Pagetoid spread, also named

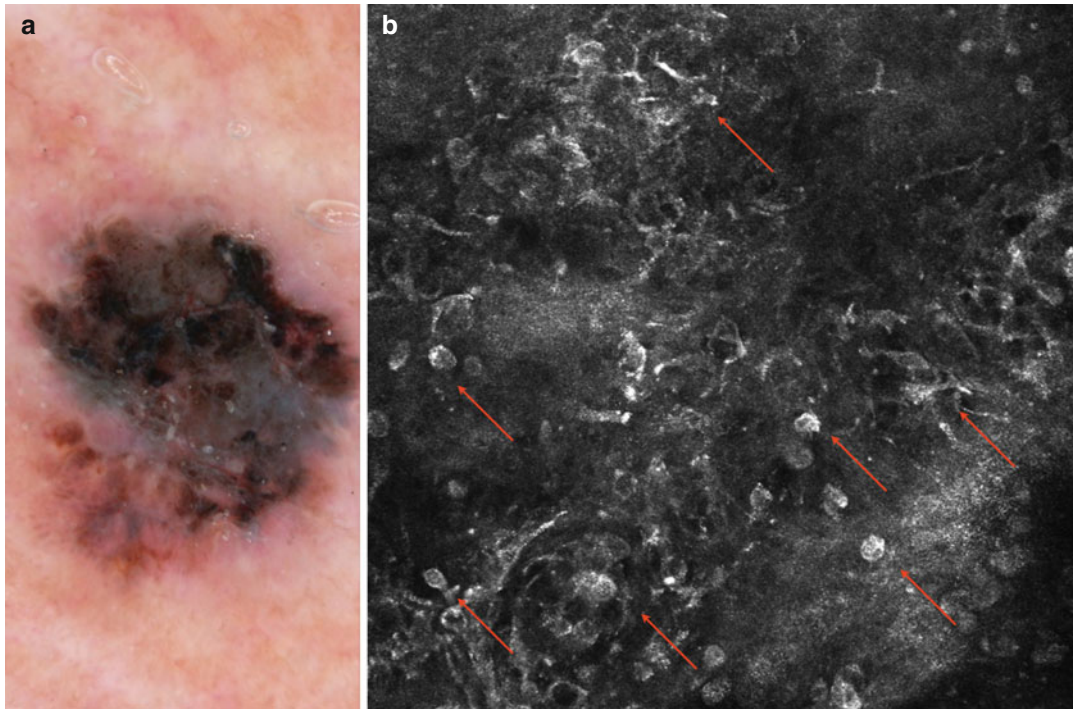

Fig. 113.1 (**a**) Dermoscopy of a melanoma showing a multicomponent pattern. (**b**) RCM reveals the presence of several pagetoid cells with bright cytoplasm and dark nucleus (*arrows*)

as epidermotropism or pagetoid melanocytosis, is one of the most striking and reproducible criteria, and it refers to the presence of atypical melanocytes, round or dendritic shaped, arranged as single cells or small nests, scattered within the epidermis. Localization of these cells, at the periphery of the lesion, in the center, or widespread, is crucial for identifying early melanomas displaying few confocal clues.

The presence of cytologic atypia is defined by the occurrence of atypical melanocytes at the dermoepidermal junction. When evaluating the architecture, melanomas typically show the absence of either a "regular" ringed, clod, or meshwork pattern as usually seen in common nevi. Instead, they are typified by an obvious interruption of the architecture with the onset of the so-called nonedged papillae associated with the presence of atypical melanocytes. Dermal nesting encompasses a wide range of confocal presentations according to distinct melanoma subtype and level of invasion (i.e., Breslow thickness). Nests can show up as dense and sparse nests, as sheetlike structures, and, rarely, as cerebriform nests. A newly defined entity named "nested" melanoma of the elderly is typified by the presence of compact nests with atypical melanocytes upon RCM.

An RCM score (based on six distinct morphologic features) was described and appeared to be the best method to differentiate melanoma from nevi. Another study (Guitera et al. 2010) established the additive value of this method when used with dermoscopy: in 326 cases, the specificity for the diagnosis of melanoma was doubled, with comparable sensitivity. RCM and dermoscopy together resulted in a false-negative rate of only 2.4 %. RCM was particularly efficient for amelanotic lesions. RCM features of difficult diagnosis were also published like nodular melanoma and small melanomas. In the largest RCM study to date, which included over 700 lesions suspicious for malignancy, a two-step method for the diagnosis of melanoma and basal cell carcinoma was reported. The diagnostic accuracy of the BCC algorithm was 100 % sensitivity and

88.5 % specificity (Guitera et al. 2010). The diagnostic accuracy of the melanoma algorithm was 87.6 % sensitivity and 70.8 % specificity.

Another field of application of RCM is represented by facial lesions for which a biopsy is not always accepted by the patients, and furthermore, a punch biopsy is not always enough material for the pathologist to make a conclusive diagnosis. RCM provides a fast diagnosis for pigmented and nonpigmented lesions on the face. The RCM diagnostic criteria of 284 difficult macules of the face were described in 2010 by Guitera et al. with a method (LM score composed of eight criteria) resulting in 93 % sensitivity and 82 % specificity for the diagnosis of lentigo maligna. The handheld RCM can be used to identify quickly and efficiently the microscopic features of malignancy, and a recent case series shows its interest in small amelanotic papules of the face.

Despite its application for the diagnosis, RCM can be used for a presurgical mapping of the tumor which often may present indistinct clinical borders. In a study analyzing 37 lentigo maligna, RCM produced "major" changes to the management in 73 % of the patients (Guitera et al. 2013).

Malignant Nonmelanoma Skin Tumors

RCM was extensively applied for the diagnosis of basal cell carcinoma (BCC) and for the characterization of actinic keratosis (AK) and, in few reports, for squamous cell carcinoma diagnosis.

Basal Cell Carcinoma

The hallmark for BCC diagnosis is the presence of basaloid islands that can show up as tightly packed aggregates with peripheral palisading and lobulated shape (Fig. 113.2). They could be more

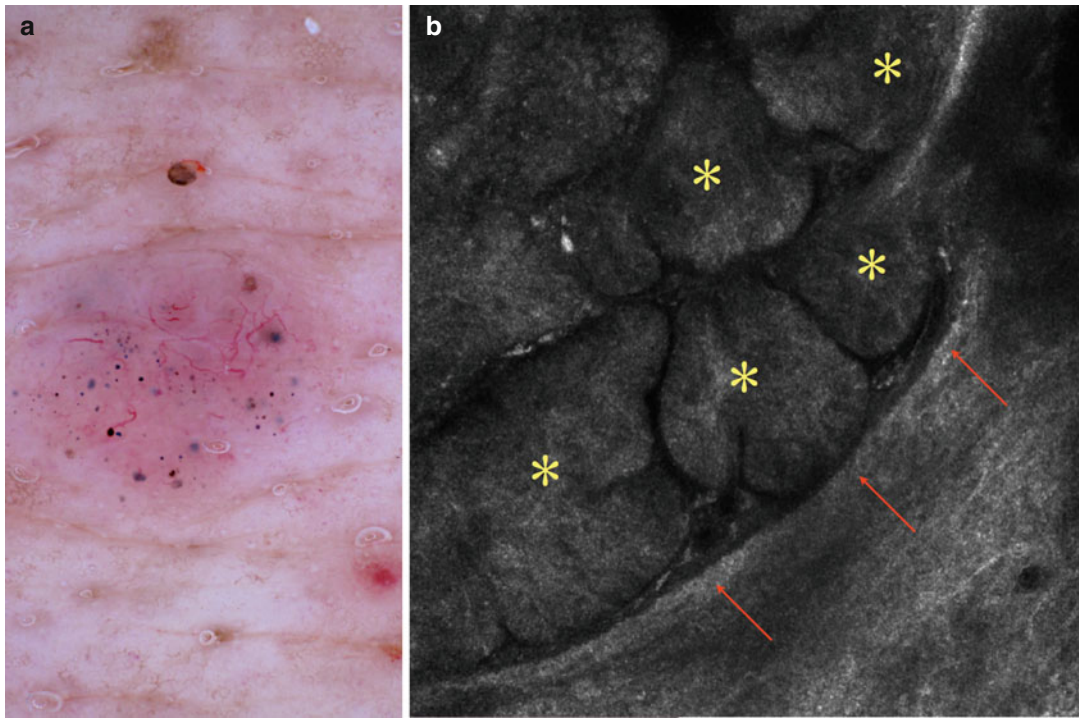

Fig. 113.2 (**a**) Dermoscopy of a nodular basal cell carcinoma typified by the presence of arborizing vessels and multiple *blue-gray dots*. (**b**) RCM shows the presence of tightly packed basaloid islands (*asterisks*) with peripheral palisading and outlined by a dark clefting (*arrows*)

or less refractive according to the presence of pigmentation within the tumor islands and in the surrounding (melanophages or free melanin). Additional features include the presence of the streaming of the epidermis and presence of blood vessels. Basaloid aggregates are outlined by dark spaces that correspond to mucin and often are surrounded by a prominent vascularity. Histopathologically, the aggregates correspond to the basaloid islands. Interestingly, RCM highlights very well the presence of dendritic melanocytes entrapped within the basaloid islands observable in heavily pigmented BCC.

Recently, the value of RCM in subtyping different BCC has been provided. The possibility to have a preoperative characterization of BCC is essential to choose the most appropriate treatment without performing a biopsy. Moreover, RCM for the diagnosis of nodular BCC showed 100 % sensitivity and 99.1 % specificity.

RCM was also used to define the specific features of fibroepithelioma of Pinkus (Longo et al. 2012) that show a typical "fenestrated pattern" that facilitate the recognition of this tumor.

Actinic Keratosis and Squamous Cell Carcinoma

Actinic keratosis and squamous cell carcinoma display the presence of variable keratinocytic atypia. At the stratum corneum, superficial disruption with single detached keratinocytes seen as bright, polygonal cells of high reflectance can be observed. Furthermore, nucleated, highly reflective cells with dark center and sharp demarcation appear within the stratum corneum corresponding to parakeratosis. Atypical honeycomb pattern and architectural disarray of variable degree are seen at the level of the stratum granulosum and stratum spinosum corresponding to different degrees of keratinocyte dysplasia on histopathological exam. In squamous cell carcinoma an atypical honeycomb or disarranged pattern of the spinous–granular layer is found along with round nucleated cells corresponding to pleomorphic keratinocytes (Fig. 113.3). Round blood vessels traversing through the dermal papillae perpendicular to the skin surface and scale crust appearing as brightly reflective amorphous

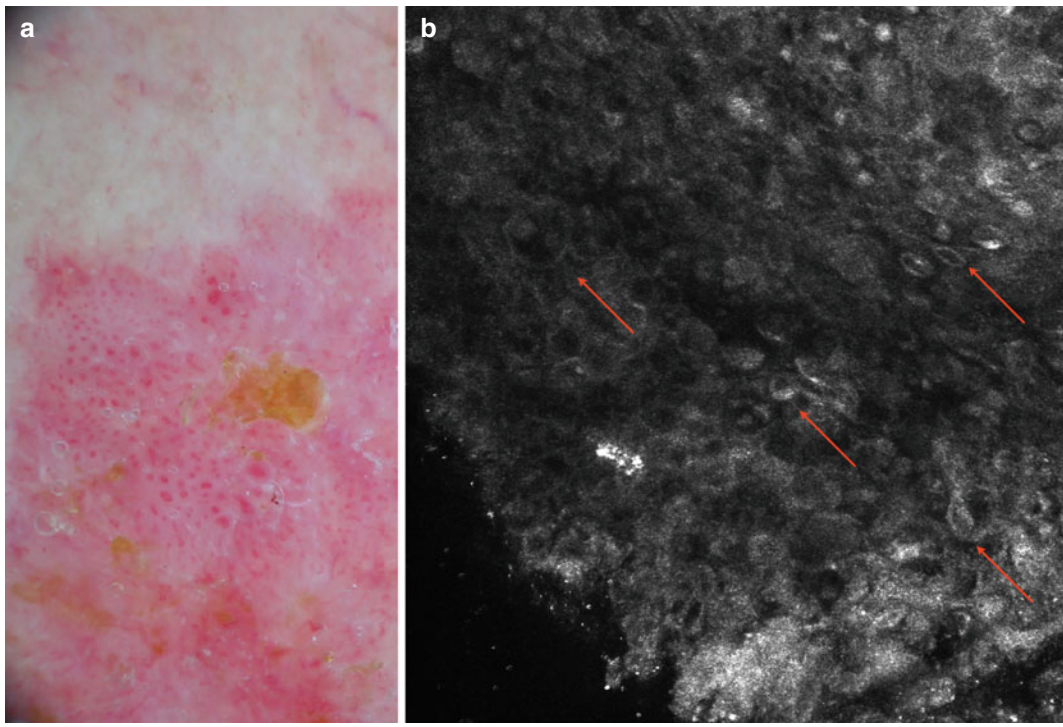

Fig. 113.3 (**a**) In situ squamous cell carcinoma that shows multiple glomerular vessels on dermoscopy. (**b**) RCM reveals the presence of marked dyskeratosis with atypical keratinocytes (*arrows*)

islands on the surface of the skin are common findings in SCC. In cases with marked hyperkeratosis or abundant scale covering the entire lesion, in-depth imaging is limited by the keratin scattering, limiting exploration of the DEJ, which is fundamental for complete diagnosis.

Other Tumors

Paget's disease is an uncommon type of intraepidermal adenocarcinoma. The first description of Paget's disease by means of RCM regarded a pigmented variant (Longo et al. 2007). Later, a case series on more cases of nonpigmented tumors was performed. As a clue, RCM shows the presence of large atypical pagetoid cells that can be present singly and in clusters. The presence of pagetoid spread and other confocal features, in the appropriate clinical context, may allow distinction from other inflammatory diseases that may appear similar clinically.

Inflammatory Skin Diseases

Inflammatory skin diseases include spongiotic dermatitis, psoriasiform diseases, diseases with interface involvement, and pigmentary nontumoral skin disorders (i.e., vitiligo, melasma).

The main feature of spongiotic dermatitis on RCM is the presence of inter- or intracellular spongiosis. This corresponds to an increased intercellular brightness due to inter- or intracellular fluid accumulation that leads to the appearance of a regular honeycomb morphology. When spongiosis is more pronounced, it is possible to detect vesicle formation that appears as well-demarcated, dark, hollow spaces between granular and spinous layer keratinocytes. Commonly, exocytosis is associated with spongiosis, whereby the inflammatory cells are seen on RCM as bright, round, highly refractive structures of about 8–10 μm, interspersed between keratinocytes. Inflammatory cells may also be observed to various extents in a perifollicular, perivascular, or interstitial dermal distribution.

Psoriasiform disease is distinguished by the presence of an increased number of nonrimmed papillae at the dermoepidermal junction, resulting in a junctional profile similar to that of normal skin but with papillae surrounded by faint rings of basal keratinocytes, instead of the typical bright rings.

The hallmark in interface dermatitis is the inflammatory involvement of the dermoepidermal junction. The inflammatory cells tend to obscure the junction profile and the dermal papillae with a more diffuse involvement in lichen planus and a focal distribution in lupus erythematosus. In the latter, the presence of inflammatory infiltrate can be seen in proximity of the adnexa that usually appear dilated (larger than 80–100 μm) and filled by highly refractive material in the lumen (hyperkeratotic infundibula).

Among the acquired pigmented disorders, RCM has been used to study vitiligo. Vitiligo lesional skin shows disappearance of the normal brightness at the dermoepidermal junction where the edged papillae appear as a remnant of the preexisting papillary ring.

Infectious Diseases

RCM has been applied in some infectious diseases although studies based on large cases are not available. Superficial mycosis can be easily detected by RCM since it has a high-level resolution for the upper epidermis. *Dermatophyte hyphae* appear as bright linear branching structures within the epidermis with an excellent correlation with the ones seen upon light microscopy. With the same high resolution, it is possible to detect the presence of *Demodex folliculorum* within the hair follicles that show up as multiple roundish well-outlined structures corresponding to the head-down mites. *Sarcoptes scabiei* is readily observed using within the burrow.

Conclusions

RCM discloses a new morphologic universe that is close to histopathology with the added value of being performed in vivo and over time.

As for any new technique, a dedicated training is needed to learn the basic notions and how to interpret them in the appropriate clinical context.

Since its first application, RCM emerged as a unique technique that may radically change the way to look at a given skin lesion and may offer not only an additional diagnostic help but also new insight into biologic phenomenon that cannot be merely explored with other devices. In the future, new studies will be performed to validate the current findings and to open new field of applications.

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Cryosurgery

114

Aleksandar L. Krunic and Leonardo G. Marini

Key Points

Cryodestruction by liquid nitrogen is a very efficient method of treatment for various benign and malignant skin conditions. Proper planning of freezing and assessment of depth by monitoring the halo around the spray freeze or cryoprobes technique can successfully ablate many suitable lesions. Complications are minimal, no anesthesia is necessary, and the cost is low.

Table 114.1 Terminology of using subzero temperatures in biology and medicine

Cryobiology	Effects of subzero temperatures on a living system
Cryogenics	Development of freezing temperatures within a living tissue or cell
Cryotherapy	Therapeutic use of cold in a wide sense
Cryosurgery	Well-aimed and controlled destruction of disease tissue by application of cold

Modified from Zouboulis (1999)

General Principles

Cryosurgery refers to well-aimed and controlled application of freezing temperatures for the destruction of diseased tissue (Table 114.1) (Zouboulis 1999). Although primarily used for cutaneous lesions, cryosurgery is now getting wider applications in gynecology, urology, ophthalmology, neurosurgery, cardiology, and oncology. Since the discovery of liquid nitrogen in the 1940s, the modern era of cryosurgery has begun with myriad of procedures being performed in the outpatient settings with high safety and effectiveness, low cost, ease of application, good cosmetic results, and no need for local anesthesia.

History

Cryosurgery has been used in dermatology for the last 150 years. The first attempts were to treat lesions of lupus vulgaris (skin tuberculosis) with cold ice. Later on liquid helium, liquid air, and liquid oxygen were used, especially upon discovery of the vacuum flasks to store cryogens by James Dewar at the end of the nineteenth century. The ideal cryogen, liquid nitrogen, once discovered in the 1940s, quickly gained popularity by having the lowest boiling temperature of

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_114, © Springer-Verlag Berlin Heidelberg 2015

−196 °C and being noncombustible. The initial application with cotton-ball method, preferable in the early 1950s, soon revealed inefficient due to the inability to achieve complete and optimal freezing of below −20 ° C at the treatment site. In the early 1960s, numerous sophisticated devices have been developed not just to preserve and deliver cryogen in the spray or contact technique, but also to monitor the temperature inside and below the treated lesions provided controlled and reliable cryodestruction of the targeted lesion. The works of dermatologist Setrag Zacarian and engineer Michael Bryne from Connecticut pioneered the use of cryogen spray units, now widely used for the application of cryosurgery worldwide.

Mechanism of Action

The biological changes that occur during the freezing process are divided to three phases, (a) direct tissue (cell injury), (b) vascular phase (vessel injury), and (c) inflammatory (immunological) phase, which is recently getting more and more attention due to the effects of improving antigen presentation in the frozen tissue and stimulation of the protective immune response.

(a) *Direct Cell Injury* – The initial drop of the temperature by rapid freezing speed of 100 °C/min first produces extracellular ice and cell dehydration (which is potentially reversible) also known as *heterogeneous nucleation*. Further freezing results in the formation of intracellular ice, since dehydrated cells open aquaporins, special channels in the cell membrane to fight the dehydration and improve water balance. The size of the ice crystals is very important, since larger crystals formed by rapid temperature decrease have more damaging effect. Intracellular ice crystals damage the mitochondria, endoplasmic reticulum, and other cell organelles inducing irreversible cell destruction also known as *homogenous nucleation*. This phase occurs when temperature drops below −20 to −25 °C, for keratinocytes, but much sooner for melanocytes (−4 to −7 °C) and sebocytes and hair follicles (−15 °C). Hence, the cryosurgery on hairy areas or pigmented skin can result in permanent alopecia or hypopigmentation, respectively. *Tissue thawing* at slow speed (spontaneously or up to 10 °C/min) contributes to more volume changes and intracellular edema due to the reversal of the osmotic gradient as well as intracellular water recrystallization. Thawing time should be at least 1.5 times longer than the freezing time for adequate cryosurgery. Fibroblasts die at −30 to −35 °C and are more resistant to freezing. That is why cryodestruction of malignant tumors requires −50 °C of freezing temperatures for the complete damage of tumor cells and its stroma, while benign lesions for optimal treatment need much lower freezing for −20 to −25 °C where just destruction of keratinocytes is sufficient without the destruction of the collagen supporting network. Furthermore, the preservation of stroma in cryodestruction of benign lesions is responsible for the lowest incidence of keloids in cryosurgery in comparison to any other surgical modality. The effect on cell viability reaches maximum at approximately 100 s of freezing, so the *optimal duration of freezing* is up to 30 s for benign lesions and 60 s for malignant tumors. A *second freeze-thaw cycle* causes more cell death and is required when malignant tumors are treated; for benign lesions, on the contrary, it is not essential. The treatment time of 30 s usually forms epidermo-dermal separation and hemorrhagic blister but never produces scarring or keloids. On the contrary, 60 s freezing (desirable for malignancies) results in cryonecrosis and formation of a scar.

(b) *Vascular Phase* – Cryogenic injury produces significant vascular changes including stasis, tissue anoxia, edema, focal capillary damage, hemorrhage, and microthrombosis. Thrombosis of all vessels is seen when temperature drops to −15 to −20 °C.

(c) *Immunological* (*Inflammatory*) *Phase* – An immunological response to cryosurgery was suggested in the late 1960s. This area is now

experiencing a great deal of research. The fact that the frozen tumor remains "in situ" after cryoablation enables macrophages, neutrophils, and dendritic cells to infiltrate in the first 48–72 h attracted by the cytokine milieu produced by cryodestructed cells. Later, lymphocytes migrate into the area contributing to augmentation of the immune response. Recent papers have suggested the stimulation of "protective response" after cryodestruction with suppression of T-reg lymphocytes, which are crucial for tumor survival and its escape from the host immune system. The evaluation of methods of augmenting the protective immune response after cryoablation with the use of adjuvants like imiquimod or cytotoxic compounds like podophyllin is currently also undergoing intensive investigation.

Equipment

Cryosurgery equipment (Fig. 114.1a–d) consists of cryogen liquid and its container, cryogun with different cryoprobes, spray tips, and attachments for intralesional cryosurgery – Luer lock and acne aperture for cryopeel. Liquid nitrogen is the ideal cryogen due to its very low boiling point of −196 °C (Table 114.2). The maximum storage

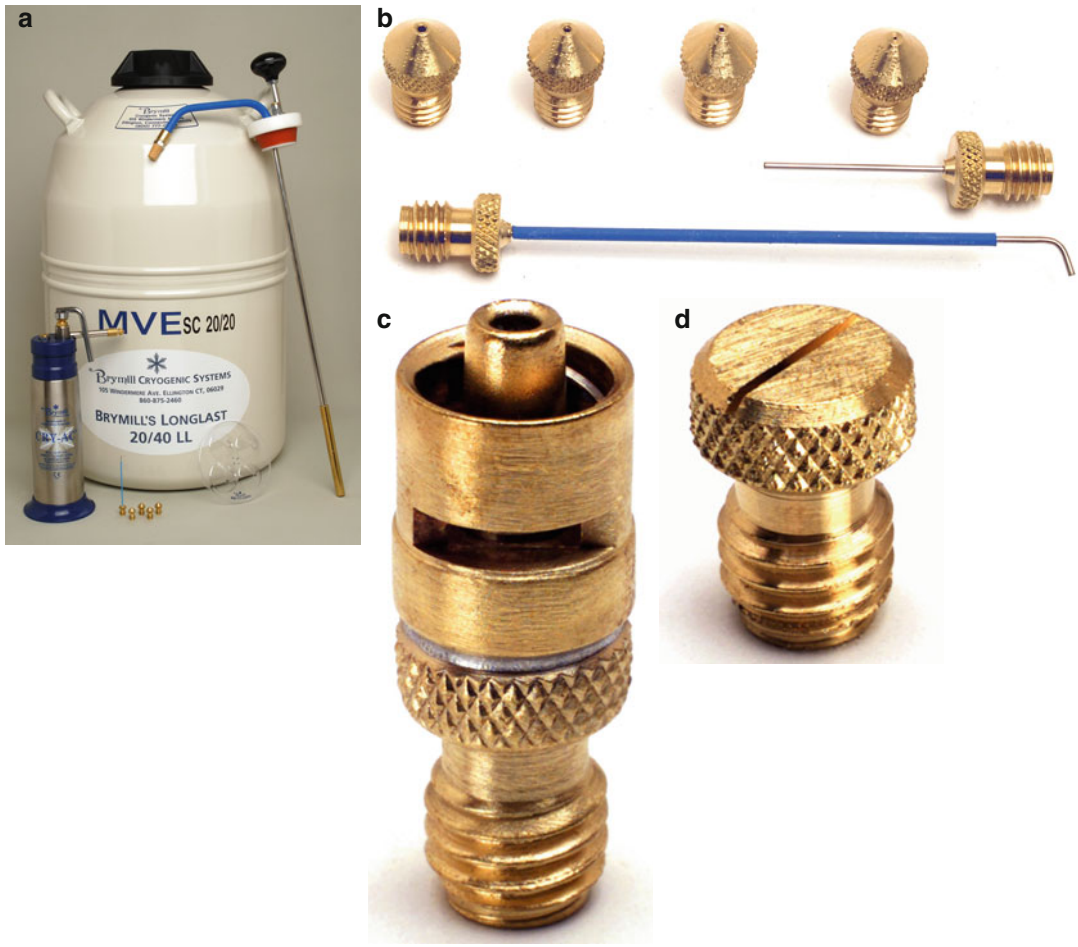

Fig. 114.1 Cryosurgery equipment. (**a**) Cryogun, withdrawal tube and container, (**b**) extensions for open spray, (**c**) Luer lock for intralesional cryosurgery, (**d**) acne aperture for cryopeel

Table 114.2 Cryogens and boiling points

Liquid nitrogen	−196 °C
Carbon dioxide	−70 °C
Nitrous oxide	−60 °C
Fluorocarbon liquids	−90 °C

capacity for containers used in skin surgery procedures is up to 50 l and for the time period of up to 300 days. The liquid nitrogen is poured into the cryogun, i.e., spray unit by using withdrawal tube (fills one bottle at the time) or withdrawal device (fills several bottles at the time). Simple decanting is to be avoided due to the risk of cryogen spillage and burns. Liquid nitrogen is odorless, inert, noncorrosive, noninflammable, and colorless and, at the room pressure of 1 atm, has temperature of 195.8 °C. Cryoguns can vary in volume from 300 to 500 ml and can store liquid nitrogen from 12 to 24 h. Simple Q-tips and plastic containers could be used for spot freeze technique with a cotton ball. This method is not precise and often does not produce complete freezing beyond desirable plateau for the treatment of benign tumors, which is below −15 °C. The used cotton ball should never be redipped into the spray bottle due to the risk of the contamination. The cryogen should be poured in the plastic/paper container to be discarded after each patient. The nozzles sizes for the spray bottle range from A through F, with F representing the smallest aperture. Different cryochambers, cryocones, and cryoprobes are used for more focused freezing when limited effect of the spray bottle is desired, without risk of damaging the sensitive surrounding skin. Bended extensions are attached to the spray nozzle to provide focused and precise application of the cryogen to cavities like the oral cavity, lips, ears, or nostrils. The variety of cryoprobes used for contact cryosurgery should be matched with the size of the treated lesions. Finally, Luer lock adapter serves for the attachment of the 16 or 18 G needle for intralesional cryosurgery mostly for keloids and some tumors. The last part of the equipment are tissue temperature monitors, obligatory with cryodestruction of malignant tumors, which work based on temperature change, electrical impedance, or ultrasound transmission. Finally, the invention of a new device – Cry-Ac Tracker (Fig. 114.2) – facilitated the controlled timely destruction of the target tissue by using the infrared monitoring method.

Fig. 114.2 Cry-Ac Tracker with infrared monitoring device

Techniques (Fig. 114.3)

The dose of liquid nitrogen and the choice of delivery method depend on the size, tissue type, and depth of the lesion. The area of the body on which the lesion is located and the required depth of freeze also should be considered. Additional patient factors to consider include the thickness of the epidermis and underlying structures, the water content of the skin, and local blood flow.

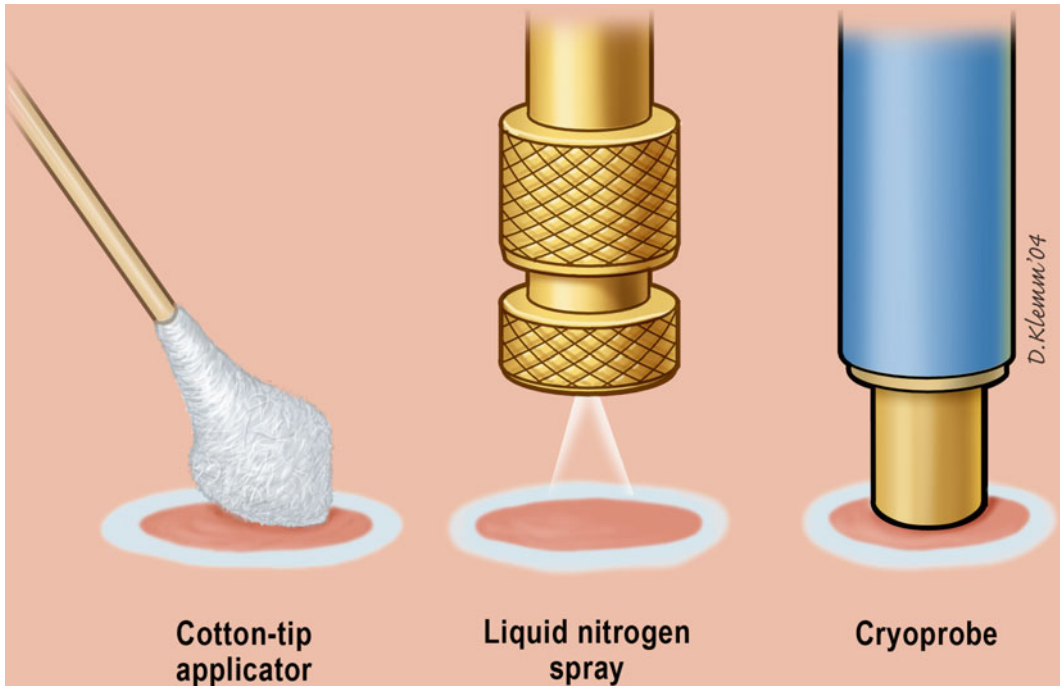

Fig. 114.3 Cryosurgery techniques (Printed with permission – Copyright David Klemm)

Liquid nitrogen spray methods for lesions of different sizes include the timed spot freeze or direct spray technique, the rotary or spiral pattern, and the paintbrush method, confined spray technique, and contact and intralesional cryosurgery (Fig. 114.4a–c). Each modality has different maximal freezing temperatures achieved in the treated tissue and should be used according to the desired depth of freeze (Table 114.3).

(a) *Timed Spot Freeze (Open Spray Technique)*. It may be the most appropriate method for physicians who are learning to perform cryosurgery. Use of this technique maximizes the ability to destroy a lesion with minimal morbidity. The freezing time is adjusted according to variables such as skin thickness, vascularity, tissue type, and lesion characteristics. Nozzle sizes B and C are suitable for the treatment of the most benign and malignant lesions; they are the apertures most frequently noted in case reports.

For the standard spot freeze technique, the nozzle of the spray gun is positioned 1–1.5 cm from the skin surface and aimed at the center of the target lesion. The spray gun trigger is depressed, and liquid nitrogen is sprayed until an ice field (or ice ball) encompasses the lesion and the desired margin. The designated ice field may need to be delineated in advance with a skin marker pen, because freezing may blur pretreatment lesion margins. The margin size depends primarily on the thickness of the lesion and whether the lesion is benign or malignant. Margins for most benign lesions are 1–2 mm beyond the visible pathologic border. Premalignant lesions need margins of 2–3 mm, while malignant lesions require margins of 5 mm of clinically normal skin to ensure adequate removal. These margin sizes allow enough depth of freeze to ensure temperatures of −50 °C to a depth of 4–5 mm. For benign/premalignant lesions freezing down to −25 °C is sufficient (Table 114.4). Once the ice field has filled the specified margin, the spray needs to be maintained (intermittently pressing/depressing the trigger) with the spray canister trigger pressure

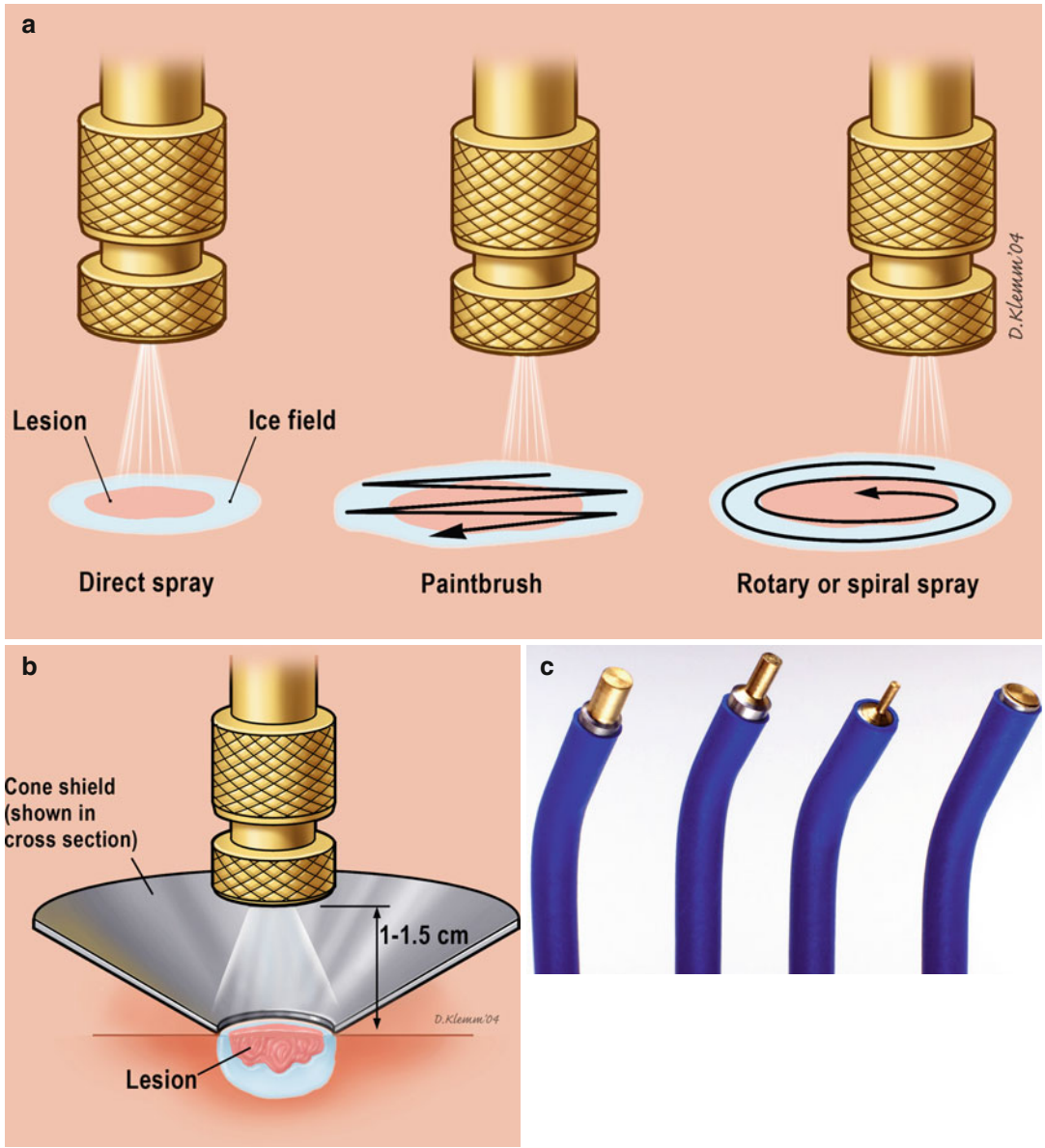

Fig. 114.4 (**a**) Spray patterns for larger lesions, (**b**) confined spray technique, (**c**) cryoprobes for contact cryosurgery (Printed with permission – Copyright David Klemm)

Table 114.3 Surface tissue temperatures attainable with various cryogens

Cryogen	Temperature (°C)
Carbon dioxide snow	−79
Nitrous oxide	−75
Liquid nitrogen Q-tip	−20
Liquid nitrogen spray	−180
Liquid nitrogen probe	−196

and, thus, the liquid nitrogen spray flow adjusted to keep the target field frozen for an adequate time. This time may vary from 5 to 30 s (60 s for malignant tumors) beyond the initial time for the formation of the ice field. If more than one freeze-thaw cycle is required for lesion destruction, complete thawing should be allowed before the next cycle. The

Table 114.4 General cryosurgical settings for skin tumors

Parameters	Benign	Malignant
Freezing speed	Moderate (≤100 °C) or rapid (≥100 °C)	Rapid (≥100 °C)
Thawing speed	Slow (10 °C/min) or spontaneous	Slow (10 °C/min) or spontaneous
Osmotic phenomena	Homogeneous and heterogeneous nucleation	Homogeneous nucleation
Probe temperature	−86 to −196 °C	−196 °C
Duration	30 s	60 s
Repetition of freeze-thaw cycles	No	Yes (twice)
Vascular reaction	Yes	Yes
Immunological reaction	Probable	Probable

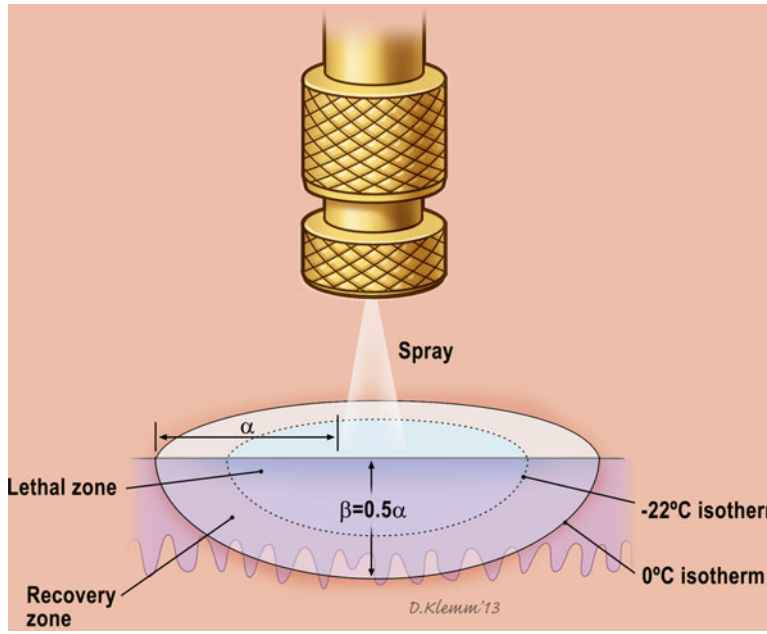

Fig. 114.5 Depth of freeze in open spray technique (Printed with permission – Brymill Corporation Inc.)

depth of freeze is approximately half of the lateral ice ball radius (Fig. 114.5). The thawing time is usually 2–3 min, i.e., 1.5 to two times longer than the freezing time. For lesions bigger than 2 cm in size, the open spray technique can be modified into the *rotary, spiral, or paintbrush pattern* to allow complete freezing.

(b) *Contact Cryosurgery*. Cryoprobes attached to liquid nitrogen spray gun can provide additional versatility especially when dealing with smaller and delicate lesions where deeper penetration is necessary (hemangiomas) or when surrounding skin is to be minimally affected like eyelid margins. The cryoprobes can vary in shape and size and are applied directly to the skin, ablating the lesions with contact exchange of the heat, and can be used with contact gel. The separate small hose is releasing liquid nitrogen from the side of the probe and should be kept away from the skin to avoid spillage of cryogen to nondesirable areas. Contact cryosurgery can penetrate up to 20 mm in depth and requires double freezing

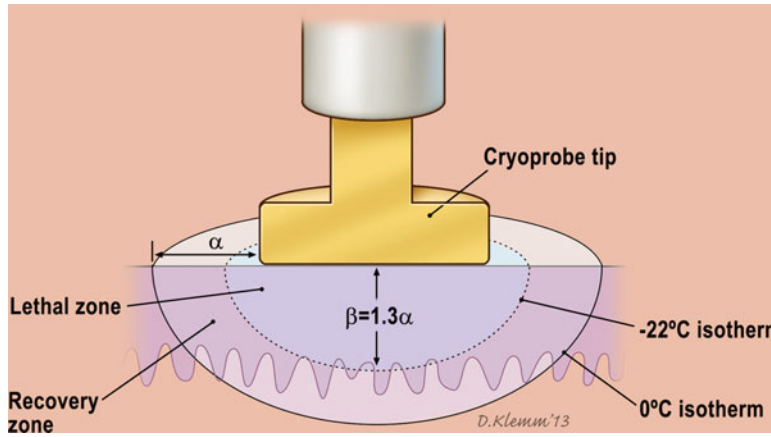

Fig. 114.6 Depth of freeze in contact cryosurgery (Printed with permission – Brymill Corporation Inc.)

times compared to spot spray freeze technique. The depth of freeze is approximately 1.3 times the radius of the ice ball (Fig. 114.6).

(c) *Intralesional Cryosurgery*. Needles for intralesional cryosurgery are applied to the nozzle using Luer lock adapter. A sprayed cryogen is then passed through the needle forming the ice cylinder. The distance of freeze can be estimated by monitoring the degree of extension of the whitish ice ball around the points of contact between the skin surface and the visible part of the needle. Depending of the size of the lesion, the needle can be reintroduced several times in order to provide more complete freezing. The main advantage of intralesional technique is the ability to freeze deeper than 20 mm, which is the maximal limit for spray and contact methods.

Clinical Applications

Most benign skin lesions can be treated successfully with any of several treatment modalities (excision, cryosurgery, electrodesiccation, and curettage). However, cosmesis, cost, and patient convenience may make one treatment modality more desirable than another. Patients should be informed about all treatment options and should be allowed to choose from the reasonable alternatives. Cryosurgery has advantages over the other modalities. Preparation time is short, and treatment requires no expensive supplies or injectable anesthesia. In addition, the risk of infection is low, wound care is minimal, and suture removal is not needed. Correct clinical diagnosis and lesion selection are as critical as the timing of the liquid nitrogen spray in producing a favorable outcome. Depending on the type of lesion, standard technique may need to be modified. Smaller flatter lesions require only 5–10 s of freezing and one cycle only. Larger thicker lesions may require longer duration of freeze up to 20 or even 30 s. Superficial keratin, especially in plantar warts, is a good insulator and should be removed by paring the lesion or application of keratolytics like salicylic acid in 2 weeks prior to cryosurgery. Before deciding about the length of freeze, one should always keep in mind the individual sensitivity of the different cell types to low temperature and adjust the duration of destruction (Table 114.5). Table 114.6 summarizes cryosurgery techniques for a variety of skin lesions.

Table 114.5 Sensitivity of different cell types to cryoinjury

Melanocytes	−4 to −7 °C
Sebaceous glands and hair follicles	−20 °C
Keratinocytes	−20 to −30 °C
Fibroblasts	−30 to −35 °C
Benign tumors	−20 to −25 °C
Malignant tumors	−50 to −60 °C

Table 114.6 Cryosurgery indications and techniques

Indications	Freeze time (seconds)	Number of freeze-thaw cycles	Margin (mm)	Typical treatment regimen	Technique
Benign lesions					
Acne	5–15	1	1	Once	Cryopeel
Angioma	10	1	<1	Once	P
Cutaneous horn	10–15	1	2	Once	OS
Dermatofibroma	20–60	1–2	2–3	Twice, bimonthly	P/OS
Hypertrophic scar	20	1	2	Once	OS/P
Ingrown toenail	30	1	2	Twice, bimonthly	OS
Keloid	30	1–3	2	Three times, bimonthly	OS/P
Myxoid cyst	20	1	<1	Once	OS/P
Molluscum contagiosum	5–10	1	<1	Twice, monthly	
Oral mucocele	10	1	<1	Once	P
Pyogenic granuloma	15	1	<1	Once	OS
Sebaceous hyperplasia	10–15	1	<1	Variable	P
Seborrheic keratosis	10–15	1–2	<1	Once	
Skin tags	5	1	1	Once	F/OS
Solar lentigo	5	1	<1	Once	OS
Warts	10–60	1–2	2–3	Three times, monthly	
Premalignant lesions					
Actinic keratosis	5–20	1	<1–2	Usually once	OS
Bowen disease	15–30	1–2	3	Three times, monthly	OS
Keratoacanthoma	30	2	5	Usually once	OS
Malignant lesions					
Basal cell carcinoma	60–90	2–3	5	Usually once	OS
Kaposi sarcoma	20–40	1–2	3	Three times, monthly	CP
Lentigo maligna	60	2	5	Usually once	OS
Squamous cell carcinoma	60–90	2–3	5	Usually once	OS

By convention, freeze time is given as the interval following visible white ice formation
OS open spray, *P* cryoprobe, *F* forceps

Malignant conditions (mostly superficial basal cell carcinoma) require 60 s of freeze, tissue temperature monitoring, and two freeze-thaw cycles (Table 114.7).

Complications, Side Effects, and Contraindications

Contraindications

The relatively few contraindications to cryosurgery generally are related to concomitant illnesses in which excess reactions to cold may occur or delayed healing may be anticipated (Table 114.8). Some relative contraindications may make alternative treatment modalities more suitable. Physicians often do not perform cryosurgery in the pretibial areas, especially in elderly patients, because of slow wound healing.

Complications and Side Effects

Common complications and side effects of cryosurgery are listed in Table 114.9. Skin discomfort, generally a burning sensation, occurs with cryosurgery, but intensity is variable. The most sensitive areas are the fingertips, ears, and temples. Freezing of lesions on the forehead or temple may produce headaches. Treatment in hair-bearing areas can result in permanent hair

Table 114.7 Features of squamous cell carcinoma and basal cell carcinoma amenable to cryosurgery

Depth <3 mm
Diameter <2 mm
Low-risk site (e.g., trunk, extremity, cheek, forehead, neck, scalp)
Nodular or superficial basal cell carcinoma subtype (not sclerosing)
Not fixed to deeper structures
Primary lesion (not recurrent)
Well-defined margin
Well-differentiated squamous cell carcinoma

Table 114.8 Contraindications to cryosurgery

Absolute contraindications	Relative contraindications (perform with caution)
Agammaglobulinemia	Anticoagulant use
Cold intolerance	Blistering disorders
Cold urticaria	Dark-skinned person
Cryofibrinogenemia (large areas)	Infants
Cryoglobulinemia (large areas)	Older persons
Immunosuppression	Sensory loss
Impaired vascular supply	Sun-damaged or irradiated skin
Multiple myeloma	Therapy overlying a bony prominence
Pyoderma gangrenosum	
Raynaud disease (digital cryotherapy most concerning)	
Unexplained blood dyscrasia	

Table 114.9 Complications of cryosurgery

Type	Adverse effect
Immediate	Bleeding, blistering, edema, nitrogen emphysema, pain, vascular headache, vasovagal syncope
Delayed	Bleeding, excessive granulation, infection, tendon rupture, ulceration
Temporary	Altered sensation, hyperpigmentation, hypertrophic scarring, milia, pyogenic granuloma
Permanent	Alopecia, atrophy, cartilage necrosis, hypopigmentation

loss. Hypopigmentation is common, especially with longer freeze times, but is less noticeable in light-skinned patients and improves within several months. Hypopigmentation is caused by the greater sensitivity of melanocytes to freezing, a situation that can be used to advantage in the treatment of dermatofibromas, which frequently have some mild overlying hyperpigmentation. Feathering of the freeze margin (lighter freeze area) often results in a better transition of pigmentary changes. Freezing for less than 30 s beyond initial freeze ball formation does not result in scarring because of the preservation of fibroblasts and the collagen network of the dermis, which allows migration of the cellular components in the healing process and rebuilds the normal integrity of the skin layers. Although rare and usually temporary, sensory nerve damage has been reported occasionally in large case series, which may sometimes take 12–18 months to resolve.

Conclusions

If performed properly, cryosurgery is a relatively safe and simple procedure with few contraindications and low complication rate (Table 114.10). It provides good to excellent cosmesis, short duration, low cost, and high healing rate in difficult areas. It is also suitable

Table 114.10 Advantages of cryosurgery vs. conventional surgical techniques

Anesthesia optional
Excellent cosmetic results
Low cost
Low risk of infection
Minimal wound care
No need for suture removal
No work or sport restriction
Portable to multiple treatment settings
Safe procedure
Short preparation time
Useful in pregnancy

for use with no general or local anesthesia in wide population of patients including older, nonoperable, or pregnant individuals.

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Dermoscopy of Nonmelanocytic Skin Tumors

115

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Key Points

- Dermoscopy is a widely accessible, inexpensive, and reliable noninvasive diagnostic tool that improves the accuracy of the clinical diagnosis of skin tumors.
- Most dermoscopic patterns correlate with specific histopathologic substrates. Accordingly, dermoscopy allows a better differentiation between specific subtypes of skin tumors.
- The common benign epithelial skin tumors, such as solar lentigo and actinic keratosis, typically display specific dermoscopic criteria, which allow their clinical recognition.
- The dermoscopic hallmark of all vascular tumors is a mixture of red-purple-blue at times black colors, which however present with different patterns.
- Adnexal tumors are generally considered as dermoscopic mimickers of basal cell carcinoma, but specific clues exist, facilitating the differential diagnosis.
- The sensitivity and specificity rate of dermoscopy in the diagnosis of basal cell carcinoma is reported to be 9 and 93 %, respectively.
- Dermoscopy reaches 98 % sensitivity and 95 % specificity in the diagnosis of actinic keratosis.
- Dermoscopy reaches 79 % sensitivity and 87 % specificity in the diagnosis of squamous cell carcinoma.

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General Principles

Dermoscopy has become an integrative part of the clinical examination of skin tumors, since most dermoscopic patterns correlate with specific histopathologic substrates. The dermoscopic patterns of several benign and malignant nonmelanocytic tumors have been described in the literature. Some dermoscopic criteria are considered specific for one diagnosis, while some others can be found in more than one entity. Overall, dermoscopy, by revealing morphologic structures

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_115, © Springer-Verlag Berlin Heidelberg 2015

invisible to the naked eye, allows a better differentiation between specific subtypes of skin neoplasms. The dermoscopic patterns of the most common benign and malignant nonmelanocytic tumors are described below.

Dermoscopy of Common Benign, Epithelial Skin Tumors

Solar Lentigo

Solar lentigo (SL, synonyms: actinic lentigo, senile lentigo) is commonly regarded as the initial presentation of seborrheic keratosis (SK), based on the frequent clinical and histopathologic association between these two entities.

SLs typically present as multiple, variably large (up to few cm), light to dark brown, irregularly outlined macules, on chronically sun-exposed body sites such as the face, dorsum of the hands, and extensor surface of the forearms. They are commonly seen in severely sun-damaged skin of elderly individuals, but may also appear at a younger age.

Dermoscopic Pattern

Although the clinical diagnosis of SL usually does not prompt diagnostic difficulties, differentiation from early lentigo maligna (LM), which also arises on sun-damaged skin, might occasionally be challenging. In such cases, the dermoscopic examination might aid the accurate diagnosis.

The dermoscopic features of SL are site-dependent, with extrafacial lesions displaying frequently densely arranged, roundish to oval brown circles, reminiscent of a delicate reticular pattern. Other features include curved parallel, brown lines (fingerprint-like structure) or a structureless brown pattern with a sharp convex-concave demarcation ("moth-eaten").

In contrast, facial SLs less frequently exhibit a structureless pattern or circles but are typified by a light to dark brown pseudonetwork pattern with sharp demarcation. The pseudonetwork pattern is caused by a structureless brown pigmentation, which is interrupted by numerous nonpigmented follicular openings. The recognition of SL is easier when the brown pseudonetwork is combined with parallel curved lines, brown elongated circles (fingerprint-like structures or fat fingers), and sharp demarcation (jelly sign or moth-eaten borders).

The dermoscopic discrimination from LM is facilitated by the characteristic patterns of SL as well as on the absence of gray structures (gray circles within the hair follicle, gray dots around the hair follicles or within the hair follicle, or gray-brown lines), which are, with only few exceptions (regressing SL), more frequently observed in LM.

Ink-Spot Lentigo

Ink-spot lentigo represents a heavily pigmented reticulated type of SL, which typically develops as a solitary, bizarre outlined, black macule on the shoulders of persons with a freckling phenotype and fair skin and with a history of severe sunburns.

In the surrounding skin, numerous additional brown freckles (solar freckles) are usually seen. Because of its irregular clinical shape and the strikingly black color, ink-spot lentigo is considered a simulator of melanoma in situ.

Dermoscopic Pattern

Ink-spot lentigo is typified by a unique dermoscopic pattern, consisting of dark brown to black and interrupted (broken up) pigment network with thick lines and wide meshes.

Mucosal Lentigo

Mucosal lentigines (also called mucosal macules or melanosis) of oral and genital mucosal membrane are benign, pigmented, nonmelanocytic macules. They may develop as solitary or multiple lesions with a tendency to confluence. Clinical differentiation between mucosal melanosis and mucosal melanoma may be troublesome, and histopathologic examination is often required to establish a definite diagnosis.

Labial lentigo of the lips commonly develops on the lower lip of fair-skinned individuals after sun exposure and appears as a small, round to oval, light brown to brown-gray macule. Importantly, the macule is strictly located to the mucosa and does not extend to the normal skin.

Genital melanosis can occur as a solitary, brown to brown-gray macule of variable size or as diffuse, multifocal, irregularly outlined, brownish-grayish confluent macules forming a speckled pattern.

Dermoscopic Pattern

The most characteristic findings of mucosal lentigines are variable shades of brown-gray color and parallel curved lines and roundish to oval circles or a structureless pattern.

Detection of blue-white, blue-gray, or white-red color in association with structureless areas, atypical pigment network, white network (syn: reticular depigmentation, inverse network), or irregular black dots and globules should always raise the suspicion of melanoma and warrant a biopsy and histopathologic examination.

A potential clue for the differential diagnosis of multifocal, genital melanosis from mucosal melanoma is based on the palpability of the lesion. While mucosal melanosis is always flat, multifocal melanoma can be regarded as advanced at time of presentation and therefore often reveals nodular, invasive areas with a dermoscopic blue-black coloration.

Seborrheic Keratosis

SK is a common, benign epithelial skin tumor, which develops commonly on the face and the trunk, but may involve any body site except the palms and soles. SKs appear as solitary or multiple, slightly raised to nodular, well-demarcated lesions with a keratotic, papillomatous, or smooth surface.

Lesions typically have a "stuck on" appearance. The color of SK varies from yellowish to opaque brown black or gray. A sharp demarcation, a dull and verrucous surface, and the prominent follicular orifices represent useful clinical signs that allow a straightforward diagnosis in most cases. At times, irritated SKs or peculiar histopathologic variants such as melanoacanthoma or clonal SK may cause diagnostic difficulties.

Dermoscopic Patterns (Definitions of Dermoscopic Criteria Are Shown in Table 115.1)

The most classical dermoscopic features of SK are multiple milia-like cysts, multiple comedo-like openings, a sharp demarcation of the border, and a brain-like pattern. In irritated SK, hairpin vessels and thick dotted vessels surrounded by a whitish halo are commonly seen. These vessels correspond to long capillary loops and can be seen in other keratinizing tumors such as squamous cell carcinoma, where they are located at the periphery of a keratotic structureless center.

Acanthotic Type

Among various histopathologic variants of SK, acanthotic, reticulated, and verrucous subtypes represent the majority of lesions, and each one of them displays a distinctive dermoscopic pattern, consisting of different combinations of the aforementioned criteria.

Acanthotic SK is the most frequent subtype and reveals upon dermoscopy multiple milia-like cysts and comedo-like openings. Its color varies from yellow to light brown to black gray. A brain-like appearance is very common in acanthotic SK, especially when located on the face. Hairpin vessels, exophytic papillary structures, and a peripheral delicate pigment network may also be seen. Fingerprinting, a sharp demarcation, and a moth-eaten border represent additional characteristics of initial SK developing from SL.

Reticulated Type

Reticulated SK usually presents as small (<6 mm) slightly raised, uniform colored, and sharply demarcated lesion. Dermoscopically, it exhibits a network structure, composed by densely aligned, brown round or oval circles or thick lines. Dermoscopic clues for differentiating the network structures of reticulated SK from the network of melanocytic tumors are based on the striking sharp

Table 115.1 Definition of dermoscopic criteria associated with seborrheic keratosis

Dermoscopic criterion	Description	Diagnostic significance
Milia-like cysts	Numerous, variously sized, white or yellowish, roundish structures	Acanthotic SK
Comedo-like openings	Brown-yellowish to brown-black, round to oval, sharply circumscribed keratotic plugs in the ostia of hair follicles	Acanthotic SK
Brain-like (cerebriform) pattern	Dark brown fissures between ridges typifying a brain-like appearance	Acanthotic SK
Network-like structures	A peculiar type of pigment network with thick, hyperpigmented lines that may end abruptly at the periphery and large grids with holes corresponding to keratin-filled structures	Reticulated SK
Fingerprint-like structures	A peculiar type of delicate pigment network consisting of curved, light brown, parallel lines	Reticulated SK
		SL
Hairpin vessels	Linear, looped vessels, usually regularly distributed and monomorphous, but sometimes elongated or twisted. Often surrounded by a whitish halo, they are typically seen in elevated or nodular area of the lesion while appearing as thick red dots in flat portions of the lesion	Irritated acanthotic SK
		Irritated keratotic SK
Sharp demarcation	Abrupt cutoff of pigmentation at the border of the lesion	Acanthotic SK
		Reticulated SK
		Keratotic SK
		SL
Moth-eaten borders	Sharp convex-concave demarcation in some parts of the lesion	Reticulated SK
		SL
Wobble pattern	The lesion follows the movement of the dermatoscope, but the static image does not change because the stiff, papular component cannot be dissociated from the surface of the lesion itself	Acanthotic SK
		Keratotic SK

Abbreviations: *SK* seborrheic keratosis, *SL* solar lentigo

demarcation of the network-like structure in SK, whereas the network of a melanocytic tumor often shows a fading towards the periphery.

Keratotic Type

Dermoscopy of SK of this type reveals only white to yellow horn masses which impede the visualization of underlying structures. As at times melanoma may reveal a similar pattern, histopathologic confirmation of solitary lesions with this pattern is generally recommended.

Lichen Planus-Like Keratosis

Lichen planus-like keratosis (LPLK) refers to an SL or an SK undergoing spontaneous regression. Clinically, LPLK presents as flat gray to gray-brown macule. The discrimination between LPLK and regressive LM is feasible only if areas of the preexisting benign lesion (SK or SL) are still preserved.

Dermoscopic Pattern

Dermoscopically, fully or nearly fully regressed LPLK is characterized by diffuse brownish-gray granules, which may coalesce to form globules, streaks, or even structures similar to rhomboids. Since LM may exhibit the same features, a lesion dermoscopically characterized by signs of evident regression (i.e., localized or diffuse gray granules) should be always biopsied, unless criteria of a preexisting SL or SK are clearly evident.

Dermoscopy of Vascular Tumors

Benign Vascular Tumors

Among a range of benign vascular tumors, herein only the most common ones, namely, hemangioma, angiokeratoma, pyogenic granuloma, Kaposi sarcoma, and angiosarcoma, will be discussed.

Dermoscopic Pattern

The dermoscopic hallmark of all vascular tumors is a mixture of red-purple-blue at times black colors, which however present with different patterns among the above referred entities.

Hemangioma

The term hemangioma in the daily practice is commonly used to refer to cherry (also called) senile angiomas. Their dermoscopic hallmark is red to purple lacunas (globules), which are well-circumscribed, round to oval, structures, histopathologically corresponding to dilated, blood-filled vessels in the papillary dermis. A white veil or white line is frequently seen among the lacunas. Cherry angiomas typically exhibit the above described lacunar pattern, which allows a safe dermoscopic diagnosis, even when the lesion is clinically equivocal.

Angiokeratoma

Angiokeratoma dermoscopically displays more commonly red-purple, purple-blue lacunas or structureless areas and sharply circumscribed black lacunas (globules), frequently associated with whitish-yellowish keratotic areas. The black globules thereby correspond to congealed blood in the stratum corneum of thrombotic vascular lacunas.

Pyogenic Granuloma

In contrast to hemangioma or angiokeratoma, pyogenic granuloma rarely shows black or purple-blue globules but is characterized by bright red, structureless areas, which are commonly associated with white intersections (white lines) and a whitish peripheral rim (collarette). Because thick, amelanotic melanoma may reveal similar features, the diagnosis of pyogenic granuloma should be always confirmed by histopathologic examination.

Subcorneal and Subungual Hemorrhage

Subcorneal hemorrhage (also called black heel due to the striking black color of congealed hemoglobin in the stratum corneum) is a result of trauma, typically developing on the heels of young athletes and less frequently on the palms. Similarly, subungual hemorrhage occurs following a nail trauma.

While patients usually recall the painful trauma of the nail, patients with subcorneal hemorrhage after sportive activity are usually highly concerned and seek urgent consultation.

Clinically, subcorneal and subungual hemorrhages appear as asymptomatic, sharply circumscribed, homogeneous, red-black macules.

Dermoscopic Pattern

Dermoscopy typically reveals a sharply demarcated dark red to black structureless pigmentation. Adjacent to the main body of pigment, which is commonly sharply demarcated, satellite red-black dots or globules are often present (corresponding to blood spots), facilitating the accurate diagnosis.

An important clue for the differential diagnosis of subungual hemorrhage from melanoma is based on the fact that subungual hemorrhage usually does not extend from the proximal to the distal nail plate but presents as partial nail pigmentation with a roundish border at the proximal end and streaks or lines along with blood spots at the distal end.

Subcorneal hemorrhage may occasionally exhibit a parallel ridge pattern, which is an important criterion in the early diagnosis of acral melanoma. In this scenario, a sharp demarcation of the lesion and presence of blood spots may be important clues for the correct diagnosis. Moreover, the positive scratch test (i.e., removal of pigmentation by scratching the stratum corneum) with a needle or scalpel aids the correct diagnosis of subcorneal hemorrhage.

Malignant Vascular Tumors

Cutaneous Angiosarcoma

Cutaneous angiosarcoma is an aggressive neoplasm that is generally divided into three clinical variants: angiosarcoma of the head and scalp (AS), lymphedema associated angiosarcoma (LAS) arising typically in the context of Stewart-Treves syndrome, and radiation-induced angiosarcoma (RIA) arising in previously irradiated skin areas. The classic AS is characterized by a tendency to metastasize to regional lymph nodes and lungs and is associated to a 5-year survival rate of 12–33 %.

Clinically, early AS develops as ill-defined, violaceous to bluish areas with an indurated border. At more advanced stages, the lesions become elevated or nodular and occasionally ulcerated. Extensive local growth is common, and margins are difficult to define surgically. In approximately half of the patients, the disease manifests with multiple separate foci. RIA and LAS tend to present as reddish to purple plaques with ill-defined borders.

Dermoscopic Pattern

On dermoscopy, the classic AS exhibits the typical colors of vascular tumors, namely red, purple, and blue. If nodules are present, white lines, corresponding histopathologically to fibrous septa between enlarged neoplastic vascular spaces, can be detected. In contrast to spontaneous AS, RIA appears to exhibit a more homogeneous pinkish-white pattern, which may be related to the high amount of fibrosis usually associated with these lesions.

Kaposi Sarcoma

Kaposi sarcoma (KS) can be categorized into four clinical and epidemiological variants: classic, endemic, epidemic, and iatrogenic. Classic KS shows a predilection for elderly men living in Eastern Europe and the Mediterranean. The early lesions of classic KS appear most commonly on the toes or soles as reddish, violaceous, or bluish-black macules and patches that spread and coalesce to form nodules or plaques. The course is slowly progressive and may lead to great enlargement of the lower extremities as a result of lymphedema.

Dermoscopic Pattern

Dermoscopically, Kaposi sarcoma usually lacks specific structures but is characterized by structureless areas of confluent red, purple, blue, yellow, and green color. This pattern has been also called "rainbow pattern."

Dermoscopy of Tumors of the Fibrous Tissue

Dermatofibroma

Dermatofibroma (DF) is a very common benign skin tumor which is considered to represent a reactive process to various causes, such as injuries, insect bites, or ruptured follicles. It most often develops on the lower legs, but may appear anywhere on the body. Clinically, DF is a firm plaque or nodule with a diameter ranging from 0.5 mm to 1 cm and a color varying from light brown to dark brown, purple, red, or yellow. A dimple-like depression following lateral compression represents a useful clinical sign for the recognition of DF. Differential diagnosis comprises a wide spectrum of benign and malignant tumors, including dermatofibrosarcoma protuberans.

Dermoscopic Pattern

The dermoscopic hallmark of DF is a sharply demarcated central white (scar-like) patch, surrounded by a delicate, regular, usually light brown pigment network. Sometimes within the central white patch several, small, roundish to oval globules of light brown coloration may be seen. A white network has also been described to occur within the central white patch, especially in large DFs. A reddish halo around the lesion may also be found, possibly reflecting external injury. Vascular structures can be found in approximately half of DFs, with erythema and dotted vessels representing the most common vascular dermoscopic criteria. In total, ten different global dermoscopic patterns have been described to characterize DF.

Atypical Fibroxanthoma and Malignant Fibrous Histiocytoma

Atypical fibroxanthoma (AFX) and malignant fibrous histiocytoma (MFH) are related tumors, sharing similar histopathologic characteristics, but differ significantly concerning their prognosis. The former, despite of its tendency to recur after incomplete excision, has an excellent prognosis, whereas MFH possesses a considerable metastatic potential, being associated with an overall survival rate of 50 %. AFX occurs mainly on the sun-exposed parts of elderly individuals. Clinically, it manifests as a rapidly enlarging, reddish, dome-shaped nodule, often with an eroded or crusted surface. MFH develops as an enlarging subcutaneous nodule that may acquire significant size and ulcerate.

Dermoscopic Pattern

Dermoscopically, AFX and MFH display reddish and whitish areas in combination with a polymorphous vascular pattern, consisting of various combinations of linear, dotted, hairpin, and highly tortuous vessels, irregularly distributed over the surface of the lesion. Ulceration, crusting, and keratin masses may also be detected. Although the findings of AFX and MFH cannot be regarded as specific, the detection of a polymorphous vascular pattern should raise the suspicion of a malignant tumor, warranting complete surgical excision.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a relatively uncommon soft tissue neoplasm, characterized by a low-to-intermediate malignant potential, characterized by a locally aggressive biologic behavior and a high recurrence rate. Clinically, it initially presents as one or multiple erythematous, firm nodules or plaques that may suppurate or ulcerate. The primary lesions gradually enlarge and become confluent, forming characteristic bulky, protuberant neoplastic masses.

Dermoscopic Pattern

Dermoscopy might facilitate the clinical recognition of early lesions, by revealing a reddish background color in conjunction with fine linear vessels. A delicate pigment network has also been described in DFSP, but it lacks the characteristic peripheral arrangement observed in DF (Fig. 115.1).

Dermoscopy of Adnexal Tumors

Adnexal tumors are classified according to their differentiation as follicular, sebaceous, eccrine, and apocrine. Their natural course is generally favorable, although for several "benign" adnexal tumors, a "malignant" counterpart also has been described. Adnexal carcinomas are associated with a poor prognosis, which is, at least partially, related to their delayed recognition.

Sebaceous Tumors

Although consistent criteria for the diagnosis and nomenclature of sebaceous tumors are lacking, they are traditionally classified into benign sebaceous hyperplasia, sebaceous adenoma, sebaceoma (sebaceous epithelioma), and sebaceous carcinoma. Apart from sebaceous cysts and sebaceous hyperplasia which are common entities, sebaceous tumors are generally rare and typically occur in the context of Muir-Torre syndrome.

Dermoscopic Patterns

Sebaceous hyperplasia is dermoscopically typified by a whitish umbilicated, polylobular or structureless center, surrounded by elongated, scarcely branching vessels (crown vessels). A similar pattern consisting of central whitish/yellowish structures and crown vessels characterizes sebaceous cysts.

Two main dermoscopic patterns of sebaceous adenoma and sebaceoma have been described: first, tumors with a central crater, dermoscopically characterized by crown vessels surrounding an opaque structureless ovoid white-yellow

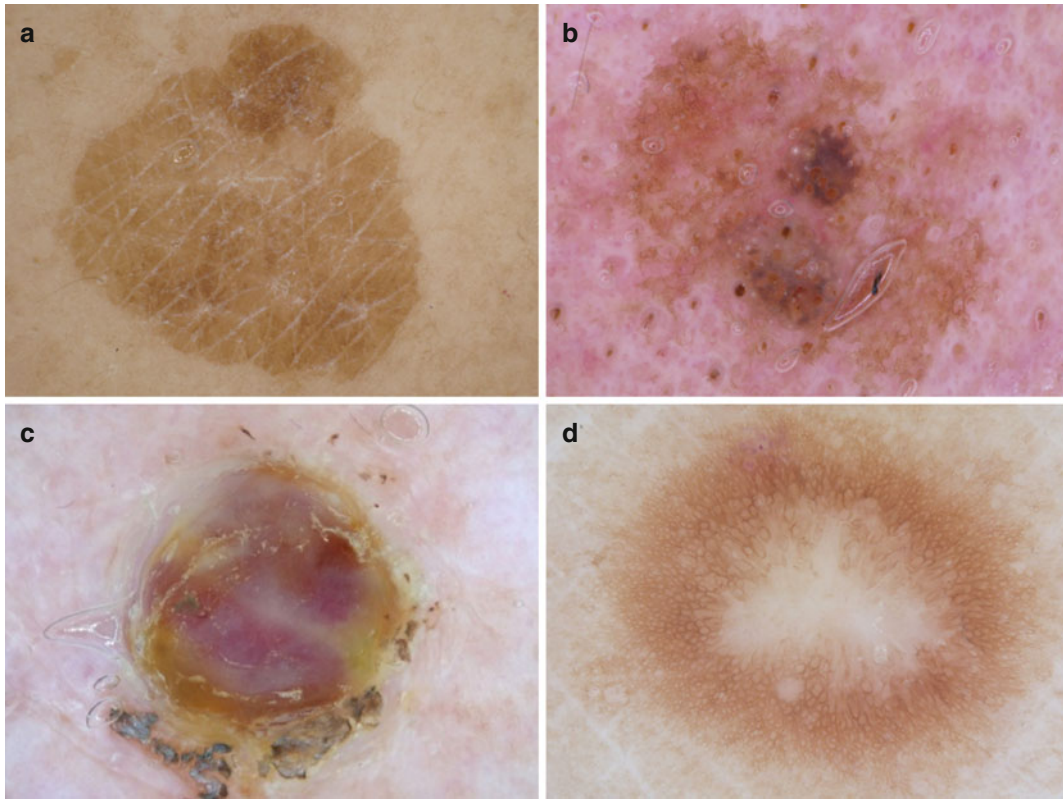

Fig. 115.1 (**a**) A solar lentigo dermoscopically typified by a structureless brown pigmentation and a sharply demarcated border. (**b**) Multiple milia-like cysts, comedo-like openings, and fingerprint-like structures are the dermoscopic hallmarks of seborrheic keratosis. (**c**) The "rainbow pattern" of Kaposi sarcoma, consisting of areas of confluent red, purple, blue, yellow, and green color. (**d**) The dermoscopic hallmark of dermatofibroma is a sharply demarcated central white (scar-like) patch, surrounded by a delicate, regular, light brown pigment network

center, which is at times covered by blood crusts, and, second, tumors without a central crater, which reveal branching but unfocused arborizing vessels over a white to yellow background and few loosely arranged yellow comedo-like globules.

Tumors of the Hair Follicle

Dermoscopic Patterns

In general, the dermoscopic pattern of follicular tumors displays overlapping features with basal cell carcinoma (BCC), namely, linear branching vessels and blue-gray dots or globules. The common presence of "white structures" has been suggested as a dermoscopic clue, suggestive of the diagnosis of a follicular tumor. Specific dermoscopic criteria are associated with some tumors, such as the unique ivory-white background color that typifies desmoplastic trichoepithelioma. Pilomatrixoma or calcifying epithelioma of Malherbe represents the commonest follicular tumor, usually affecting children and adolescents. Irregular white and/or yellow structures, white streaks, reddish homogenous areas, and linear vessels represent the most frequent dermoscopic criteria of pilomatrixoma, while ulceration and blue-gray areas are common additional findings. The white structures, histopathologically corresponding to calcification or keratin masses, represent the most useful single criterion for differentiating pilomatrixoma from melanoma and BCC.

Sweat Gland Tumors

Dermoscopic Patterns

Eccrine poroma is the most extensively studied sweat gland tumor, concerning its dermoscopic pattern. It is characterized by a high degree of dermoscopic variability, which is possibly explained by the existence of distinct histopathologic subtypes, depending on the location of the basaloid aggregations in relation to the epidermis.

Eccrine poroma may be pigmented or nonpigmented. In the former case, it may show overlapping dermoscopic features with BCC, such as blue-gray globules and arborizing vessels. Nonpigmented variants are composed by a polymorphous vascular pattern of coiled, hairpin, or linear vessels and represent important simulators of amelanotic melanoma and vice versa.

Mucinous carcinoma is characterized by eccrine sweat gland differentiation and represents a low-grade malignant tumor with a potential of local recurrence. Dermoscopy of mucinous carcinoma has been reported to mirror its peculiar histopathology, revealing a whitish network and light brown globules, which histopathologically correspond to fibrous septum and mucinous deposition, respectively.

Dermoscopy of Nonmelanoma Skin Cancer

The term nonmelanoma skin cancer (NMSC) encompasses basically all cutaneous malignancies that are not melanoma. However, it is mainly used to define BCC and SCC. With some exceptions, most BCC and SCC will not spread to other body sites, but may cause, if left untreated, significant morbidity including functional and cosmetic disfigurement. Early diagnosis and adequate treatment represent therefore key strategies in reducing BCC- and SCC-related morbidity and costs. Within the spectrum of NMSC, we also include Merkel cell carcinoma (MCC), which is a less common, but highly aggressive skin neoplasm, characterized by a rapidly increasing incidence.

Basal Cell Carcinoma

BCC accounts for approximately 80 % of all skin cancers, and its incidence has doubled over the past 25 years. Although BCC is observed in people of all races and skin types, dark-skinned individuals are rarely affected, and it is most often found in light-skinned individuals, particularly among those with a very fair skin color and red or blond hair. There are several histopathologic subtypes of BCC, which differ also with respect to their dermoscopic patterns.

Dermoscopic Patterns (Definitions of Dermoscopic Criteria Are Shown in Table 115.2)

The reported diagnostic accuracy of dermoscopy to recognize BCC ranges from 95 % to 99 %. The hallmark of nodular-cystic basal cell carcinoma is focused, bright red, and branching arborizing vessels. Although also sclerodermiform BCC reveals branching vessels, they are usually finer and more scattered and show fewer branches compared to the classic vessels of nodular BCC. In addition, the underlying fibrosis of sclerodermiform BCC results in a dermoscopically whitish background, whereas dermoscopy of nodular BCC typically reveals a translucent pinkish tumor. The most classical presentation of superficial BCC is that of a red, translucent, or opaque structureless plaque with multiple small erosions which are at times associated with short focused "microarborizing" fine telangiectasias with relatively few ramifications. Dermoscopy of pigmented nodular and superficial BCCs reveals different pigmentation patterns. Pigmented nodular BCC exhibits loosely arranged blue-gray globules that differ in size and number. These features are typically combined with arborizing vessels.

Instead pigmented superficial BCC tends to display translucent light brown to grayish finger-like projects (leaflike areas) which are typically located at the border of a nonpigmented center. Other features that are seen in pigmented superficial BCC are concentric structures composed by oval areas with a darker center and spoke wheel

Table 115.2 Definition of dermoscopic criteria associated with different subtypes of BCC

Dermoscopic criterion	Description	Diagnostic significance
"Classical" arborizing vessels	Stem vessels of large diameter branching irregularly into finest terminal capillaries. The vessels' color is bright red, being perfectly in focus in the images due to their location on the surface of the tumor (just below the epidermis)	Nodular-cystic BCC
Fine arborizing vessels	Scattered, fine, focused, elongated telangiectasias with fewer ramifications compared to the classic, thick arborizing telangiectasias	Sclerodermiform BCC Infiltrating BCC Nevoid BCC
Short arborizing vessels	Short, focused telangiectasias with very few branches. In FeP they are often associated with dotted and glomerular vessels	Superficial BCC Sclerodermiform BCC FeP
Large blue-gray ovoid nests	Well-circumscribed, confluent or near confluent pigmented ovoid or elongated areas, larger than globules and not intimately connected to pigmented tumor body	Nodular-cystic BCC
Multiple blue-gray dots and globules	Numerous, loosely arranged round to oval well-circumscribed structures, which are smaller than the large gray blue ovoid nests	Nodular-cystic BCC Nevoid BCC FeP
Focused dots	Loosely arranged well-defined small gray dots which appear sharply in focus	Nevoid BCC Infiltrating BCC
Concentric structures	Irregularly shaped globular-like structures with different colors (blue, gray, brown, black) and darker central area; they represent variations of the leaflike areas	Superficial BCC
Spoke wheel areas	Well-circumscribed radial projections, usually tan but sometimes blue or gray, meeting at often darker (dark brown, black, or blue) central axis	Superficial BCC
Leaflike areas	Translucent brown to gray/blue peripheral bulbous extensions that never arise from pigmented network and from adjacent confluent pigmented areas	Superficial BCC
Ulceration	Large structureless areas of red to black-red color	Nodular-cystic BCC
Small erosions	Small brown-red to brown-yellow crusts	Superficial BCC
Pink-white areas	Areas of structureless pink to white color	Superficial BCC FeP
Short white streaks (chrysalis)	Orthogonal short and thick crossing lines that are seen only by polarized dermoscopy	Superficial BCC FeP

Abbreviations: *BCC* basal cell carcinoma, *FeP* fibroepithelioma of Pinkus

areas (central darker globule surrounded by lighter, peripheral fingerlike projections).

Other variants of BCC including FeP and nevoid BCC may mimic a range of benign skin tumors such as dermal nevus, skin tag, or seborrheic keratosis, which are not routinely excised. As it became a rule to examine almost all skin lesions by dermoscopy irrespective whether they look clinically benign or malignant, these rare subtypes of BCC can be however easily identified by dermoscopy. This is because they reveal classical BCC-specific vascular or pigmented patterns. Finally, in patients with Gorlin–Goltz syndrome, dermoscopy allows the rapid identification of palmar pits by disclosing dotted vessels (Fig. 115.2).

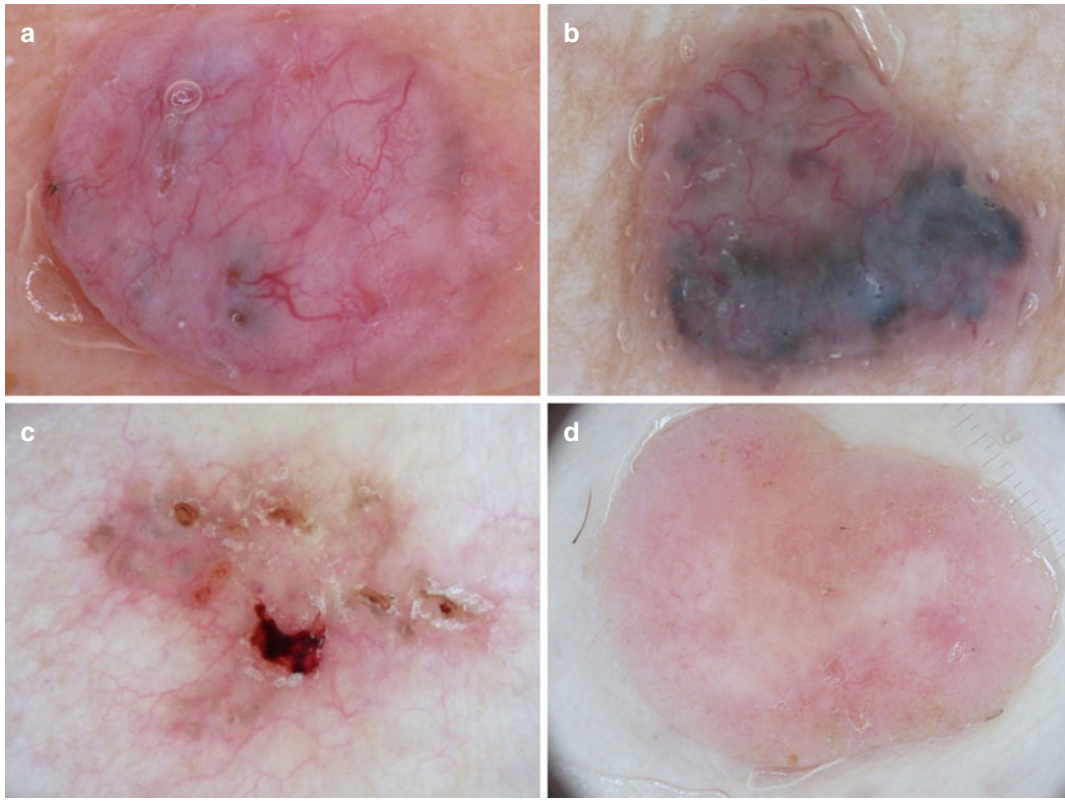

Fig. 115.2 (**a**, **b**) The dermoscopic prototype of nodular BCC, characterized by prominent, focused arborizing vessels and blue-gray ovoid nests. (**c**) A superficial BCC exhibiting short fine superficial telangiectasias, multiple small erosions, ulceration, and small foci of pigmentation. (**d**) A FeP dermoscopically displaying a white-pinkish background color with fine arborizing vessels in the center and dotted vessels at the periphery

Keratinocyte Skin Cancer

The term keratinocyte skin cancer refers to actinic keratosis (AK), intraepidermal carcinoma (IEC), and invasive squamous cell carcinoma (SCC).

Actinic Keratosis

Actinic keratoses (AKs) are the most common neoplasms within the continuum of keratinocyte skin cancer. They are nowadays defined as the earliest form of squamous cell carcinoma. AKs rarely develop as single lesion; effectively multiple lesions affecting an entire field of chronically actinic damaged skin are commonly present. This has lead to the concept of "field cancerization," which refers to the presence of genetically altered cell clones in normal appearing skin contiguous to fields of neoplastic cells, which have the potential of clonal expansion and thus give rise to locally recurrent skin cancer.

In 2007, a clinical classification for grading AK (grade 1, 2, and 3) was developed; grade 1 describes slightly palpable AK (better felt than seen), grade 2 shows moderately thick AK (easily felt and seen), and grade 3 is very thick, hyperkeratotic, and/or obvious.

Dermoscopic Patterns (Definitions of Dermoscopic Criteria Are Shown in Table 115.3)

The three different clinical grades of AK correspond dermoscopically to three different patterns. Grade I AKs are dermoscopically typified by red pseudonetwork pattern and discrete white

scales; grade II corresponds to an erythematous background intermingled by white to yellow, keratotic and enlarged follicular openings (these features are reminiscent of the surface of a strawberry; therefore, this pattern has been termed strawberry pattern). Grade III AK exhibits either enlarged follicular openings filled with keratotic plugs over a scaly and white-yellow appearing background or marked hyperkeratosis seen as white-yellow structureless areas. The diagnostic sensitivity and specificity of dermoscopy in the diagnosis of AK have been reported to reach 98 % and 95 %, respectively.

Intraepidermal Carcinoma and Bowen's Disease

IEC and Bowen's disease (BD) refer to an SCC in situ (SSCIS) with full-epidermal thickness dysplasia that has the potential for significant lateral spread before invasion. IEC and BD are often named synonymously to describe SSCIS. Clinically, lesions may be solitary or multiple and appear as slowly enlarging, erythematous, well-demarcated scaly patch or plaque.

Dermoscopic Patterns (Definitions of Dermoscopic Criteria Are Shown in Table 115.3)

Dermoscopically, BD is typified by the presence of dotted and/or glomerular vessels, white to yellowish surface scales, and a red-yellowish background color. Glomerular vessels represent a variation of dotted vessels but are larger in size and characterized by tortuous capillaries. Both dotted and glomerular vessels often appear within the same lesion and are distributed in small, densely packed clusters or groups or as lines at the periphery.

In cases of pigmented BD, in addition to the above-described criteria, small brown/black globules arranged either in a patchy distribution or in peripheral lines are seen. Dermoscopy was also shown to be useful for follow-up of a case of pigmented BD treated with laser ablation. Disappearance of disease-specific dermoscopic criteria was shown to predict a histopathologic clearance of the disease.

Squamous Cell Carcinoma

Primary cutaneous SCC is a malignant tumor that may arise from the keratinizing cells of the epidermis or its appendages. It is locally invasive and has the potential to metastasize to the regional lymph nodes and to other organs of the body.

SCC is the second most common skin cancer after basal cell carcinoma and causes the majority of deaths among the nonmelanoma skin malignancies. When detected and treated early, (less aggressive) SCC has a 95 % cure rate. However, if neglected, SCC may cause local tissue destruction and may metastasize. In the latter occasion, prognosis is extremely poor. Clinically, SCC usually presents as an indurated hyperkeratotic nodule with or without ulceration, or it may manifest as an ulcer without evidence of keratinization. Since SCC commonly develops on the background of AK, presence of the latter on the surrounding or neighboring skin may be clinically evident.

Dermoscopic Pattern (Definitions of Dermoscopic Criteria Are Shown in Table 115.3)

Dermoscopically, SCC is characterized by targetoid-appearing follicular openings (white circles) over a structureless white background. Additional features that are commonly seen are amorphous masses of white-yellow keratin (often located in the center) and polymorphic vessels consisting of peripheral hairpin, dotted/glomerular, and/or linear-irregular vessels.

This variability of vascular structures, along with more recently described criteria related to keratinization, may be useful to discriminate invasive SCC from in situ variants (AK and BD). In detail, according to a recently proposed model, progression from AK into invasive SCC is characterized by dermoscopically evident increase in vascularization and keratinization structures. The former is reflected by the development of initially dotted/glomerular vessels and latter, hairpin and linear/irregular vessels. Instead, keratinization is characterized by the early appearance of diffuse yellow-whitish opaque scales, followed by the development of white structureless areas or a central mass of keratin, associated with ulceration.

Table 115.3 Definition of dermoscopic criteria associated with actinic keratosis, intraepidermal carcinoma, and invasive squamous cell carcinoma

Dermoscopic criterion	Description	Diagnostic significance
Erythema	Structureless pale red areas without any recognizable areas of hypopigmentation or morphology	AK I
Red pseudonetwork	Structureless red areas which, intermingled with small roundish white areas, resemble a network structure; the small white areas correspond to the follicular openings of the skin	AK I
Strawberry pattern	Structureless red areas which, intermingled with evident, targetoid inner yellow and outer white roundish structures, resemble the surface of a strawberry; the targetoid areas correspond to keratin-filled follicular openings	AKII
Red starburst	Radial-arranged structureless red lines or hairpin vessels that surround a yellow to white structureless scaly center and which resemble overall a starburst appearance	AK II IEC
Dotted vessels	Tiny red dots densely aligned next to each other	IEC
Glomerular vessels	Variation on the theme of dotted vessels; they are larger than dotted vessels, have a convoluted morphology, and are often distributed in clusters	
Hairpin vessels	Vascular loops sometimes twisted and bending, usually surrounded by a whitish halo when seen in keratinizing tumors	SCC
Linear-irregular vessels	Linear or slightly curved, irregularly shaped, sized, and distributed red structures	SCC
Targetoid hair follicles	Variably large roundish structures composed of a yellow to light brown structureless center and a white outer structureless rim; this pattern corresponds to keratotic plugs within the follicular openings of the skin	AK II SCC
Rosettes	Four closely aggregated white, small dots in correspondence to the follicular opening and resembling a 4-leaved clover; if one imagines connecting the four dots with a line, a geometrical figure of a rhombus can be formed	AKI I–II
White structureless areas	White structureless areas in the absence of any structure; they may cover large areas of the tumor and may be associated with large targetoid hair follicles	SCC
Yellow to light brown opaque scales	Yellow to light brown opaque structureless areas with a scaly or keratotic aspect that do not cover large areas of the tumors surface	IEC
Erosions	Small and irregularly distributed orange to red to red-brown structureless areas; they correspond to superficial hemorrhages and are usually associated with yellow opaque structures	IEC SCC

In addition, keratin masses and white circles surrounding follicles have been recently proposed to specifically predict the diagnosis of SCC or KA among nonpigmented tumors.

Similarly, whitish background and keratin have been suggested to discriminate invasive SCC from amelanotic melanoma, which commonly exhibits a polymorphic vascular pattern associated with a pinkish background hue. Taken all the above into consideration, white structures and keratin represent valuable dermoscopic clues for diagnosis of invasive SCC.

It should be noted that well-differentiated SCC often presents as a rapidly growing nodule, which dermoscopically exhibits structureless white areas, central masses of keratin, and elongated

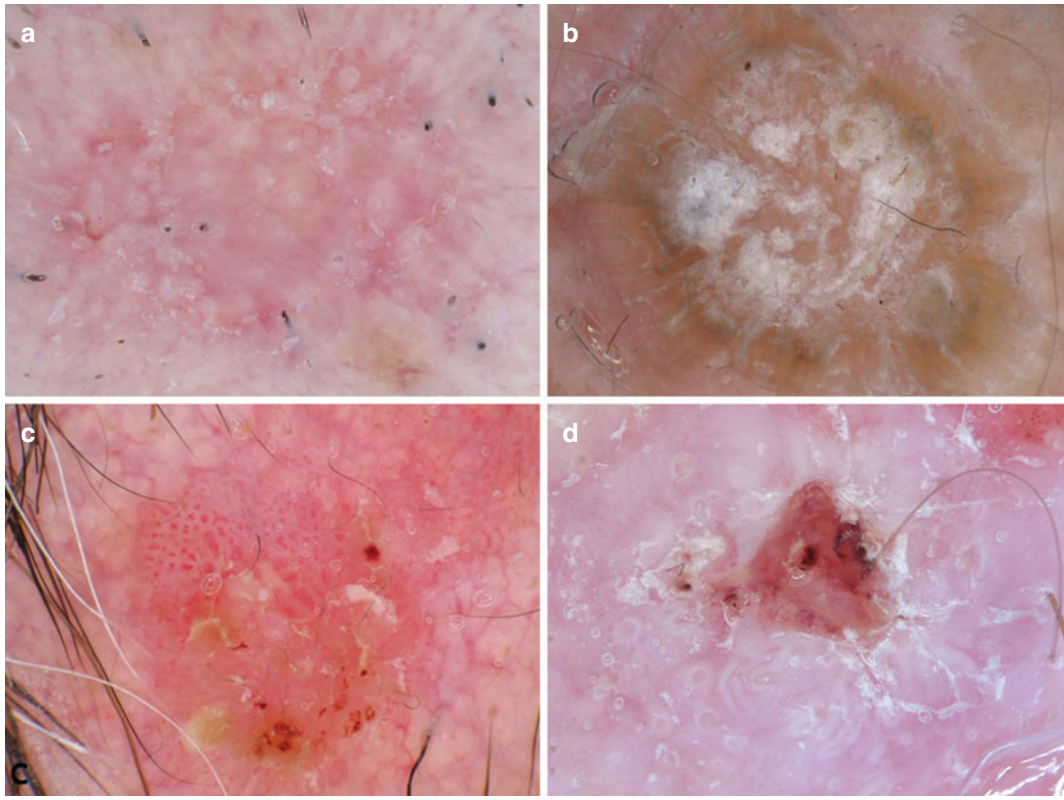

Fig. 115.3 (**a**) Grade I actinic keratosis is dermoscopically typified by the "strawberry pattern," consisting of a reddish background interrupted by whitish follicular openings. (**b**) A grade III actinic keratosis exhibiting marked hyperkeratosis seen as white-yellow structureless areas. A few dilated follicular openings filled with keratin plugs are visible. (**c**) Bowen's disease is dermoscopically characterized by glomerular vessels and white to yellowish surface scales. (**d**) A typical example of SCC, exhibiting white perifollicular circles, whitish structureless areas, and a large ulceration

peripheral vessels that remind to the arborizing vessels of BCC. Instead, poorly differentiated SCC lack signs of keratinization both dermoscopically and histopathologically and presents often as ulcerated plaque (endophytic growth) showing only polymorphous vessels (Fig. 115.3).

Merkel Cell Carcinoma

MCC is a very aggressive neoplasm, associated with a high risk of locoregional and distant spread and poor survival. Clinically, MCC most commonly develops as a persistent, asymptomatic, red/pink nodule that rapidly increases in size over a period of weeks to months. The most common sites of presentation are the head/neck region and extremities, followed by trunk and oral and genital mucosa. Because of its unspecific clinical presentation, the differential diagnostic spectrum of MCC is broad. Diagnosis is often delayed, since more than half of MCCs are thought to be benign at the time of biopsy.

Dermoscopic Pattern

Dermoscopy of MCC typically reveals a milky red background and a polymorphous vascular pattern, comprising dotted, arborizing, linear–irregular and glomerular vessels. This dermoscopic pattern cannot be considered as specific, since similar findings characterize amelanotic melanoma and other malignant tumors. However, dermoscopy may enhance the discrimination of MCC from benign tumors by

revealing features predictive of malignancy. Specifically, milky red areas, which represent the commonest criterion of MCC, are very rarely present in benign lesions (with the exception of pyogenic granuloma), whereas they are frequently detected in AM. Additionally, the synchronous presence of more than one morphologic type of vessels (forming the so-called polymorphous vascular pattern) is also suggestive of a malignant tumor, such as AM or squamous cell carcinoma (SCC). Effectively, detection of one or both of the above criteria should warrant complete surgical excision.

Future Perspectives

Up to date, much research has concentrated on the identification of criteria that aid the clinical diagnosis of skin, whereas only few well-designed and prospective studies focused on the impact of dermoscopy in the management. However, there is an increasing trend towards conducting such studies, and it can be expected that more evidence on the real value of dermoscopy in the treatment decision process and in the follow-up will be available in the next few years.

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Dermoscopy of Pigmented Skin Lesions

116

Silvija Duma

Key Points

- Dermoscopy (epiluminescence microscopy) is a non-invasive diagnostic method. Apart from dermoscopy, digital dermoscopy and videodermoscopy are used to monitor the patients, as well as teledermoscopy, which provides new opportunities in this field.
- The first step in dermoscopy is determining melanocytic or non-melanocytic lesions, while the second one requires the use of some of the dermoscopic algorithms (pattern analysis, ABCD, 7-point checklist, Menzies analysis) for further categorization of the lesions into benign and malignant.
- The melanocytic as well as the non-melanocytic lesions present their own specific dermoscopic structures.

General Principles

Dermoscopy (also known as epiluminescence microscopy, dermatoscopy and amplified surface microscopy) is an in vivo non-invasive method for observation of pigmented skin lesions.

Dermoscopy requires optical magnification and liquid immersion. With dermoscopy, we can visualize the structures which are not visible to the naked eye, like structures in the epidermis, dermoepidermal junction and superficial and reticular dermis.

These morphological features (dermoscopic structures) have specific histopathological correlation. By understanding the histopathological equivalents of such structures, the investigators are able to understand the dermoscopic structures better and to make a distinction between benign vs. malignant pigmented skin lesions.

History of Dermoscopy

- Kolhaus started skin surface microscopy (1663).
- Ernst Abbe described the use of immersion oil in light microscopy (1878).
- Una introduced the term “diascopy” (1893).
- Zeiss created the first binocular dermatoscope (1916).
- Johann Saphier introduced the term dermoscopy and first published an article on dermoscopy (1920).
- Goldman was the first dermatologist who used a sophisticated dermoscopy technique (1950).

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_116, © Springer-Verlag Berlin Heidelberg 2015

- Rona Mackie was the first to write about the preoperative use of dermoscopy and the benefit of it (1971).
- H. Pehamberger et al. introduced pattern analysis for the diagnosis of pigmented skin lesion (1987).
- H. P. Soyer et al. discussed that dermoscopic criteria are correlated with underlying histopathological structures.
- J. Kreusch and G. Rassner published the first atlas of dermoscopy in literature.
- W. Stolz et al. discussed that the application of the ABCD rule of dermoscopy represents a new practical method for early recognition of melanoma malignum.
- G. Argenziano et al. discussed the introduction of an algorithm for the detection of melanoma called 7-point checklist (1998).
- Consensus net meeting in Rome (2001).

Technique and Instruments

The technique consists of placing mineral oil, alcohol or even water on the skin lesion that is subsequently inspected by using a hand-held lens, a hand-held scope, a stereomicroscope, a camera or a digital imaging system. The magnification of the instrument ranges from 6× to 40× and even up to 100×. The widely used dermatoscope has a tenfold magnification permitting sufficient assessment of the pigmented skin lesions in daily routine.

The diagnostic instruments commonly used for dermoscopic examination and image acquisition are

1. Dermatoscope
2. Dermaphot
3. Stereomicroscope
4. Stereomicroscope according to Kreusch
5. Videodermatoscope
6. Teledermatoscope

Two-Step Dermoscopy Algorithm

The first step in performing a dermoscopic evaluation of a lesion is to determine whether it is melanocytic or non-melanocytic (not all pigmented lesions are melanocytic).

The classification is based on certain structures (network, pseudonetwork, globules, streaks, homogeneous blue pigmentation and parallel pattern). If the lesion does not have any positive criteria for a melanocytic lesion, it needs to be considered, by default, to be melanocytic/non-melanocytic.

If the lesion meets the criteria for melanocytic lesion, the second step in the two-step algorithm can be applied. With the second step we can differentiate benign naevi and melanoma by using the dermoscopic algorithm "pattern analysis", the ABCD rule, the Menzies method and the 7-point checklist.

Dermoscopic Colours and Structures

The eumelanin pigment has a brown colour. Colours in dermoscopy depend on the location of the melanin in the skin (black, stratum corneum; brown, epidermis; grey, upper dermis; steel blue, medium dermis).

Other colours seen in dermoscopy are red (inflammation, vascularity), white (depigmentation, scarring), yellow (hyperkeratosis, sebaceous material), orange (serum) and jet black (congealed blood).

Dermoscopic Structures

1. Pigment network

   The network represents the rete ridge pattern of the epidermis. The hypomelanotic holes in the network correspond to the tips of the dermal papillae and the overlying suprapapillary plates of the epidermis.

   The pigment network is the most important morphologic structure in the pigmented lesions. It is a net-like structure with a honeycomb look.

   The typical pigment network is uniform, with regular lines and holes, homogeneous in colours and usually thinning to periphery. The melanocytic naevi usually have this kind of network.

   An atypical network is non-uniform, with darker and broadened lines and holes, with heterogeneous area. It may abrupt at the periphery – usually seen in malignant lesions.

   A negative network is a term which describes the downgrowth of hypomelanotic

rete ridges into the dermis. In dermoscopy, this element is visualized as a pale, net-like structure with a brown hue filling the holes. This is in stark contrast to what is usually seen in pigmented lesions. It could actually be a feature of invasive melanoma or Spitz naevi.

A pseudonetwork on the face, palms and soles results from junctional pigment outlining hair follicles, sebaceous glands and eccrine duct. The pigment on the palm and soles outlines linear skin markings along or across the skin furrows, resulting in a parallel, lattice-like or fibrillar pattern.

2. Dots and globules
   Dots and globules are formed when aggregation of melanocytes or melanophages in the skin arises or when pigment occurs in clumps. Dots are dark brown to black or blue-grey small spherical structures less than 0.1 mm.

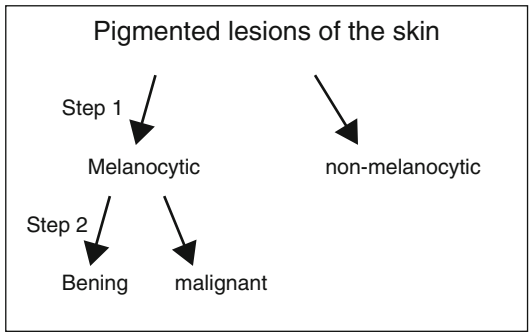
   Globules are brown, black or red spherical or ovoid structures with diameters usually greater than 0.1 mm.
3. Branched streaks and radial streaming
   Streaks are brownish-black linear structures of variable thickness found in benign and malignant lesions. They may be present at the periphery of a lesion or in the centre of the lesion. Streaks are formed by heavily pigmented, confluent junctional nests/fascicles of melanocytes that extend through the epidermis and by bridging nests of melanocytic cells within the epidermis and papillary dermis.

   Streaks at the periphery are a sign for superficial spreading melanoma and symmetric arrangement at entire lesion, seen in Reed and Spitz naevi (pigmented type).
4. Structureless areas
   Structureless areas are regions devoid of structures (e.g. globules, network) which tend to be hypopigmented.
5. Blotches
   Blotches are dark brown to black, usually homogeneous areas of pigment obscuring underlying structures. A blotch usually does not encompass the entire lesion.
6. Regression pattern
   Regression pattern is a white, scar-like depigmentation often combined with a blue-grey periphery.
7. Blue-white veil
   Blue-white veil is an irregular, indistinct, confluent blue pigmentation with an overlying white. The pigmentation cannot occupy the entire lesion.
8. Vascular pattern
   The dermoscopically visible vascular pattern includes comma vessels, point vessels, tree-like vessels and hairpin-like vessels.

   The atypical vascular pattern includes linear, dotted or globular red structures irregularly distributed within the lesions.
9. Milia-like cyst
   Small white or yellow cystic structures resemble milia, which often shines brightly. Pigmented milia-like cysts can resemble brown globules.
10. Regression pattern – it is a white, scar-like depigmentation, often combined with blue-grey peripheral zone or peppering.
11. Blue-white veil is an irregular, indistinct, confluent blue pigmentation with overlying white, ground-glass haze. The pigmentation cannot occupy the entire lesion.
12. Vascular patterns (structures) – they are dermoscopically visible vascular patterns, which include “comma vessels”, “point vessels”, “tree-like vessels”, “wreath-like vessels” and “hairpin-like vessels”.
    The atypical vascular pattern includes linear, dotted or globular red structures irregularly distributed within the lesion.
13. Milia-like cysts – they are small, white or yellow cystic structures resembling milia which often shine brightly. Pigmented milia-like cysts each resemble brown globules.
14. Comedo-like openings – they are blanched-like plugs, keratin-filled invaginations of the epidermis. They are mainly seen in seborrhoeic keratosis.
15. Fissures and ridges (brain-like appearance) are irregular, linear keratin-filled depressions, commonly seen in seborrhoeic keratosis.
16. Fingerprint-like structures – they are thin light brown parallel running lines resulting in patterns that resemble a fingerprint. They are usually seen in flat seborrhoeic keratosis.
17. Moth-eaten borders – they are concave invaginations of the lesion border resembling

defects shaped like those of the edges of a moth-eaten garment.
18. Leaf-like structures (maple leaf-like areas) – they are brown, blue-grey, discrete structures resembling a leaf-like pattern.
19. Spoke wheel-like structures – they are well-circumscribed, brown to grey-blue-brown, radial projections meeting at a darker brown central hub. In the absence of a pigment network, they are highly suggestive of a basal cell carcinoma.
20. Large blue-grey ovoid nests – they are well-circumscribed confluent or near confluent, pigmented ovoid areas, larger than globules, and not intimately connected to a pigment network. When a network is absent, ovoid nests are highly suggestive of basal cell carcinoma.

Two-Step Dermoscopic Pattern



Algorithms in Dermoscopy

Differentiate between benign naevus and melanoma
1. Pattern analysis
2. ABCD rule
3. Menzies method
4. 7-Point checklist

Pattern Analysis According to Pehamberger et al. (1993) (Modified)

Benign melanocytic lesions tend to have a few colours, architectural order, symmetry of pattern and homogeneity. Malignant melanoma often has many colours and many architectural disorders, asymmetry of the pattern and heterogeneity.

In general there are six kinds of patterns:
1. The reticular pattern is the most common in melanocytic lesions. This pattern represents the junctional component of a melanocytic naevus (Clark, dysplastic naevus).
2. The globular pattern is characterized by the presence of numerous "aggregated globules". It is usually seen in congenital naevus, superficial type.
3. The homogeneous pattern is seen like diffuse pigmentation in brown, grey-blue, grey-black or reddish black colour. An example for this pattern is the blue naevi.
4. The starburst pattern – what is specific in this pattern is the presence of the streaks in a radial arrangement, which are visible at the periphery of the lesion. This kind of pattern can be seen in Reed and Spitz naevi.
5. The parallel pattern is found on the palms and soles.
6. The multicomponent pattern refers to network, dots, globules, hyperpigmentation and hypopigmentation. This pattern is highly suggestive of melanoma.

The ABCD Rule of Dermoscopy According to Stolz et al. (2002) (Modified)

This algorithm is based on a scoring system for melanocytic neoplasms that categorizes them into benign, suspicious and malignant categories.

ABCD rule of dermoscopy according to Stolz et al. modified

Asymmetry-complete symmetry

		Points	Weight factor	Subscore range
Asymmetry	Complete symmetry	0	1.3	0–26
	Asymmetry in 1 axis	1		
	Asymmetry in 2 axes	2		

		Points	Weight factor	Subscore range
Border	8 segment, 1 point for abrupt cut-off of pigment	0–8	0.1	0–0.8
Colour	1 point for each colour	1–6	0.5	0.5–3.0
	White, red, *light b*rown, dark brown, black, blue-grey			
Dermoscopic structures	1 point for each structure	1–5	0.5	0.5–2.5
	Pigment network, structureless areas, dots, globules, streaks			
			Total score range	1.0–8.9

Benign <4.75
Suspicious 4.75–5.45
Malignant >5.45

The 7-Point Checklist (2003)

A 7-point checklist algorithm distinguishes three major and four minor criteria. These features are selected for their frequent association with melanoma. Each major criterion has a score of 2 points, while each minor criterion has a score of 1 point. A minimum total score of 3 points is required for the diagnosis of malignant melanoma.

7-Point Checklist Argenziano

The 7-point checklist according to Argenziano et al. (2003)	
Macro criteria	
Atypical pigment network	2
Blue-white veil	2
Atypical vascular pattern	2
Minor criteria	
Irregular streaks	1
Irregular pigmentation	1
Irregular dotes or globules	1
Regression structures	1

Sensitivity range 85–93 %

The Menzies Method According to Menzies et al. (2003)

This is an algorithm based on the two negative features (presence of a single colour, point and axial symmetry of pigmentation). Also, this algorithm is based on nine positive features (favouring melanoma diagnosis).

The Menzies method according to Menzies et al.
Negative features
Point and axial symmetry of pigmentation
Presence of a single colour
Positive features
Multiple brown dots, blue-white veil
Radial streaming
Pseudopods
Multiple colours (5–6)
Peripheral dots/globules
Multiple blue-grey dots
Broadened network
Scar-like pigmentation

The 3-Point Checklist

The 3-point checklist was designed to be used as a screening method.

The sensitivity is much higher than specified to ensure that melanoma is not misdiagnosed.

3-Point checklist according to Argenziano	
Asymmetry	1
Atypical pigment network	1
Blue-white structures	1

Each of these points means 1-point score. If the score is 2 or more, we must decide for further investigation (biopsy or excision).

Dermoscopic Features in Most Common Pigmented Lesions

The key points in dermoscopic diagnosis are specific dermoscopic features in each pigmented lesion.

Benign melanocytic lesions have a well-organized, tending to be symmetrical and uniform, structures. They may be flat, raised centrally or entirely elevated.

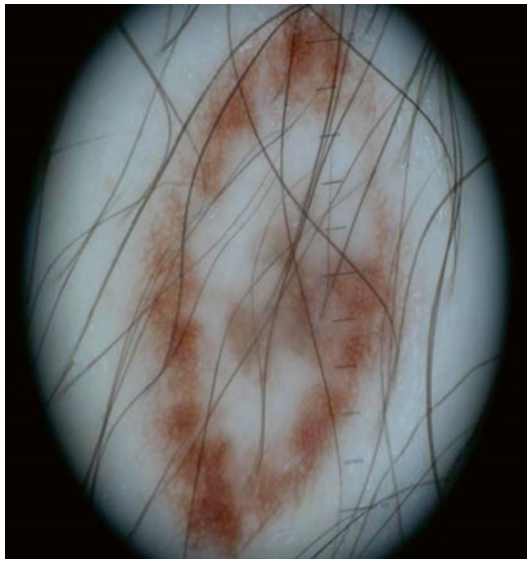


Fig. 116.1 Dermoscopic picture of benign naevi "fried egg-like" pattern

Naevi

Argenziano et al. (1999) proposed a new classification of naevi into seven categories based on specific dermoscopic features:

1. *Globular* (*congenital*) *naevus*. Specific dermoscopic features are globular pattern in children, cobblestone or fried egg pattern in adults (Fig. 116.1).
2. *Reticular* (*acquired*) *naevus*. Reticular pattern with or without hypopigmented, distributed or structureless area, sometimes atypical features (Fig. 116.2).
3. *Starburst* (*Spitz/Reed*) *naevus*. Peripheral pigmented streaks or globules, symmetrically distributed, reticular depigmentation and dot vessels in nonpigmented lesions.
4. *Blue* (*homogeneous*) *naevus*. Homogeneous structureless blue coloration, sometimes white areas of fibrosis or hypomelanosis.
5. *Site-related naevi* (acral and facial naevus). Facial naevus in children presents often pseudoreticular pattern and in adults presents remnants of pigmentation and comma vessels. Among this group we can include acral

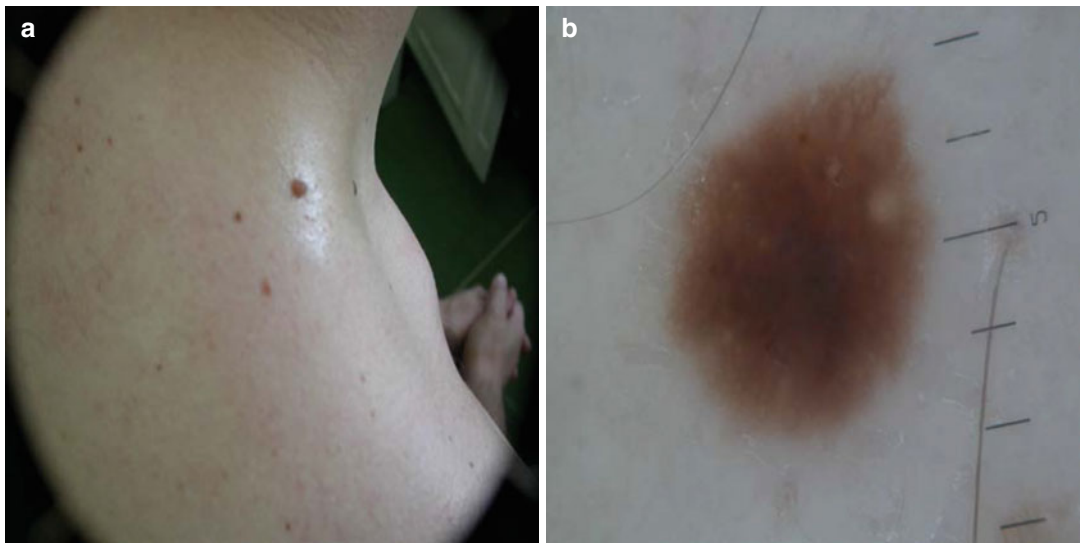


Fig. 116.2 (**a**) Clinical picture of naevi with reticular pattern. (**b**) Dermoscopic picture of naevi with reticular pattern

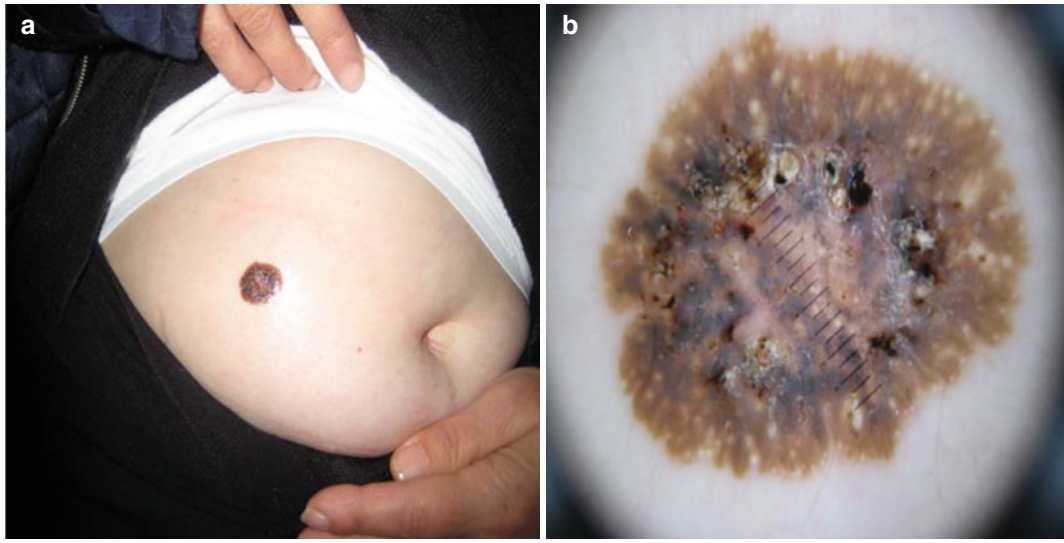


Fig. 116.3 (**a**) Clinical picture of seborrhoeic keratosis. (**b**) Dermoscopic picture of seborrhoeic keratosis

naevi – parallel, furrow pattern, lattice-like pattern and other patterns.

6. *Naevi with special features. Among this group it is possible to remember*:
   - Combined naevus – combination of globular, reticular, starburst and homogeneous patterns
   - Halo naevi – globular pattern with blue granules with scar-like areas
   - Irritated – globular, reticular or structureless with variable grey or red areas
7. *Unclassifiable melanocytic lesions*. They can have any of the previous patterns with atypical features; melanoma cannot be ruled out.

Dermoscopic Features of Seborrhoeic Keratosis (Fig. 116.3)

1. Fissures and ridges (brain-like or cerebriform appearance):
   Fissures are irregular linear keratin-filled depressions. They may also be seen in melanocytic naevi with congenital patterns and in some dermal naevi.
2. Fingerprint-like structures:
   Some flat seborrhoeic keratosis can show thin, brown, parallel lines resembling fingerprints.
3. Comedo-like openings:
   Brown-yellowish, round to oval or even irregular-shaped, sharply circumscribed structures.
4. Milia-like cysts:
   White, yellowish, roundish dots.
5. Moth-eaten border:
   Some flat seborrhoeic keratosis has a concave border.
6. Hairpin vessels:

Usually grouped together, surrounded by a whitish halo.

Dermoscopic Features of Dermatofibroma

1. Central white patch:
   Centrally situated white scar-like macule. Globule-like structures and vessels can be found. There are numerous variations of the white patch seen in dermatofibroma.
2. Peripheral thin reticulation:

Brown reticulation at the periphery of the lesion.

Dermoscopic Features of Solar Lentigo

1. Pigment network:
   The network corresponds to melanocytes and melanin-filled keratinocytes in the elongated rete ridges.
2. Moth-eaten border:

Irregular concave borders, sharply demarcated.
3. Fingerprint-like structures
4. Structureless area:
   Some lesions do not have a distinct dermoscopic structures, and they appear as light brown structureless areas.
5. Pseudonetwork

Dermoscopic Features in Malignant Pigmented Lesions

Dermoscopic Features of Basal Cell Carcinoma (BCC) (Fig. 116.4)

BCC is the most common skin cancer. It tends to be locally invasive but rarely metastasizes. In 6.5–8.5 % of the cases, it presents as a pigmented lesion. There are five distinctive types (nodular, morpheaform, fibroepithelial, infundibulocystic). Dermoscopy gives a sensitivity of 97 % in diagnosis of pigmented BCC.

Positive Dermoscopic Features of BCC

1. Leaf-like areas. Brown-grey to grey-black patches revealing a leaf-like configuration
2. Spoke wheel areas. Well-circumscribed radial projections, usually tan in colours but sometimes blue or grey, often with darker centre
3. Large blue-grey ovoid nests. Well-circumscribed, confluent or near confluent pigmented ovoid or elongated areas, larger than globules and not intimately connected to a pigmented tumour body
4. Multiple blue-grey globules which should be differentiated from blue-grey dots (melanophages)
5. Arborizing vessels. Telangiectasia with distinct tree-like branching
6. Ulceration. Absence of the epidermis, often associated with congealed blood, not due to a history of trauma

Lentigo Maligna

The main dermoscopic features of LM have been described by Stolz et al. (2002):
1. Hyperpigmentation of follicular opening (circles, semicircles, irregular circles and double circles)
2. Annular-granular structures
3. Obliterated hair follicles

Pralong et al. proposed four new dermoscopic features for LM:
1. Darkening at dermoscopic examination
2. Target-like pattern
3. Red rhomboidal structures
4. Increased density of the vascular network

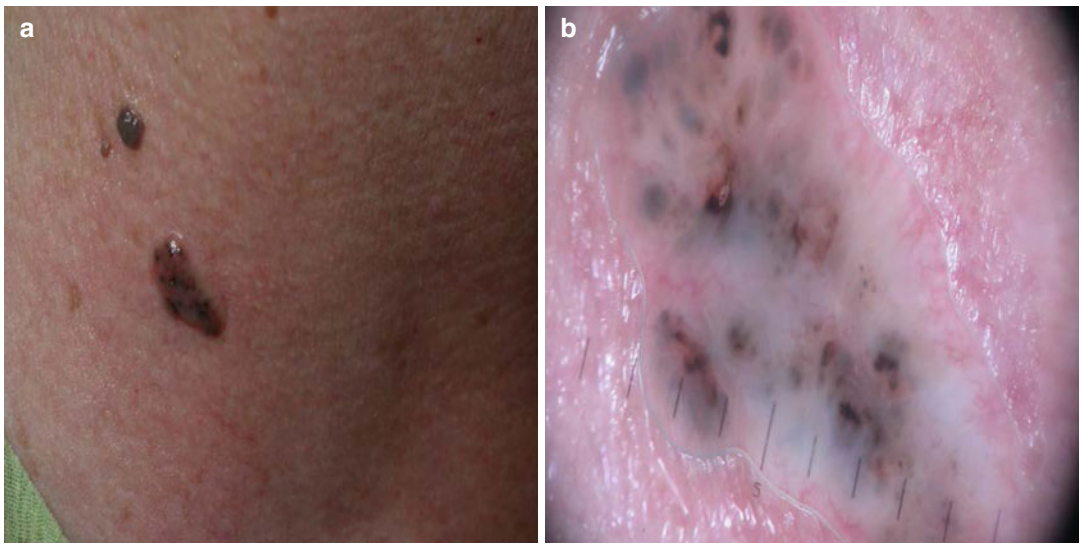


Fig. 116.4 (**a**) Clinical picture of pigmented BCC. (**b**) Dermoscopic picture of BCC

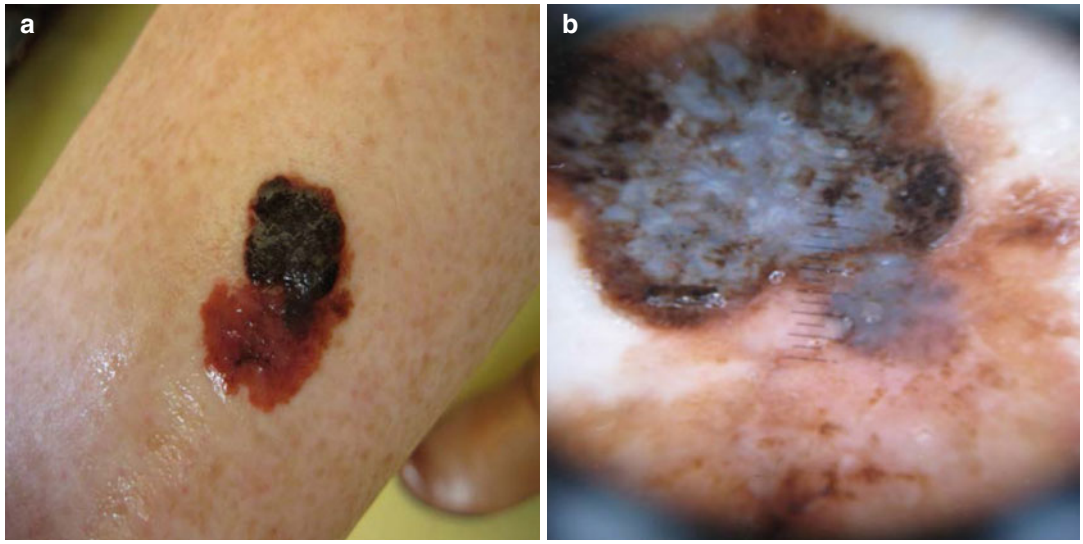


Fig. 116.5 (**a**) Clinical picture of melanoma. (**b**) Dermoscopic picture of melanoma

Melanoma (Fig. 116.5)

1. Atypical pigment network:
   Black, brown or grey network with irregular meshes and thick lines
2. Streaks:
   Irregular, linear structures not clearly combined with pigment network lines at the margins
3. Blue-whitish veil:
   Irregular, confluent, grey-blue to whitish blue diffuse pigmentation
4. Regression structures:
   White (scar-like) areas, blue (pepper-like) areas or combinations thereof
5. Dots/globules:
   Black, brown and/or grey round to oval, variously sized structures irregularly distributed within the lesion
6. Blothes:
   Black, brown and/or grey pigmentation areas with irregular shape

Nodular Melanoma

Nodular melanoma is 15–30 % of all melanomas. It is the most aggressive and has more rapid phase of growth and higher number of mitoses. It is frequently symmetric, with regular borders, often with a single colour or black/brown pigment.

ABCD algorithm is not useful, but EFG (elevation, firm on palpation, continuous growth for 1 month) is valuable. The blue-black rule recently proposed by Argenziano et.al. described a new dermoscopic feature characterized by combination of blue and black pigmented areas involving at least 10 % of the lesion surface. A blue-black colour is combined with one or more of classic dermoscopic feature, thus improving diagnostic accuracy for nodular melanoma.

Simple Rules Which Should Be Taken into Consideration in Dermoscopy

- For each change, we should make a decision in 10 s. If more time is necessary, it means that biopsy or excision is necessary.
- When dermoscopy is carried out, attention is given to what is in the focus, i.e. to what is predominant upon the basis of which decisions are made.
- Granuloma pyogenicum should not be carried out with cryo- or electrotherapy, since it does not have clear dermoscopic features and could be confused with amelanotic melanoma.

- When numerous changes are present, "the ugly duckling" should be chosen, i.e. the one which is different from the others.
- The age of the patient is crucial, since at a certain age different types of naevi are expected (children, globular; adults, reticular; elderly, papillomatous).
- The white colour in the middle of the change which is whiter than the surrounding is fibrosis. The white colour which is present in the surrounding skin is hypopigmentation.
- Lentigo maligna has specific grey granules which are located perifollicularly.
- Suspected solar lentigo means that biopsy is necessary.
- Not only is the age important, so is the skin type. With brighter phototypes, the naevi are brighter, with a possibility of a brighter area in the centre. Unlike people with darker complexion, the naevi themselves are darker especially in the central area.
- The blood vessels are different in case of different types of tumours – they are of great importance in dermoscopic diagnosis:
  - Melanoma: dots, linear, irregular, crazy vessels
  - BCC: arborizing vessels
  - Dermal naevus: coma-type vessels (Fig. 116.6)
  - SK, SCC, keratoacanthoma: hairpin vessels, with a white hue around the keratoacanthoma
- Negative network (or white network) is present in Spitz naevus and in amelanotic melanoma.
- Junctional naevi on the face do not exist, as well as dysplastic naevi. Then we go on further examination biopsy or excision.

Dermoscopy is a useful and valuable tool especially when applied by an experienced dermatoscopist. It gives us a new perspective on skin tumours, with great specificity and sensitivity. The greatest benefit is its non-invasive approach and the speed with which a diagnosis can be given.

New technologies in field of dermoscopy, high quality of digital images and teledermoscopy will offer us to communicate true dermoscopy network.

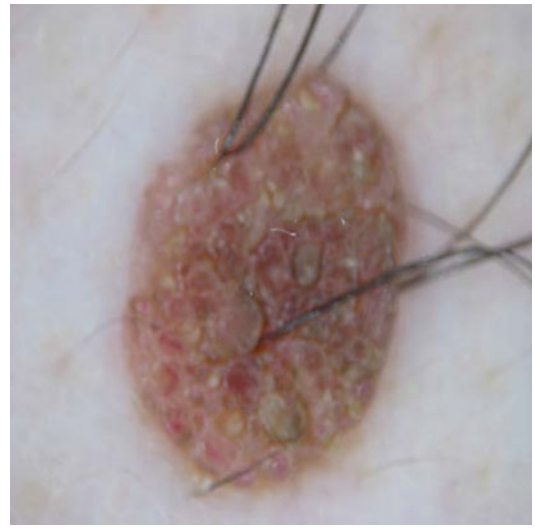


Fig. 116.6 Dermoscopic picture of dermal naevi

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Electrosurgery

117

Eckart Haneke

Key Points

Electrosurgery comprises

- Hot electrocautery
- Electrofulguration
- Electrodesiccation
- Electrocoagulation
- Electrosection
- Electric epilation
- Radiofrequency resurfacing (coblation)

General Principles

Electrosurgery is mainly used to destroy both benign and malignant lesions, to cut and excise tissue and to control bleeding. In general, it is easy to perform, inexpensive and time honouring. The more modern radio wave surgery uses approximately 3.8 MHz as compared to the old technique using kHz electric current. Radio wave surgery allows cutting almost without thermal destruction of the margin and thus is very similar to CO_2 laser surgery. There are many different electrosurgery machines on the market permitting specific outputs to be used for various indications.

Terminology in electrosurgery is often incorrectly used. Monopolar means that the electrode has only one point, whereas bipolar means that two tips are used to coagulate or heat tissue in between them. Monoterminal refers to the use of only one electrode and biterminal when two connections or electrodes, usually an active surgical and an indifferent ground plate electrode, are used.

Table 117.1 summarizes the indications for electrosurgery.

Electrocautery

Metals are heated by electric current from a battery or an outlet-dependent device. The tip of the unit consists of a wire with high electrical resistance. When the current is turned on, the wire starts glowing. It is then gently held onto the anaesthetized lesion to be destroyed. The heat does not penetrate deeper than the papillary dermis; thus, the method is best used for superficial lesions or small pedunculated lesions, such as flat seborrhoeic keratoses or small acrochordons. When the glowing tip of the instrument touches the lesion, this starts bubbling until it becomes carbonized. A crust forms that is shed after a few days.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_117, © Springer-Verlag Berlin Heidelberg 2015

Table 117.1 Indications for electrosurgery

Electrodesiccation	Electrocoagulation	Electrosection
Molluscum contagiosum	Acrochordons	Condylomata acuminata
Flat warts	Telangiectasia	Hidradenitis suppurativa
Epidermal naevi	Spider naevi	pyodermia fistulans sinifica
Flat seborrhoeic keratosis	Sunburst veins	Rhinophyma
Dermatosis papulosa nigra	Venous lake	Incisions in skin and plastic surgery
Sebaceous hyperplasia Syringoma	Pyogenic granuloma	
Xanthelasma	Pyogenic granuloma	
After curettage of basal cell carcinoma	Granulation tissue	
	Bleeding vessels in surgery	
	Oozing lymph vessels in surgery	
	Hypertrichosis, hirsutism	
	Actinic keratosis	
	Nodular BCC	

Electrofulguration

An electrical spark is used to treat small superficial lesions resulting in carbonization of the skin surface. This method is often used to treat telangiectasias.

Electrodesiccation

A high-voltage, low-amperage damped current from a spark gap unit is used in a monoterminal fashion for electrodesiccation. If the electrode is held at a slight distance from the tissue, a spark is created causing very superficial destruction (electrofulguration), whereas direct tissue contact of the electrode is used for electrodesiccation. These techniques are suited for very superficial lesions such as seborrhoeic keratoses, plane warts, acrochordons and xanthelasmas, and they also provide haemostasis for small capillary bleeding after curettage.

Electrodesiccation requires local anaesthesia except for small skin tags. Alcoholic skin cleansers must be avoided as they may ignite with electrosurgery. Postoperative care includes a sterile dressing. Delayed bleeding may occur but is very rare.

Curettage and electrodesiccation (E&D) are very often combined to treat small basal cell carcinomas. This approach has a high cure rate for nodular BCCs but is not recommended for larger ones and for all aggressive BCC types.

Electrocoagulation

Electrocoagulation uses moderately damped, partially rectified current with active concentrating and dispersing neutral electrodes. The voltage is lower and the amperage higher than in electrodesiccation. It penetrates deeper, thus causing more tissue destruction.

Indications for electrocoagulation are deep tissue destruction and surgical haemostasis.

- Tissue destruction: a ball electrode is directly applied to and slowly moved over the lesion. The charred tissue is removed with a wet gauze pad or a curette. This procedure is repeated until the lesion is completely destroyed. Usually three passes are necessary for malignant tumours.
- Haemostasis: the electrode may directly touch the bleeder vessel or the vessel may be grasped with a fine pincer or clamped with a haemostat which is touched with the electrode. The power of the device should be set as low as possible in order to achieve coagulation of several millimetres which reduces the risk of delayed bleeding. Bipolar electrocoagulation with special forceps is used for less traumatizing pinpoint haemostasis. However, it requires a dry operative field.

Electrocoagulation is the most effective means for treating spider naevi. A needle electrode is lightly held on the central pulsating vessel and a nurse assistant slowly turns on the

power. The needle sinks into the tissue, gently coagulating the feeding vessel. No scarring is observed when using this technique cautiously.

Electrosection

Cutting is performed using slightly damped, fully rectified current in a biterminal fashion. High amperage and low voltage are further characteristics. Cutting and haemostasis are achieved by tissue vaporization. Lateral heat spread is low, reducing peripheral tissue damage. The higher the power, the easier the cutting and the less is the coagulation, and vice versa.

The narrow electrode passes effortlessly through the tissue leaving an almost dry cut surface. If the electrode drags, the power setting is too low. If it sparks, it is too high. For incision, a needle or blade electrode is commonly used. A thin loop electrode is optimal for removing tissue slices such as in rhinophyma and of pedunculated or protruding lesions such as condylomata acuminata or to excise small tumours with one stroke. We also use the electrical loop in chronic hidradenitis suppurativa, keloidal acne and other deep-seated infections not amenable to conservative therapy.

Radio wave electrosurgery uses higher frequencies of 1.2–4 MHz. In the cut mode, fully filtered current is used. There is minimal heat generation and therefore almost no coagulation. Specimens thus excised can be submitted for histopathological control of margins. Lateral tissue damage is even less than with the continuous wave surgical CO_2 laser. The device can also be set to fully rectified current for cutting and coagulation and to partially rectified current for coagulation. This machine is optimal for surgery of the face and for creating skin flaps.

Electroepilation

Removal of unwanted hair by electrical current is usually performed by cosmeticians. Two different techniques are available:

- Electrolysis
- Thermolysis

Electrolysis uses direct current to induce a chemical reaction in the hair bulb. The anode is inserted into the follicle and the patient holds the cathode as a moist pad. When being switched on, the current produces an electrochemical reaction generating sodium hydroxide, which is caustic. The procedure takes 30–60 s for each follicle to be destroyed.

Thermolysis is much faster, causing heat destruction of the hair root. In the slower technique, lower heat is generated for 3–20 s. In the flash technique, high temperatures are delivered for less than 1 s.

A blend of both methods was developed to speed up treatment and increase efficacy.

For all techniques, a very fine needle is inserted into the follicle down to the bulb. The needle tip is rounded to avoid puncturing through the follicle wall, and its length is insulated (Kromayer needle) in order to avoid damage to the superficial follicular portion with the risk of scarring. However, the stem cells are located in the bulge region relatively high above the hair bulb and even very efficient and precise destruction of the root may be followed by a recurrence.

Side effects are rare. Electrolysis is less painful and has probably a higher success rate when carried out by an experienced therapist. Post-treatment pigmentary disturbance depends on skin type.

Devices for home self-use are not effective. Hair shafts are not conductive for electrical current; therefore holding a hair with tweezers and applying electrical current cannot permanently destroy the hair root.

It has to be stressed that special lasers or high-energy light pulses for hair removal are now the preferred methods with at least as good results but performed with much more ease and more rapidly.

Radiofrequency Resurfacing

The removal of superficial skin layers including skin resurfacing is a new electrosurgical method although it may have been used for similar

purposes decades earlier. Whereas CO_2 laser resurfacing works by thermal damage, this is replaced by a much cooler and more controlled ablation (hence the new term 'coblation'). A fine layer of an electrically conductive solution, usually physiological saline, is sprayed on the skin. The hand-held bipolar electrode-tipped wand is set on this layer on the target. When the current is switched on, the saline between the electrodes is converted into an ionized vapour layer, called plasma. Ions accelerate across this gradient towards the skin, dissociating molecular bonds within tissue structures, thus removing tissue layers and ultimately causing collagen neosynthesis and improved skin appearance. The process runs at only 80–90 °C as compared to 300–600 °C with the CO_2 laser. Heat damage to the surrounding tissue is considerably lower, suggesting that the risk of persistent erythema and scarring is lower and wound healing considerably faster.

Risks of Electrosurgery

Preoperative discussion includes information about the procedure, healing time of at least 2 weeks for small wound, scab formation and scarring. Preoperative evaluation discusses bleeding disorders, hepatitis, human immunodeficiency virus, immune defects, individual scarring, pacemaker, prosthesis and other electronic implants.

Some risks are inherent to electrosurgery, such as ignition of inflammable gases and fluids. Therefore, preoperative disinfection requires non-alcoholic solutions. Electrosurgical electrodes are not self-sterilizing and spread of infection is possible if they are not properly sterilized. Furthermore the plume generated by the heat may contain intact virus particles and effective smoke evacuation is therefore mandatory. Smoke evacuation is also recommended for large operations such as hidradenitis suppurativa. Experience has shown that drying up the wound is easier for the patient immediately after surgery but takes longer to heal than occlusive or semi-occlusive treatment.

Delayed postoperative bleeding is due to incomplete coagulation of vessels, particularly when local anaesthesia with vasoconstrictors was used. Postoperative pain may be intense. Some reddening around the wound is frequently seen. Eschar formation and sloughing of necrotic tissue are obligatory. Electrosurgery carries the risk of delayed wound healing and hypertrophic scarring. They are dependent of the amount of tissue coagulation. Hyperpigmentation in dark-skinned and hypopigmentation in fair-skinned persons are common. Electrosurgery is thought by many to be contraindicated on the soles of the feet as it may cause very painful hypertrophic scars and even keloids. Improper contact with the ground plate electrode may cause large burns. However, also the epoxy resin of the ground plate may cause allergic contact dermatitis potentially misinterpreted as a burn. Patients with sensitive electrical facilities such as demand-dependent pacemakers or implantable cardioverter defibrillators are at risk. There may also be interference with cardiac monitoring devices in anaesthesiology.

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Excimer Laser Therapy

118

Carmen Maria Salavastru

Key Points

- Excimer laser therapy is a new valuable option for treating various dermatologic conditions.
- The most part of the published results focuses on efficacy and safety in treating psoriasis and vitiligo, both in adults and children.
- New encouraging results for treating atopic dermatitis and alopecia areata, in all age groups, are under evaluation.
- The mechanism of action is similar to the UVB phototherapy; however, the cumulative dosage is lower, and the targeted area is strictly the lesional one; currently, fewer side effects are noticed.

General Principles

In addition to narrowband ultraviolet type B (nb-UVB) (311 nm), a new UVB source generated by a 308-nm excimer laser has been introduced for the treatment of various dermatological conditions.

The excimer laser is a gas laser emitting in the UV-wavelength range from 157 to 351 nm. The name excimer laser is derived from *ex*cited di*mer*. This type of laser utilizes as its active medium a mixture of a noble gas, a halogen, and a buffer gas, and the various wavelengths emitted depend on the combination of the noble gases and the halogen. In dermatologic treatments, the 308-nm laser is used and it implies a XeCl gas mixture as an active medium.

This type of laser operates at a rate pulse of 100 Hz and a pulse width of approximately 10 ns. It emits a monochrome radiation in the UVB spectrum, it does not produce heat, and the beam energy is absorbed by the tissue at most 1 nm in depth.

The size of the spot may be adjusted between 14 and 30 mm; in this way there is the possibility of treating precisely the affected area without the irradiation of the non-affected skin.

Mechanisms of Action

The 308-nm wavelength, which is very close to 311 nm, used in nb-UVB phototherapy, is considered to have a similar mechanism of action with the latter. The radiations of the UVB spectrum show immunosuppressive effects by inducing T-lymphocyte apoptosis and immunomodulatory effects, too. A single 308-nm UVB dose reduced the number of pathogenic memory/effector T cells infiltrating psoriatic lesional epidermis and dermis, and, consistent with apoptosis induction, caspase activation increased in lesional T cells

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_118, © Springer-Verlag Berlin Heidelberg 2015

after treatment. Another interesting finding is the preferential induction of endothelin-1 in a human epidermal equivalent model by narrowband ultraviolet B light sources. This molecule is associated with UVB-induced migration of melanocytes and stimulates DNA synthesis in melanocytes.

Clinical Applications

The first use of an excimer laser was in eye surgery. In dermatology, the XeCl excimer laser, 308 nm, is used in treating inflammatory conditions: vitiligo, psoriasis, atopic dermatitis, alopecia areata, and others.

There are important advantages in using excimer lasers in dermatological treatments: the radiation is limited strictly to the affected area, and the exposure time and the cumulative dosage are lower than with the conventional UVB phototherapy.

Vitiligo

The monochromatic excimer laser has the advantage of targeted treatment with less body irradiation and less impact on non-lesional skin. It works well for patients with higher Fitzpatrick skin types. The mechanism of action is thought to be similar to conventional therapy. The xenon chloride monochromatic excimer laser (308 nm) is the most used laser therapy for vitiligo and it is approved by the FDA for the treatment of this disease.

Efficacy

When used as monotherapy, repigmentation rates higher than 75 % are seen in 16.6–52.80 %; response rates may be as high as 95 %.

It has been observed that repigmentation starts at the margins of the lesions especially for the acral ones. In the area where hair follicles are present, there is a perifollicular debut of repigmentation, too. The onset of repigmentation negatively correlates with the total number of treatments but may be sooner on the face, neck, and axillae compared to the trunk and limbs.

The face and neck respond better than the hands and feet and with less total irradiation.

Approximately 30 % of the patients may achieve repigmentation on more than 75 % of the treated area, with an average of 32 sessions. Higher Fitzpatrick skin types achieve better results. Age, skin types, duration, and evolution of the disease do not confound treatment outcomes. Even some previously nb-UVB treatment nonresponders may achieve repigmentation, and compared to nb-UVB, it shows better clinical outcomes. Most cases are stable at 1 year of follow-up. However, there are also patients who may not respond to this type of therapy.

The results improve when used in combination with other therapies. Topical tacrolimus and calcipotriol or topical hydrocortisone have been assessed for possible additive effects.

The 632.8-nm helium neon laser is used in treating patients with segmental vitiligo.

Treatment regimen and dosage for vitiligo treatment, as it is followed in our clinic, is illustrated in Table 1.

Side Effects

Side effects are minimal and local. The treatment is well tolerated with some patients experiencing mild to moderate erythema and pruritus. Vesiculation and blistering are seldom. Because of the absence of photosensitizing substances and drug-induced toxicity, patients who work outdoors, pregnant women, and patients with liver or kidney failure can also be treated.

Use in Children

In children the therapy is widely used with good results.

Psoriasis

Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2 % of the population.

Various spectra of UVB and UVA wavelengths have been used to treat psoriasis.

Although a minimum of 10 % body surface area has been traditionally used as a prerequisite to starting ultraviolet (UV) light or systemic therapy for psoriasis, a subset of patients with limited disease have debilitating symptoms: psoriasis of the palms and soles or severe scalp psoriasis. The significant negative effect on the quality of life of this type of patient makes treatment with systemic therapies an appropriate approach.

Traditional UVB radiation has been used for the treatment of psoriasis for more than 75 years. In recent years, phototherapy has maintained its important role in the treatment of psoriasis, either as monotherapy or in combination with topical or systemic agents.

Although nb-UVB is reported to be less phototoxic than UVB in some studies, other studies failed to show this discrepancy.

Efficacy

There are several studies showing the efficacy of laser excimer therapy in plaque psoriasis; the patients treated achieve remission in a lower number of sessions and with a lower cumulative dosage compared to the patients treated by nb-UVB. The energy delivered during one session is bigger than the one delivered during the nb-UVB treatment; therefore there are a larger number of side effects: erythema, vesiculation, and hyperpigmentation.

The chromophore for the excimer laser is DNA.

The efficacy of the excimer laser in treating plaque psoriasis relies, besides the direct cytotoxic effect on DNA T lymphocytes, on lowering the TNF and IL-1 skin levels and on inhibiting the antigen presentation by the Langerhans cells.

During the past years, there are a number of papers showing the efficacy and safety of excimer laser in treating plaque psoriasis. The main drawback of the published papers is the small number of patients treated. The results are variable but generally they show a better outcome when using this method compared to nb-UVB. Fifty to eighty-five percent of the patients obtain remission (PASI 90) in 10–24 sessions, and the time needed to obtain the remission is up to 3.6 times shorter than for nb-UVB. Additionally, the cumulative dosage is significantly lower than the nb-UVB dosage, for the same clinical result. There is also an observation that the guttate type responds better than the plaque type. There are encouraging results for the difficult responding lesions of elbow and knee areas. The free disease interval ranges between 1 and 6 months.

There are some successful treated cases of patient showing predominantly skin fold psoriasis, leading up to a 6-month remission.

For the palmar and plantar forms, the efficacy is similar to PUVA therapy, with a better compliance. Up to 75 % of the patients experienced an 80 % improvement. Good results were seen in treating scalp psoriasis, too; around half of the patients experienced a 90 % decreasing of the lesional area, after an average of 21 sessions. Nail psoriasis seemed not to be influenced by this procedure.

The 308-nm excimer laser appears to be a safe and effective treatment for localized psoriasis in children as well as in adults.

Treatment Regimen and Dosage

Before starting the therapy, the minimal erythematous dose (MED) should be identified.

The treatment may be tailored either by increasing the dosage at the beginning of each session (the exposure dosage is a multiple of the MED and it is increased every other session) or by accelerated dosage increase per exposure. The second option leads to a smaller number of sessions needed and ultimately to a lower cumulative dosage.

The excimer laser therapy is well tolerated by the patients, which may experience a mild stinging sensation during exposure. Side effects depend mostly by the dosage: erythema and hyperpigmentations appear in 40 % of the patients following the increase of the dosage every other session. Erythema, vesiculation, and crusts are manifest to all the patients who experience the accelerated increase in dosage per exposure.

Recently, there is a recommendation of adjusting the dosage according to the plaque thickness and Fitzpatrick skin type. The frequency of the treatment is two to three times a week, with a minimum of 48 h between treatments.

Side Effects

Since the excimer laser therapy is delivered directly to the treated areas, the side effects are limited to the treated area: erythema, burning, and hyperpigmentations. Vesiculations and blistering may occur with higher fluences. The long-term safety remains to be fully established.

Pregnancy and Breastfeeding

There is no study conducted in pregnant patients but it is suggested that it is unlikely to have any teratogenic effects.

Pediatric Use

Data regarding the use of the 308-nm excimer in children for psoriasis are limited, but it seems to be safe, according to expert opinion.

Contraindications

Excimer laser therapy should be used with caution in patients with photosensitivity.

Atopic Dermatitis

New devices such as 308-nm monochromatic excimer light expand the therapeutic options in patients with localized and therapy-resistant atopic dermatitis, even though they can treat only limited surfaces. However, this therapeutic option has not yet been properly assessed in atopic dermatitis.

Data available at the moment refers mostly to patients with flexural lesions and moderate severity. They show decrease in pruritus, edema, and lichenification by more than 50 %, some results being noticeable after only two sessions.

The side effects are comparable with the ones experienced by the patients treated for vitiligo.

Alopecia Areata

There are only scarce data regarding the efficacy of excimer laser treatment for alopecia areata. The initial dosage is usually lower than the MED, and the dosage is increased, according to the patients' tolerability, every other session. By using this procedure, there was a regrowth of the hair in 41.5 % of the alopecia areas with the beginning of the effect during the second month of therapy. The scalp lesions respond better than the beard or acral lesions. In adults the regrowth is present in 75 % of scalp lesions and in children in 60 %. The remission lasts less than 6 months. The usual side effects, erythema, hyperpigmentation, and vesiculation, are limited but they are increased by higher dosage.

Other Skin Diseases

There is an increasing number of short reports published about the results of treatments by excimer laser therapy on skin conditions such as striae distensae, granuloma annulare, or mycosis fungoides. The gathered data indicate that excimer laser therapy is helpful in treating various chronic dermatologic conditions, with a good clinical tolerance and some advantages compared to UVB phototherapy.

Table 1: Protocol Excimer Laser Treatment Vitiligo

I. *Selection criteria*:
   (a) Inclusion criteria:
      – <20 % lesional skin of total body surface
      – Recent diagnosis (<5 years)
   (b) Exclusion criteria:

Phototherapy within the last 3 months
Any other cause of photosensitivity/photomediated diseases
Medication which forbids UV exposure
Total depigmentation of the face and/or dorsal aspects of the hands
Fitzpatrick skin phototype I
Cutaneous malignant tumors
Pregnancy and lactation

II. *Clinical type of vitiligo*
III. *Assessment of Vitiligo Disease Activity* (*VIDA*)
IV. *Assessment of Dermatology Quality of Life Index* (*DLQI*)

V. *Assessment of thyroid function* – TSH, ATPO, FT4
VI. *Signing of the informed consent by the patient/tutor*
VII. *Pictures*:
  (a) Before starting the therapy
  (b) Every other week during the therapy and by 6 and 12 months after the end of the therapy
VIII. *Therapy*:
  – Excimer laser monotherapy
  – Combined excimer laser therapy
  – Specify
IX. *Assessment of Minimal Erythematous Dosage – MED*
X. *Excimer Laser Therapy*
  (a) First exposure: 85 % of MED.
  (b) Second exposure: according to the clinical result
    – Increasing by 30–50 J/cm^2 every session if no side effects (e.g., erythema).
    – Maintain the dosage if slightly pruritus and erythema are observed.
    – Stop the treatment if important side effects develop; upon remission of the side effects, the treatment is resumed at a dosage lower than the one which induced the side effects.
    – For facial lesions, the initial dosage is 50 J/cm^2 and increases by 20–30 J/cm^2 during every session.
  (c) During the procedure, the surrounding non-lesional skin should be covered.
XI. *Frequency of the exposure*: 2–3 sessions/week, non-consecutive days
XII. *Immediately postprocedure care instruction*
  – Sun avoidance – sun blockers.
  – Makeup may be used as desired.
XIII. *In case of side effects*
  (a) Patients report any side effects immediately after their appearance.
XIV. *Total number of sessions*
  (a) Average: 20 sessions/patient.
  (b) If total repigmentation is achieved sooner, the therapy is stopped.
  (c) If after 20 sessions the doctor consider the result satisfying although not yet total repigmentation achieved, the therapy may be continued up to a total of 30–35 sessions.
XV. *Patient evaluation*
  (a) According to the degree of repigmentation:
    0 – no repigmentation
    1 – repigmentation 1–25 %
    2 – repigmentation 26–50 %
    3 – repigmentation 51–75 %
    4 – repigmentation >75 %
  (b) Assessment is scheduled by the twentieth session and/or by the last scheduled session.
  (c) Assessment of the patient by 6 and 12 months after the end of the therapy.
  (d) Assessment of DLQI by the end of therapy.
  (e) Pictures of the patient are taken at session 20 and/or last session.

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Fillers and Soft Tissue Augmentation

119

Christopher M.E. Rowland Payne and Ines Verner

Abbreviations

BDDE	1, 4 butane-diol-diglycidyl ether
CHA	Calcium hydroxylapatite
HA	Hyaluronic acid
HBOT	Hyperbaric oxygen therapy
PLLA	Poly-L-lactic acid
PMMA	Polymethylmetacrylate
SILS	Serial intralesional steroid
SMDS	Serial microdroplet silicone
SOOF	Sub-orbicularis oculi fat

Key Points

- Loss of facial volume is one of the most important determinants of facial ageing.
- Facial volume loss can be partially restored by the injection of soft tissue fillers into the subcutaneous tissue. With the vast technological developments of the last few decades, many different soft tissue fillers have become available. Soft tissue augmentation has now become one of the most popular non-invasive cosmetic procedures worldwide.

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- Fillers may be divided into inert and fibrogeneic. Inert fillers, such as hyaluronic acid (HA) and fat, are injected and remain inert until the body resorbs them. Fibrogeneic fillers, such as silicone, calcium hydroxylapatite and poly-L-lactic acid, elicit a fibrosis-granuloma host response which ensures a longer-lasting effect.
- Fillers provide many opportunities for therapeutic benefits, both medical and aesthetic. Medical indications include, for example, correction of the perioral rhitids of systemic sclerosis or creation of missing volume in patients with cleft lip or Romberg's hemiatrophy. Aesthetic indications are legion. Many relate to replacement of facial volume. As facial volume involutes with time, the overlying skin becomes less tightly stretched. Skin ptosis (e.g. lateral to the mouth) and concertina-like wrinkles (e.g. perioorally) ensue. These phenomena can all be improved using fillers.
- Fillers can be injected using needles or microcannulae. They can be implanted at the intradermal, subcutaneous and deeper levels. The most widely used filler now is HA. Fillers can be injected using a threading 'tagliatelle' technique or as multiple puncture 'pearls'. Many fillers can be used in both ways. Most

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_119, © Springer-Verlag Berlin Heidelberg 2015

fillers may be injected in aspiration bolus, in retrograde or in antegrade, sometimes perpendicular and sometimes tangential to the skin's surface. Silicone is usually only used as serial microdroplet silicone (SMDS). Subcision alone can treat very fine early lines. Intradermal subcision is often also a useful adjunctive treatment when other fillers are used at the dermosubcutaneous junction. Hypodermal or deeper subcision can be useful for more established rhitids.

- Specific injection technique at specific facial sites is discussed. Complications and their treatment and prevention are reviewed.
- Fillers and soft tissue augmentation offer enormous therapeutic opportunities.

General Principles

From time immemorial, human beings have sought to enhance natural beauty and tried to slow ageing. With the advent of anaesthesia and surgery, towards the end of the nineteenth century, more invasive cosmetic procedures became available, including soft tissue fillers. Fat was the first soft tissue filler to be used after trauma and is still widely used today. However, autologous fat transplantation is considered a relatively major procedure, as it necessitates the transplantation of fat from another site, and its results may be variable. Towards the end of the nineteenth century, paraffin oil was used for the restoration of volume and symmetry. However, its use was accompanied by a high incidence of inflammatory foreign body granulomatous nodules (*paraffinomas*) with consequent facial distortion and, occasionally, life-threatening paraffin pulmonary emboli. Hence, the use of paraffin oil was discontinued.

Liquid silicone gained some popularity in Europe in the 1940s, when thousands of patients were treated with it. Since the 1960s and through to the present day, excellent, safe and durable results have been reported with silicone, using the serial microdroplet technique. On the other hand, the use of inappropriately large volumes of silicone or impure silicone has been followed by horrific complications, such as neurological dysfunction, blindness and erysipelas-like inflammatory reactions. These problems have cast an unwarranted cloud of unease over the safe and proper use of serial microdroplet silicone (SMDS).

Injectable bovine collagen was the first biodegradable filler available. The FDA approved it in 1981 for soft tissue augmentation because of its relative safety. The minimally invasive nature of the procedure, with no downtime, led to a growing demand for soft tissue augmentation. Its very short duration in the tissue and its high incidence of allergic reactions led to the development of other fillers with enhanced longevity and safety, notably hyaluronic acid (HA). According to the annual report of the American Society of Plastic Surgeons, filler injections were the second most commonly performed minimally invasive procedure with two million injections performed in 2012, second only to botulinum toxin injections: 6.1 million in 2012 (www.plasticsurgery.org). The use of HA fillers has now become commonplace.

Facial Anatomy

Fat Compartments

Like the flesh of an orange, the facial subcutaneous fat is divided into segments or compartments (Fig. 119.1).

These compartments are separated from one another by fibrous septa, which are condensations of the retinaculum cutae. The septa arise from the superficial fascia and insert into the dermis. These septa form the interconnecting framework that limits shearing forces on the face and which helps prevent migration of skin, subcutaneous fat and injected filler (Rohrich and Pessa 2008).

Mid-facial fat is arranged in two and paranasally in three independent anatomical layers. The

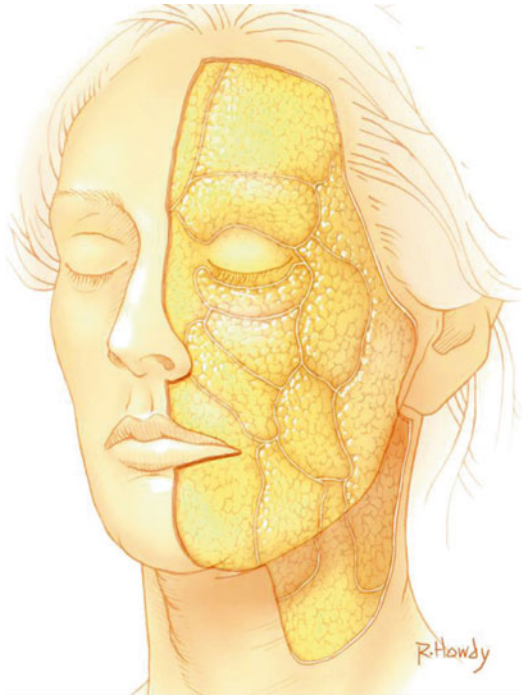

Fig. 119.1 The fat compartments of the face (Courtesy of Dr R Rohrich)

superficial layer is composed of the nasolabial fat, the medial cheek fat, the middle cheek fat, the lateral temporal cheek compartment and three orbital compartments. Deep midfacial fat is composed of sub-orbicularis oculi fat (SOOF) (medial and lateral parts) and deep medial cheek fat (medial and lateral parts) (Gierloff et al. 2012).

Different compartments age differently. Some atrophy (e.g. at the temples), others bulge and sag (e.g. at the jowls). The mid-facial fat compartments migrate inferiorly.

In youth, these compartments are more or less ideally inflated. With age these various fat compartments deflate. Like the female breast, fully inflated fat compartments stand out from the underlying tissues with an anterior projection. As the fat involutes, the compartments deflate and gravity determines that anterior projection gives way to vertical descent with festooning of relatively deflated fat compartments and consequent facial ptosis. If the fat compartments have been subject to any episodes of overinflation, for example, due to obesity or periodic oedema of women, then there may also have been some stretching of the fibrous septa. In such patients, the ptosis of subsequent deflation will be aggravated by septal weakness consequent upon the physical effect of having been stretched. The pattern of inflation, stretching, deflation and puckered festooning is the same process as that which leads to cellulite in the panniculus adiposus of other parts of the body.

Facial Ligaments

Arising from the bone or from the deep fascia and inserting into the skin are various facial ligaments. These tie the skin, at various points, to the deeper structures. Since these stretch little with age, they act as fixed points and so aggravate the appearance of festooning of the intervening skin and fat. This is mostly so at the jaw line.

Skeletal Changes

Ageing of the facial bones is characterised by bony involution with concomitant morphological changes in the orbit, midface and mandible. The mandibular angle increases, whilst mandibular length and mandibular body height decrease. The maxillary angle decreases. There is widening of the orbital aperture with inferolateral and superomedial expansion. Similar to the axial skeleton, facial mineral bone density decreases (Shaw et al. 2010, 2012). These changes lead to changes in the skeletal support of the soft tissue and a consequent redraping of the soft tissue, further contributing to a sagging appearance around the eyes (Warren et al. 2011).

Facial Structure

Changes in the fat compartments together with changes in the facial skeleton lead to changes in the support of the soft tissues and thus changes in facial morphology. Gradual sagging of the soft tissues and changes in the shape of the bone result in a metamorphosis from the heart-shaped

or inverted triangular-shaped face of youth to the rectangular or 'bottom heavy' face of late middle age. When the youthful face is observed obliquely, a double ogee (an S-shaped curve) is apparent, running from the brow into the lateral orbital wall and from the upper into the lower midface. This line is considered to be the line of beauty. With age, it flattens or reverses.

Medical Indications

Fillers can be used for many different indications, not only to treat the manifestations of ageing but also to treat facial defects and asymmetry due to trauma or disease (Verner and Rowland Payne 2009).

In the upper third of the face, forehead asymmetries or depressions can be corrected, such as sunken scars or tissue loss due to certain skin diseases, such as Romberg's hemidystrophy and morphoea en coup de sabre.

In the middle third of the face, bilateral lipodystrophy is seen in patients receiving retroviral treatment for HIV disease. Lipotransfer or the use of other fillers may help greatly. Minor nasal imperfections, such as nasal tip descent or an overdeep nasal bridge, can be corrected, sparing the need for surgery (Fig. 119.2).

In the lower third of the face, lip asymmetries or defects can be corrected. Cleft lip scars can benefit from SMDS. Systemic sclerosis may result in disfiguring perioral radial rhitids and so may congenital syphilis. SMDS or HA may be

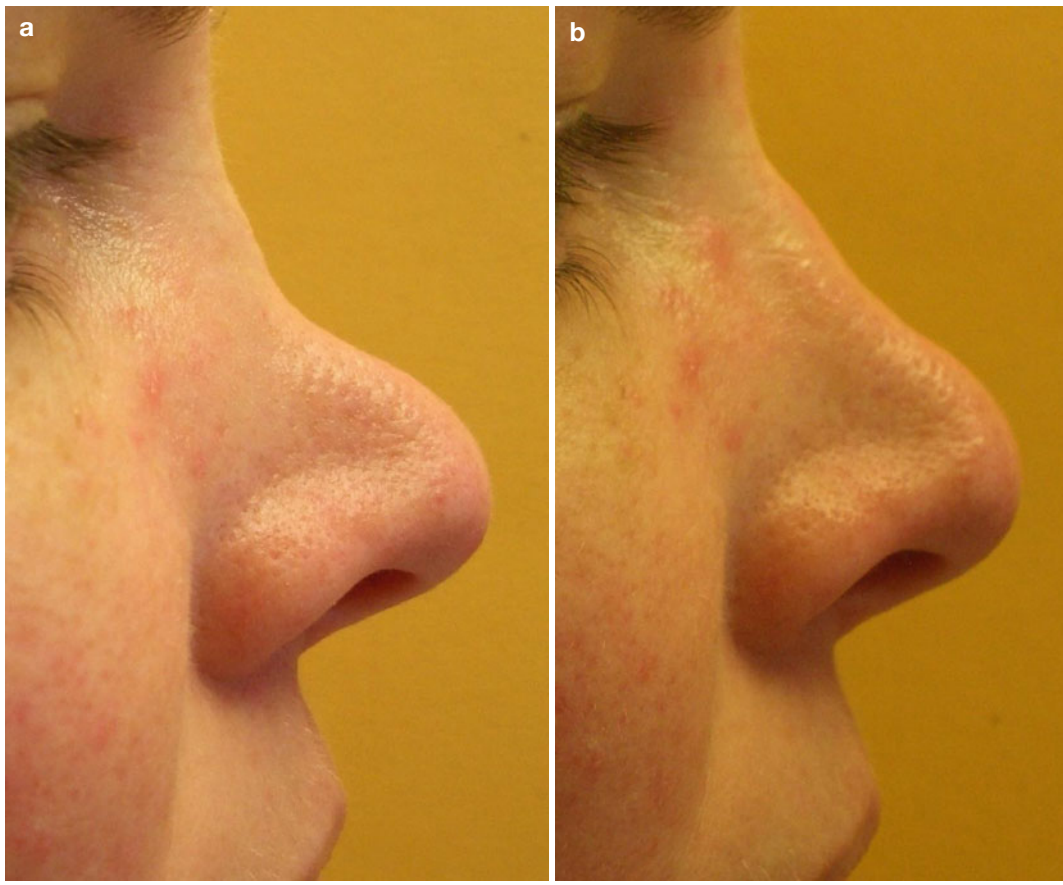

Fig. 119.2 (**a**) Post-traumatic nasal deformity. (**b**) Post-traumatic nasal deformity. After treatment by HA filler (Courtesy of Dr C Rowland Payne)

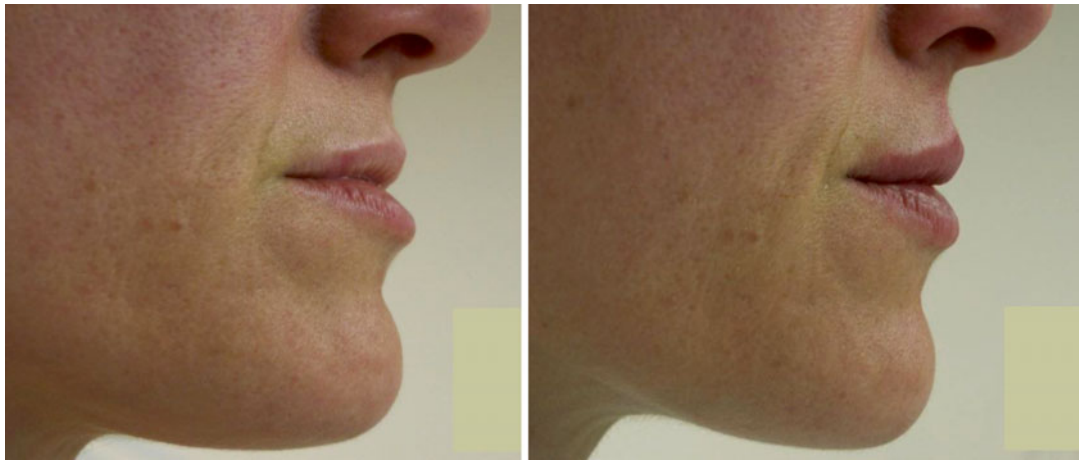

Fig. 119.3 (**a**) Prognathism. Before treatment. (**b**) Prognathism. After treatment by submucous filler in the upper lip (Courtesy of Dr C Rowland Payne. Reproduced from Shai A, Maibach HL & Baran R. Handbook of cosmetic skin care. 2nd ed. p. 196, with permission of the publishers)

very helpful in attenuating these stigmata. Acne scars can be treated by SMDS. If the chin is too small, chin augmentation can also be achieved by fillers. A prominent mandible can be made less evident by submucosal filling of the upper lip (Fig. 119.3).

Cosmetic Indications

The face, especially the central face, is well suited to the use of fillers. Tissue involution, muscular activity and gravity all take their toll in this area. Moreover, the central face is less amenable to improvement by rhytidectomy than is the lateral face, and the benefits possible from botulinum are limited by the need to preserve muscular expression and oral sphincter function.

Correction of Changes Due to Ageing

The upper third of the face ages with a loss of the convex projection of the supraorbital ridge with a consequent descent of the eyebrows. Laterally, there is loss of volume at the temporal region leading to temporal fossa hollowness and lateral brow ptosis. Fillers can also be used in these areas to elevate the eyebrows, to treat deep glabellar folds (between the eyebrows) and to treat wrinkles lateral to the eyes (crow's feet) (Carruthers and Carruthers 2010; Busso and Howell 2010). Filling the temporal fossa improves the shape of the face and lifts the lateral brow.

The middle third of the face ages by the appearance of hollows under the eyes and loss of volume in the medial and lateral cheek. By correcting the hollows under the eyes, a tired appearance can be effaced and the face can gain a smoother appearance. Fillers can restore volume loss in the medial and lateral cheeks and can accentuate the cheekbones (Montes 2012).

The lower third of the face ages with deepening of the nasolabial fold and the appearance of marionette or 'drool' lines. These lines run from the corners of the mouth down towards the sides of the chin. There are changes in the position and structure of the lips and jowling of the jaw line. The nasolabial fold is one of the most popular indications for fillers. Filling this fold can give excellent and durable cosmetic results. However, often a more natural midface appearance can be achieved by filling and correcting the medial and lateral cheek. Filling the cheek not only improves the nasolabial folds but also lifts the mid and lower face and improves a tired appearance. Treating marionette lines also helps support the sides of the mouth, but care should be taken not

to overfill this area. Ageing also leads to loss of jaw line definition with jowling. Fillers can help redefine the jawline. Ageing lips become thin and flat; fine radial or cross-hatched wrinkles develop on the upper and lower lips, and the lipstick may 'bleed' out from the vermillion into the surrounding skin, giving the lipstick a smudged appearance. Natural fullness and definition can be improved and restored. One of the most difficult aims of lip augmentation is to achieve natural looking lips. To achieve this requires a study of lip anatomy and awareness of natural lip structure (Verner 2012). The first and most important point to consider when examining lips from the anterior view is the proportion between the upper and lower lip. The lower lip should be 1.6 times taller than the upper (i.e. about one third taller than the upper). If the lower or the upper lip is too thin relative to the other, just correcting this one feature will lead to great improvement. Many times, less is more when approaching lip enhancement, and even thin lips with correct proportions can be pleasing aesthetically. In Rowland Payne's 'Mona Lisa smile' (Rowland Payne 2003), fillers are injected into the angles of the mouth to correct downturning.

Types of Fillers

Soft tissue fillers can be divided into two large groups: inert and fibrogeneic.

'Cushions or Oysters'

Inert fillers are the equivalent of stuffing a *cushion* with feathers. Fibrogeneic fillers are the equivalent of putting a grain of sand into an *oyster*, and the oyster then makes a pearl. With inert fillers, the filling effect is proportional to the amount of filler substance introduced. With fibrogeneic fillers, the filling effect is proportional to the intended foreign body granuloma reaction of the host.

The inert fillers are biodegradable. They mostly have the advantage of a high safety profile and the advantage that if a problem arises after injection (e.g. an inflammatory nodule or if the patient is dissatisfied with the result), the filler will eventually resorb and the problem will resolve. They have the commensurate disadvantage of a temporary result.

The fibrogeneic fillers, on the other hand, mostly have the advantage of long durability but carry a greater risk of long-lasting problems, such as granulomatous inflammatory nodules and the problem that misplaced injections will not disappear effortlessly in 6–12 months.

In the past, the longevity of most inert biodegradable fillers was very short (a few months), and therefore some preferred the more permanent fibrogeneic fillers (Vert 2009). Nowadays, some biodegradable fillers have enhanced longevity and remain 12–18 months in the tissues, providing a longer term result. The need for permanent fillers, with their attendant risks of permanent problems, has thus gradually lessened (Wang et al. 2007). Also faces change with ageing. What is a good result in a young person may look strange in an older face: lips that stay large, whilst the rest of the face becomes smaller due to the volume loss of ageing.

With inert fillers the result of the injection is immediately apparent so there is seldom a need for a 'touch-up' visit. Inert fillers seldom stimulate a host reaction, so unwanted granulomas are rare with inert fillers (unless they become microbiologically contaminated). The archetypal inert filler is HA. HA has the added advantage of being easily available, dissolvable with hyaluronidase and not excessively expensive.

Inert Fillers

Most of the filling effect of inert fillers stems from the volume of gel injected.

Autologous Fat: The Ideal Filler

The patient's own fat is, in many ways, the ideal filler. Transient fat has the advantage of tissue compatibility and durability, often lasting many years (Fig. 119.4).

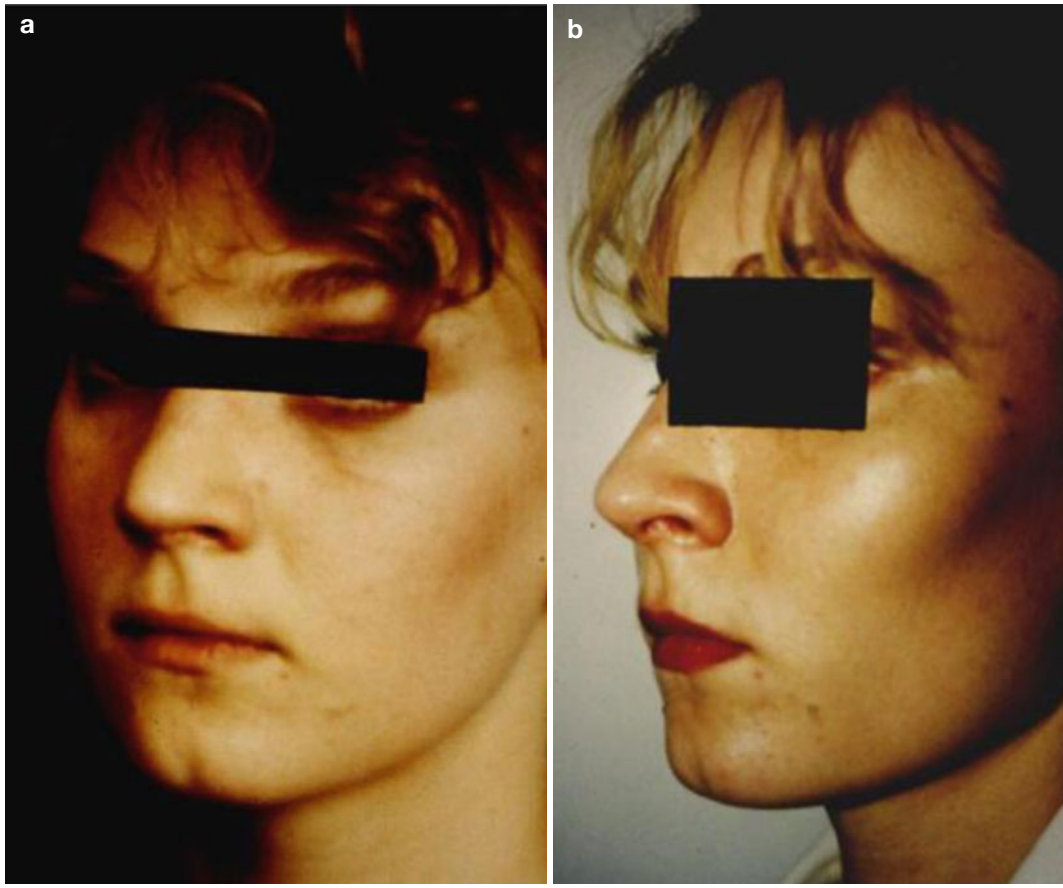

Fig. 119.4 (**a**) Syringe lipotransfer. After 4 treatment sessions at three monthly intervals. (**b**) Syringe lipotransfer. Same patient, 15 years later (Courtesy of Dr P Fournier)

When fat is harvested with minimal trauma and handled gently and correctly, 30–70 % of the volume injected will remain long term. Therefore the injection process should be regarded as a two- or three-stage procedure, aiming for a small overcorrection at the initial treatment and, 2–3 months later, a second injection with perhaps a third a few months later. Even after that, fine-tuning with HA filler may be helpful. Many patients have faces which would benefit from enhanced volume. Sometimes they also have unwanted, diet-resistant fat pads at love handles or buttocks. This is particularly the case in obese patients who deliberately follow a weight-reducing diet: the fat is lost from the face but not from these diet-resistant fat pads. These fat pads make an ideal donor site for lipotransfer. Thin patients are unsuitable as they may have insufficient donor fat.

The processes of harvesting, washing and preparation of the fat, prior to its injection, take time and require aseptic technique. Harvesting and injection require a needle or cannula of at least 14 g diameter. Using narrower gauge instruments results in adipocyte cell wall rupture with a reduction in graft survival rates. Harvested fat may be implanted either immediately or stored in a deep freeze for later use. Ecchymosis may occur at donor or recipient sites.

Fat is best suited to a fuller face in a patient who has lost substantial amounts of weight and where several ml of filler are required. If HA was used, these volumes would be excessively expensive to repeat on an annual basis.

Hyaluronic Acid (HA)

Non-animal-derived HA fillers have come to dominate tissue augmentation. With their longer duration of action and low immunogenicity, HA, presented in a homogenous gel, has become the gold standard for soft tissue augmentation worldwide.

HA is a linear polysaccharide composed of disaccharide units (glucuronic acid and n-acetylglucosamine) which are linked together by β 1-4 glycosidic bonds forming a polymer. HA is present in the tissues of all vertebrate animals. In the skin, it is the viscous fluid in which the collagen fibres, elastic fibres and other intercellular structures are embedded. HA binds water into the tissues. Unlike collagen, its chemical structure is not specific to any particular organism; it is identical in all species. Therefore, in its pure form, it is not immunogenic. With ageing, the amount of HA in the skin decreases, which results in reduced volume and reduced intradermal hydration.

When injected into the skin, native HA will stay for only 1–2 days, making it a poor candidate for tissue augmentation. To improve the longevity of HA in the skin, cross-linking of the HA molecules was developed in the 1980s. In this process, a chemical binds single HA into large macromolecules. This makes the HA more resistant to degradation, thereby increasing its durability after injection. The first cross-linked HA preparation that was widely used for tissue augmentation was Hylaform®. This was produced from cocks' combs; it was cross-linked with divinyl sulfone. As it lasted only 3 months in the tissue after injection, it lost much of its initial appeal. The most commonly used cross-linking agent nowadays is 1, 4 butane-diol-diglycidyl ether (BDDE) (Edsman et al. 2012).

The first HA product to receive FDA approval was Restylane® (December 2003). Its results last 6–18 months. It is produced by bacterial fermentation followed by cross-linking with BDDE. Restylane® products differ according to the size of the HA particles and the number of gel particles per ml. The product with the highest number and the smallest size of particles is the least viscous product of all and is designed to correct fine lines and superficial, easily distensible defects by injection into the dermis. The product with the least number and largest size of particles is the most viscous and is designed to correct deep folds or wrinkles by injection into the subcutis.

Juvederm® is another widely used HA filler that was approved in Europe in 2001 and received FDA approval in 2006. This filler, like Restylane®, is also produced by bacterial fermentation and cross-linked by BDDE. Although many different Juvederm® products are available, all are composed of a homogeneous gel with 24 mg HA per ml. The products differ by their degree of cross-linking. The greater the cross-linking, the more viscous the product and the more deeply it should be injected. Thus, the denser product is more suitable for deeper wrinkles and folds, and the less viscous, less cross-linked product is more suitable for more superficial wrinkles.

Many other products containing HA are available in various parts of the world, such as Teosyal®, Surgiderm®, Emervel® and many others. Most HA products have a good safety profile, good viscoelastic properties and good durability in the tissue.

After injection of HA into the tissues, the process of degradation or breakdown of the polymer begins. This process includes glycosidic bond cleavage, dissociation of the chains, enzymatic degradation by hyaluronidases and free radical degradation (De Boulle 2004)

Injectable Collagens

Collagens are proteins that form the bulk of the extracellular matrix and comprise 80 % of the dry weight of the dermis of the human skin. The physiological role of collagen fibres in the skin is

to provide the tensile properties of the skin. With ageing, the amount of collagen in the dermis decreases. This contributes to the development of wrinkles.

The first biodegradable soft tissue filler was bovine collagen. It was introduced in 1951 and was the first soft tissue filler to receive FDA approval in 1981 (Zyderm I®, followed by Zyderm II® and Zyplast®). Bovine collagen was the most popular US filler until 2003, when Restylane®, an injectable HA filler, also received FDA approval. Bovine collagen is not used any more as it had a very short longevity (3–6 months) and a high level of immunogenicity. Sensitivity to bovine collagen affected 3 % of patients, and a skin test was needed prior to treatment.

Some human collagen products that were less immunogenic were produced from cadaver skin (Alloderm®, Cymetra®, Cosmoderm®, Cosmoplast®, Dermalogen®), but, owing to insufficient longevity, none is currently used anymore.

Another collagen filler was produced from porcine collagen, Evolence. Even though the allergenic part of the collagen (telopeptide) was removed, cross-linking was performed using the non-toxic sugar ribose, and its longevity was improved (12–18 months). It has now been withdrawn (for unclear reasons) from the market (Christensen 2007).

Fibrogeneic Fillers

Subcision

Subcision induces a natural filler reaction. Subcision is the act of using the bevel of a needle to divide the skin or deeper tissues in a plane parallel to the skin surface (Orentrich et al. 1995). Into the space created by the subcision, blood and serous exudate seep. Wound healing eventuates in fibroblast proliferation and collagen neogenesis, i.e. the formation of natural filler substance. Usually a yellow 30 gauge needle is used (Fig. 119.5).

Chicken pox scars and rolling acne scars are particularly well suited to treatment by subcision, and best results are achieved over two or three sessions. Two subcision treatments will achieve a two-thirds improvement in the depth of a typical facial chicken pox scar. If the chicken pox scar has an alabaster white colour, the whiteness can be improved by additional perpendicular needling. Intradermal subcision can also be used to treat fine early rhitids. Hypodermal or deeper subcision can be useful for more established rhitids.

Subcision is very easy, quick and inexpensive. It has the disadvantage of necessarily and unavoidably causing small ecchymoses. In the

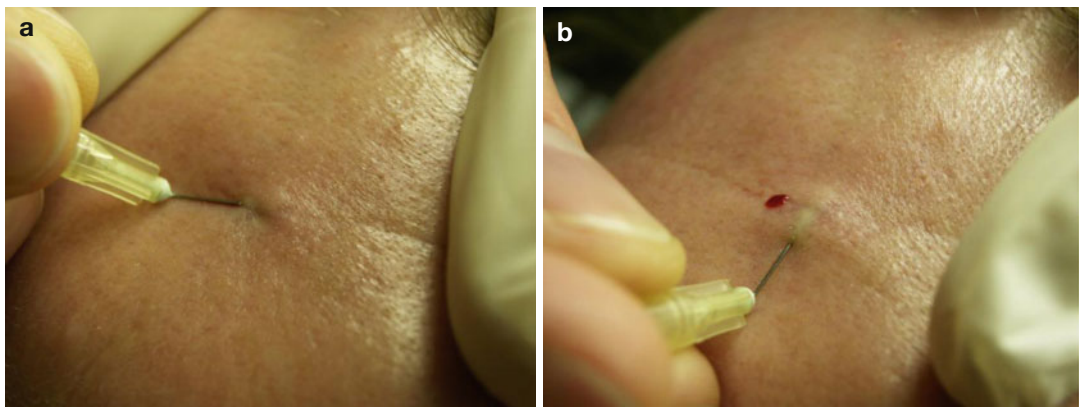

Fig. 119.5 (**a**, **b**) A chicken pox scar being treated by subcision (Courtesy of Dr C Rowland Payne)

case of intradermal subcision on the face, these bruises last up to 4 days. The alternative of treating such lesions with SMDS avoids this inconvenient ecchymotic phase.

Deep nasolabial rhitids can be helped by deep subcutaneous filler injection followed by adjuvant subcision in the same layer.

Silicone: The Queen of Fillers

Liquid silicone is the most controversial of the permanent soft tissue fillers. Its advocates are adamant that when used correctly it is extremely safe and effective. Its adversaries point out that silicone has on occasions been associated with massive, deforming and sometimes unresolvable inflammatory nodules (granulomas), sometimes developing even many years after injection (Christensen 2009, Dayan et al. 2011).

Liquid silicone is a synthetic polymer of dimethylsiloxane. Its viscosity is a function of its polymerisation and is measured in centistokes. Silicone has a product licence for long-term replacement of the vitreous humour extracted during vitreoretinal surgery. The most suitable for use as a filler is 100 % silicone oil (1,000 centistokes) injected into the deeper dermis and/or subcutis. Silicone elicits an intended fibrosis-granuloma tissue response with new collagen formatting around the injected silicone, such that tiny collagen pearls develop around each microdroplet.

Injecting silicone into the skin is like putting a grain of sand into an oyster, and the oyster makes a pearl. Injection of a tiny drop of silicone into the skin and the body will coat it with a layer of fibrosis or foreign body granuloma. These 'silicone pearls' offer possibilities for greater precision. To achieve the desired result, a series of at least four or five sessions of injections, at 4–6 week intervals, are needed – serial microdroplet silicone (SMDS) (Fig. 119.6).

In SMDS, microdroplets of silicone, 0.005–0.01 ml, are injected at 1–2 mm intervals along the length of a rhitid. Each tiny injection is made in the deep dermis or at the dermosubcutaneous border.

Silicone can reach parts that other fillers cannot reach. SMDS can do things that HA cannot do.

HA cannot easily correct deep V notch rhitids. When HA fillers are used to attempt to treat deep V notch rhitids, for example, at the angles of the mouth, the HA cannot be introduced in a sufficient amount at the very bottom of a deep V notch. The HA either passes deep, lifting proud the whole V notch, or it passes to one side of the V, resulting in a bulging V, i.e. a γ shape. On the

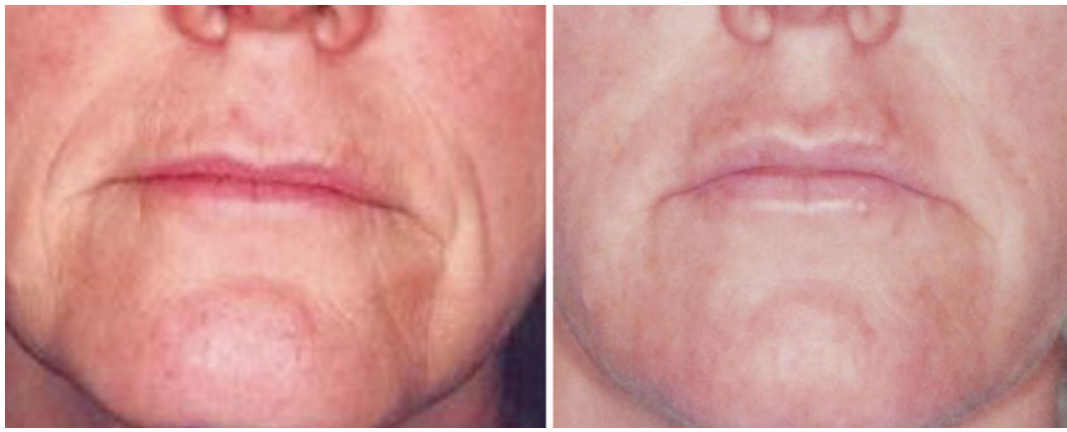

Fig. 119.6 (**a**) Perioral rhitids. Before treatment. (**b**) Perioral rhitids. Twelve months after ten treatment sessions of serial microdroplet silicone (SMDS) (Courtesy of Dr D Orentreich)

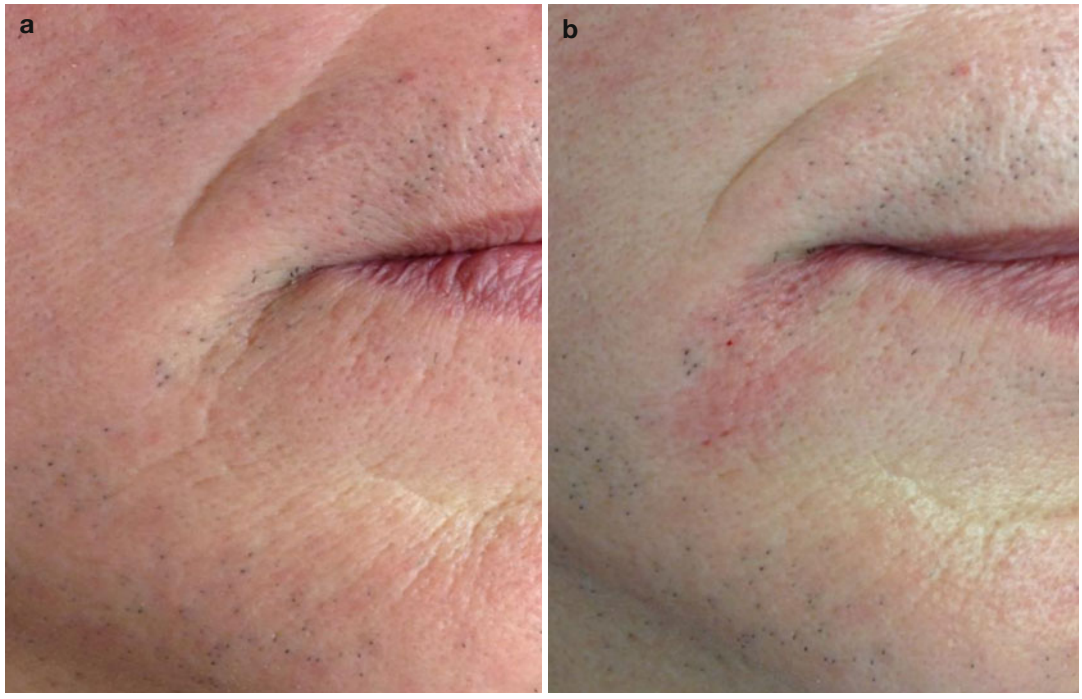

Fig. 119.7 (**a**) Deep V notch angular marionette lines in a man. Before treatment. (**b**) Deep V notch angular marionette lines in a man. After microdroplet silicone (Courtesy of Dr C Rowland Payne)

other hand, microdroplets of silicone can be seeded precisely at the bottom of a V notch rhitid. Over 4–6 weeks, the silicone will become coated by a host fibrotic reaction which will serve to blunt the bottom of the V and lift it. SMDS, repeated at monthly intervals, will go further towards effacing deep V notch rhitids than will any other filler. SMDS can achieve excellent results in these V notch rhitids at the angles of the mouth (Fig. 119.7).

HA cannot lift depressed scars like chicken pox scars. Silicone can. To do this, tiny microdroplets of silicone are serially injected into the scar. These stimulate the host tissue response which gradually, over the ensuing weeks, lifts the scar. Because of the densely fibrotic nature of the scar tissue, it is not physically possible to inject sufficient volume of an inert filler, such as HA, into a bound down scar to achieve the same effect. Worse still, the HA may enter the neighbouring skin, so potentially aggravating the 'sofa button' appearance of the scar. SMDS can lift depressed scars.

HA is short-lived. Silicone is long lasting. This is a clear advantage, but it also means that silicone is unforgiving and imperfect results, for whatever reason, will also be long-lasting. Correct injection technique is critical. It avoids 'silicone lakes' (injection of droplets that are too large) and 'beading' (the formation of palpable lumps just under the skin due to too superficial an injection). Silicone fills by inducing an intended fibrosis-granuloma host response. Since there is variability of intensity of fibrosis-granuloma response between different people and even variability within the same person over time, great care is needed to avoid overcorrection – hence the use of four or five injection sessions, SMDS. When silicone is administered as SMDS, adverse reactions are very rare (Lemperle 2009). Occasionally, unexpectedly severe granulomatous reactions occur (in perhaps 1 in 1,000 patients), even in very experienced hands using the right technique. In the hands of an inexperienced practitioner, the frequency of such events is probably higher. These reactions may even

happen many years after injection of silicone and without any obvious precipitating event (e.g. infection). At least some of these late cases may be due to the unrelated coincidental later development of sarcoidosis, since a feature of sarcoidosis is that foreign body silica granulomas and old scars may become affected by sarcoidal granulomas (Rowland Payne et al. 1983). Such reactions can be treated by serial intralesional steroid (SILS).

Calcium Hydroxylapatite (Radiesse®)

Radiesse® is a biodegradable fibrogeneic filler composed of 30 % microspheres of calcium hydroxylapatite (CHA) particles suspended in a carboxymethylcellulose gel carrier. After injection, the carrier gel is gradually absorbed by macrophage phagocytosis, and a local fibroblastic response develops around the CHA particles. These particles are gradually degraded after 12–24 months, which is the duration of action of this filler. As a more viscous filler, it is especially suitable for the deeper folds or for facial volume replacement and should be injected into the deeper subcutaneous tissue. For the same reason, it is not suitable for lip augmentation or for areas with a lot of movement and thin skin, as it may become palpable or visible in these areas. With the right injection technique, this filler has an excellent safety profile (Christensen 2009).

The *combination gels* contain microparticles (e.g. calcium hydroxyl apatite or poly-L-lactic acid) that are dissolved in a short-lived transient biodegradable carrier gel. The filling effect of these gels relies initially on the carrier gel and later on the host tissue foreign body response. The carrier gel disappears slowly (months to years after injection depending on the filler), and at the same time the host response to the remaining microparticles gradually creates its own filling effect. This host foreign body response eventuates in permanent fibrous tissue formation. As the host response continues to develop due to continuous gradual product degradation, there is a higher incidence of late granulomatous reactions (Christensen 2007).

Poly-L-Lactic Acid (PLLA) (Sculptra®)

Poly-L-lactic acid (PLLA) (Sculptra®) is considered a slowly biodegradable filler (or semi-permanent filler), as it may take up to 40 months or even longer to degrade. It works by stimulating the production of new connective tissue. In due course, the PLLA slowly breaks down to carbon dioxide and glucose. It is mainly suitable for facial volume replacement. PLLA was approved in Europe as New-Fill in 1999 and was the first filler to be used as a volumizer. Even though its clinical results were quite satisfying, about 10 % of the patients developed subcutaneous papules and nodules. Also, the product information used to state erroneously that it should be injected intradermally. Consequently, it lost popularity and was then taken off the European market (Christensen 2009). In spite of this, in 2004 the FDA approved it for the treatment of lipoatrophy in HIV patients and in 2009 for aesthetic use as Sculptra. Compared with New-Fill, Sculptra has a similar molecular composition but a larger particle size and is reconstituted using a larger volume (8–9 ml water instead of 5–6 ml in the past). With the larger particles and this higher dilution, the papule and nodule ratio is now between 0 % and 13 % according to different publications. Some clinicians state that the high rate of complications was due to wrong dilution, incorrect injection technique, incorrect injection volume or inappropriate sites of injection. Apparently, by using large dilution volumes, by preparing the mixture 12–24 h before treatment and by injection in the subcutaneous plane, the risk of complications is relatively low (Dayan et al. 2011).

Polymethylmetacrylate (Artefill® and Artecoll®)

Artefill® is composed of 20 % homogenous polymethylmetacrylate (PMMA) microspheres evenly suspended in 3.5 % bovine collagen and 0.3 % lidocaine (Lemperle et al. 2003). It was available in Europe from 1994 as Artecoll. In 2006 it was taken off of the market due to the high incidence (2.5 %) of treatment-resistant

granulomas. Interestingly, in the same year, Artefill which is a smoother product, with its negative charge removed, was approved in the USA. After this improvement in the product, the incidence of granulomas dropped from 2.5 % to 0.1 %. Nevertheless, Artefill granulomas may arise even 10 years or more after treatment and are mostly resistant to therapy. The newer HA products with their improved longevity and excellent safety record make Artefill, with its attendant risk of treatment-resistant granulomas, obsolete (Park et al. 2012).

Polyacrylamide Gels

Aquamid® is composed of 2.5 % polyacrylamide gel in water. Bio-Alcamid® is composed of 4 % cross-linked polyacrylamide with polyalkylimide. These two gels are very slowly resorbed by the body over many years. They either dissipate (like Aquamid®) or are kept in place (like Bio-Alcamid®) by a fibrous capsule. When injected in large quantities, these gels have a relatively high incidence of complications. Their use is obsolete (Christensen 2009; Dayan et al. 2011).

Filler Selection

Which Filler for Which Indication?

HA is the most widely used filler. Experience is enormous. Its molecular size, its rheological properties and its water holding capacity can be manipulated to tailor it to its various therapeutic indications and to modify its durability. Its adverse effects are well known, well understood and fortunately relatively rare. The existence of hyaluronidase is another factor in favour of HA. HA is usually the filler of choice but not in every case.

For deeper HA injections, such as deep zygomatic region injections, water retention and lack of deformability are advantages. Water retention provides greater volume correction. Lack of deformability means that the position of the filler is less likely to be modified by external forces, such as sleeping on the cheek.

For superficial HA injections, such as infraorbital injections, water retention and stiffness (lack of deformability) are disadvantages. After infraorbital injections, water retention may cause unsightly 'puffiness', and lack of deformability may be regretted if the filler leaves ridges just beneath the surface that are resistant to digital compensation.

Fat is the ideal filler for a fallen or drawn face in a patient who has lost weight but who still has diet-resistant areas of body fat suitable for use as donor material.

SMDS and/or subcision are the only fillers that can treat chicken pox scars and deeper V notch fine-line rhitids, e.g. at the angles of the mouth. SMDS is the ideal filler to treat small-volume lifelong defects, such as post cleft lip surgery. SMDS requires four or five treatment visits, and then the benefits are lifelong without the need for further treatment visits.

Not all fillers are suitable for all indications, and different fillers may be used in the same patient. For example, it may be better not to use the same filler in the cheeks as in the lips or in fine rhitids at the angles of the mouth or in chicken pox scars. In the cheeks, a large particle stiffer HA filler may provide more and longer-lasting volume enhancement. In the lips, a finer particle HA filler with greater deformability may allow more precision of placement and also the use of a finer, and therefore less uncomfortable, needle. At the angles of the mouth and in chicken pox scars, SMDS may be a better choice.

Injection Technique

Needles or Microcannulae

A needle or a cannula may be used to introduce filler. Needles and microcannulae are available in a wide range of gauges. The finest gauges are reserved for needles and the widest for cannulae.

For needles, typically a 30 gauge needle is used. For microcannulae, typically a disposable 27 gauge microcannula of 37 mm length (e.g. Magic Needle) is selected. Most types of HA filler can pass through this very useful instrument.

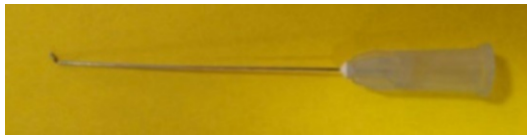

Fig. 119.8 A microcannula, whose tip was bent over by being forcibly advanced against tissue resistance

Microcannulae require a port for entry, which is swiftly made using a needle of a slightly broader gauge.

Advantages of needles include availability, ease and speed of use, lack of dead space, low cost and accuracy of placement of filler.

Advantages of microcannulae include the reduced risk of accidental intra-arterial injection and filler embolisation, and the requirement for fewer cutaneous piercings owing to the length and flexibility of microcannulae, as all parts of the face, is easily attainable through relatively few points of entry. Disadvantages of cannulae include the possibility of a bending over of the tip, if it is forcibly advanced against resistance (Fig. 119.8).

Fine needles and fine microcannulae are probably both capable of inadvertently entering a small artery of the face, and so neither tool is exempt from the risk of filler embolisation, though it is less likely with cannulae.

Level of Filler Implantation

Fillers may be used at any level from intradermal to supraperiosteal.

Superficial injections require smaller volumes, allow greater precision and are well suited to finer work, such as V notch fine lines. They need to be made with greater accuracy.

Deeper injections (and other types of implants) require greater volumes, are more forgiving and are well suited to the treatment of broader contours, such as wide U-shaped trough defects.

Pearls or Threads

Fillers can be injected in pearls or threads.

A pearl may be large or small, e.g. a bolus of 0.1–0.5 ml or a microdroplet of 0.005–0.01 ml.

Bolus injection lends itself to deeper injections. Using a needle or a cannula, a relatively large volume of filler may be introduced relatively swiftly through a single injection point. It has the advantage of minimising the risk of intra-arterial injection by allowing for aspiration prior to injection. Its large volume retains a centre that is relatively far from the microvasculature and therefore the macrophage system, so ensuring enhanced durability of the implant. On the other hand, a lake of filler may migrate more easily than threads of filler which have been interlaced into the recipient tissues, and, if a bolus is microbiologically contaminated, its distance from the blood stream will impair the efforts of host immunity and of antibiotics.

Microdroplet injection lends itself to superficial injections. Using a fine needle, repeated microinjections may be made with great precision. Intradermal and just subdermal microdroplet injections are relatively safe from embolic risks. Microdroplets are of such small volume that, even if injected intra-arterially, they are highly unlikely to cause embolic sequelae. Moreover, the intradermal plane is entirely safe from risk of embolisation as its vessels are of such fine diameter. The subdermal plane is also relatively safe.

Threads may be very fine if a 30 g needle is used or relatively thick, like tagliatelle, if a 14 g needle or cannula is used.

Fine threads are suitable for subdermal injection into the white line roll of the lip. Layered fine threads suit the nasolabial folds.

Tagliatelle-like threads are the ideal form for fat injections. The diameter of the threads should be at least 14 gauge which is wide enough to contain a core of intact, and therefore viable, adipocytes and yet thin enough to allow adequate diffusion of oxygen, nutrients and metabolites to facilitate graft survival until revascularisation has been achieved.

Injection Method: Bolus, in Retrograde or in Antegrade?

Classic teaching advises insertion of a needle, aspiration to check if the tip is not in a vessel and

then a bolus injection which may be a very small dot bolus or a more substantially large bolus.

The aspiration-bolus injection technique comprises injection of the needle into a given site; this is immediately followed by aspiration, to check that the needle tip is not within a vessel; then a bolus of filler is injected. Aspiration-bolus injection avoids retrograde or antegrade injection. It avoids injection from a moving needle tip. The aspiration-bolus needle injection technique may be preferred when injections are made by needle into zones where arteries are plentiful because at these sites there is a greater risk of accidental intra-arterial injection, with its attendant hazards of ischaemic necrosis or distant embolisation. The zones that are rich in blood vessels of sufficiently wide diameter include the subcutaneous and muscle layers (but not the dermal, immediately subdermal or immediately submucosal layers). This is especially so at the glabella, the ala nasi and the modiolaris. These are not the only zones of the face that are at risk of accidental intra-arterial injection. Caution needs to be exercised in all zones.

Retrograde injection is when the needle is first advanced to the farthest part of the injection site and then a threading injection is made in retrograde. This assists the formation of a very evenly formed thread of filler. This is very suitable for the white line of the lips or for injection deep to the eyebrows.

Antegrade injection, by contrast, is when the needle is inserted and then a threading injection is made in antegrade. This helps to push vessels away from the tip of the advancing needle, so minimising bruising. This is very suitable in the tissue of the infraorbital skin where small vessels are plentiful.

Perpendicular or Tangential

The needles through which the filler is injected can pass through the skin perpendicularly or at an angle which is so oblique that it is almost parallel ('tangential') to the surface of the skin.

Perpendicular injection is less uncomfortable and quickly passes deep, eventually, in many places, reaching periosteum. Perpendicular injection can only easily be done by needle, not by cannula. The periosteum is well innervated, and touching it with a needle is therefore somewhat uncomfortable. Touching the periosteum almost always also means touching the bone itself which blunts the needle tip. Thus a new needle is needed for each supraperiosteal injection. The periosteum also has a good blood supply, so the aspiration-bolus technique is needed at this anatomical level.

Tangential injection (whether by needle or cannulae) maintains a relatively superficial plane of implantation carrying with it the commensurate advantages of implants made in the superficial plane.

Pretreatment Considerations

As with all elective procedures, the good physician needs to remember that patient selection, mutual trust and good communication are at the heart of a successful doctor/patient relationship which itself is an important determinant of patient satisfaction with treatment. Verbal exchange and eye contact are essential steps in this process. All of this is much more easily achieved if the initial consultation follows the classical medical model with a clinical history, physical examination, a diagnosis and a discussion with the patient of the treatment options. All the better for the patient and the patient's confidence in you if your consultation reveals other matters of a non-cosmetic nature that you can help with. If there is depression or anxiety, these are best treated before filler treatment is undertaken.

During the preoperative consultation, the patient will usually indicate which area of their face they wish to have improved. The patient should be observed at rest and in animation. Before treatment, it is helpful to demonstrate in a hand mirror to the patient any facial asymmetries. Often patients are entirely unaware of quite major facial asymmetries.

It is very important for the patient to have realistic expectations of the treatment. Using the mirror, the physician discusses the face with the patient before treatment, so that the patient understands what can and what *cannot*

be corrected by fillers. Patients with severe photo-ageing and disseminated wrinkles are not such good candidates for fillers and may be better treated in other ways, e.g. ablative resurfacing by a deep chemical peel (Verner 2014). Patients with wrinkles that are caused by excessive muscular movement (e.g. deep glabellar furrows) will only achieve a transient improvement from the injection of a filler, unless the muscles that cause the wrinkling are also relaxed by botulinum.

Once the choice of treatment has been decided upon, the patient needs to give verbal and possibly written informed consent. Patient advice sheets may be useful. The more that can be explained to a patient preoperatively about what they can expect, the less that needs to be explained postoperatively.

Preoperative explanation is '*knowledge*'. *Postoperative explanation is an* '*excuse*'.

Attention to all of these steps increases patient confidence. The patient who is confident and positive in their approach to treatment will find the experience of the treatment session easier and often less uncomfortable than the patient who is more diffident or doubtful. A patient who has confidence in the doctor is more likely to tolerate well any minor inconveniences of the treatment, such as small bruising.

Pretreatment Preparation

To minimise bruising, patients are asked to avoid aspirin and other nonsteroidal anti-inflammatories for 14 days preoperatively. For 2 days before treatment, patients may also avoid ginkgo, vitamin C, vitamin E and supplements of fish oil or garlic (cooked garlic in food need not be avoided). If pain relief is needed during 14 days prior to treatment, patients are asked to use only paracetamol or codeine or co-codamol 30/500 (which is a combination of both paracetamol 500 mg and codeine 30 mg).

It is very helpful to have an assistant who can exert pressure as soon as any bleeding is observed and who can also make detailed contemporaneous notes.

Analgesia

A relaxed, unhurried and trusting patient will tolerate filler treatment well. Topical anaesthetic, such as EMLA, is applied when the patient arrives in the waiting room and then again 2–5 min before treatment. During treatment, the patient should be kept at their ease by talking. Vocal anaesthesia, especially if it is the patient who is talking, will help. Oral anaesthesia is usually not required but, if it is, co-codamol 1–2 tablets 1.5 hours before treatment is helpful (patients should be advised to avoid driving for a few hours after the first time of taking codeine as it makes some patients drowsy or nauseous). Anxious patients may also benefit from diazepam 5–10 mg 1.5 hours before treatment.

Discomfort and the risk of bruising are also related to the number of injections, the depth of the injections, the angle of the injections and the sharpness of the needle. To avoid the increased discomfort that would come from using a dulled needle, no one needle should make too many injections.

Injection Technique for Specific Facial Anatomical Sites

The facial region offers many opportunities for filler treatment.

Nasolabial filler treats nasolabial rhitids. Nasolabial fillers can be introduced in the deep dermis, at the dermosubcutaneous junction or in the upper subcutis. The latter is particularly useful for 'U'-shaped rhitids. It is a good site to gain experience.

The Paris lip is the standard filling technique around the mouth. As lips age, full lips with a smooth vermillion surface and a well-defined vermillion border gradually become less full, their surface becomes cross-hatched, and radial rhitids begin to traverse the vermillion border into which the lipstick 'bleeds'. Thinning of the lips, cross-hatching of the surface, lipstick 'bleeding' and radial rhitids can all be corrected by fillers. Radial rhitids at the lip are usually best filled not by direct injection into the rhitids but by

injection perpendicular to the rhitids running parallel to the vermillion border either inside the white line roll of the lip or within the pulp of the vermillion. Filler is introduced into the anatomical potential tunnel which lies beneath the white line (the border between vermillion and glabrous lip) (Fig. 119.9).

A refinement of this technique includes a threading intradermal injection into the philtrum. An excellent indication for the Paris lip is radial 'bleeding' of lipstick. Patient anxiety is greater with injection in the lips than at any other site. Many fear the 'trout pout'. Any injections made at this site will be scrutinised particularly closely by the patient. The Paris lip should not be the first filler injection made by a tyro.

The Mona Lisa smile (Rowland Payne 2003) lifts the angle of the mouth. A point is chosen on the white line of the *upper* lip 3 mm superomedial to the existing angle of the mouth. The needle is inserted at this point into the white line space and passed inferolaterally towards the angle of the mouth and on along 0.5 cm, still in the white line space of the lateral part of the *lower* lip. Filler is injected in retrograde. To further enhance the effect, a little extra filler is injected into the body of the vermillion part of the lower lip, just medial to the angle of the mouth. Downturning of the angle of the mouth can be corrected in this way (Fig. 119.10).

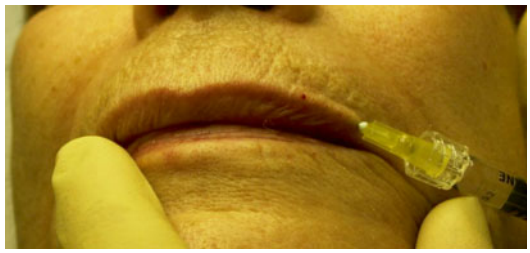

Fig. 119.9 The white line of the lip being injected by HA (Courtesy of Dr C Rowland Payne)

Wet line injection produces a fuller lip. Wet line injection increases the visible vermillion, 'the kissable surface'. The wet line of the lip is where the vermillion changes from mucous membrane to stratified epithelium. The wet line injection is made deep to the wet line. If HA is used, the injection is a threading injection along the length of the lip. If SMDS is used, it is as microdroplets. Either way, the filler is deposited deeply in the lip, ¼–½ cm deep to the wet line.

Submucosal lip injection displaces the lip anteriorly. Microdroplets of HA filler are introduced just submucosally opposite the teeth. Threading submucosal injections carry a high risk of ecchymosis, and so pinpoint submucosal microdroplets of HA are best. The lips drape over the teeth. As the lips involute and become thinner, the skin of the lips lies in closer relation to the teeth themselves. Any dental asymmetry results in lip asymmetry which becomes more obvious with age. Asymmetrical submucosal injection can compensate for dental asymmetry, a common problem in the middle aged British mouth. Submucosal injection opposite the upper

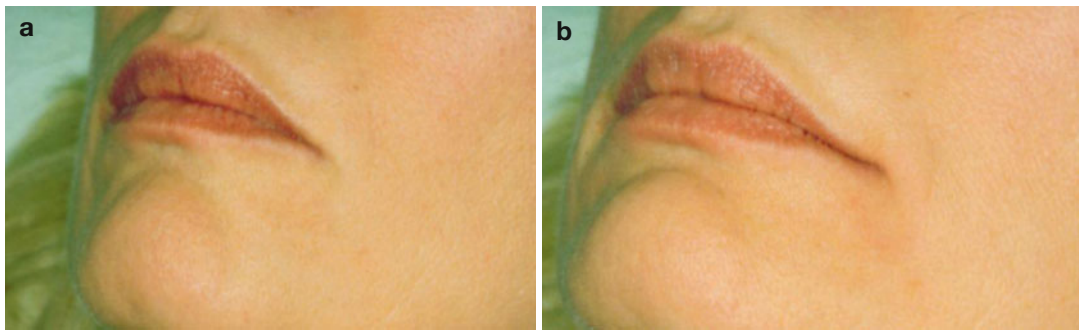

Fig. 119.10 (**a**) The Mona Lisa smile. Before HA treatment. (**b**) The Mona Lisa smile. After HA treatment (Courtesy of Dr C Rowland Payne. Reproduced from Shai A, Maibach HL, Baran R. Handbook of cosmetic skin care. 2nd ed. p. 195, with permission of the publishers)

dentogingival line can also be used to offset maxillary bone resorption. Submucosal injection behind the lateral parts of the lower lip improves the shadowing that occurs inferolateral to the angles of the mouth. Prognathism can be treated by mandibular surgery, but it can also be disguised by submucous filler injections in the *upper* lip (Fig. 119.3).

Marionette line injections help efface shadowing inferolateral to the angles of the mouth. They also improve the rhitids that run out inferolaterally from the angles of the mouth. When the rhitids are U shaped, they can be filled directly by a threading injection of HA, best made with a cannula inserted at their inferolateral end. If there is notable shadowing at their superomedial end, i.e. at the angle of the mouth, some HA is also implanted perpendicularly into the body of the glabrous part of the lower lip, just inferolateral to the angle of the mouth. This inferolateral injection can be made subdermally, subcutaneously or submucosally or all three. At this site the arterial supply is rich and tortuous providing a theoretically enhanced risk of accidental intra-arterial injection during subcutaneous injection. For subcutaneous injection at this site, the aspiration-bolus technique is therefore advised. Fine deep V notch angular marionette rhitids are very common in men. They are not easily amenable to HA. SMDS offers precision of filler placement precisely into the bottom of these V notches (Fig. 119.7).

The tribolus technique provides anterior projection to the medial cheek (Carey 2012). Two perpendicular aspiration-bolus injections are made in the upper medial cheek. To avoid the neurovascular bundle that exits the maxillary foramen, one is made just medial and the other just lateral to the midpupillary line. The third injection is made paranasally, 1–2 cm inferior to the upper medial injection.

Zygomatic injection improves anterolateral projection of the zygomatic part of the cheek which serves also to improve nasolabial folds and jowls. It can be achieved by aspiration-bolus injection or by cross threads introduced by microcannulae.

Ala nasi injection restores support for the inferior part of the nose. Imagine a person lying on their back, the nose is the 'tent pole' of the supine face, not only holding up the nose itself but also supporting the neighbouring structures. In a person standing erect, this 'tent pole' provides anterior projection not only for the nose itself but also for the ala nasi fossa and the superior part of the nasolabial groove as well as the cheeks as far laterally as the pupillary line and as far superiorly as the tear trough. All this is evident if a small amount of HA (0.05–0.1 ml each side) is injected deep to the ala nasi. In the ala nasi injection, the needle enters the skin 0.5 cm inferior to the ala nasi running in a slightly superior direction to reach a point lying deep (i.e. posterior) to the ala cartilage. Using the aspiration-bolus technique, 0.05–1 mm of HA is implanted. The technique is repeated on the contralateral side. With the ala nasi injection, aspiration should always be performed before injection to avoid compression of the angular artery. If, instead of this anterior approach, a lateral approach is used, the risk of intra-arterial injection is greater as this is where the tortuous facial artery runs, just before it splits into the lateral nasal artery and the terminal branch of the facial artery itself, known as the angular artery.

Medical rhinoplasty can supplant the need for aesthetic surgical rhinoplasty. The bridge, the dorsum and the tip can be filled, usually using HA (Fig. 119.2). The tip can be lifted by a filler injection in the columella. A point is selected two-thirds of the distance from the nasolabial angle to the tip of the nose. Pointing tipward, the needle is inserted almost parallel to the surface of the skin; HA 0.05–0.1 ml is injected in antegrade which serves to lift the tip of the nose (Fig. 119.11a, b).

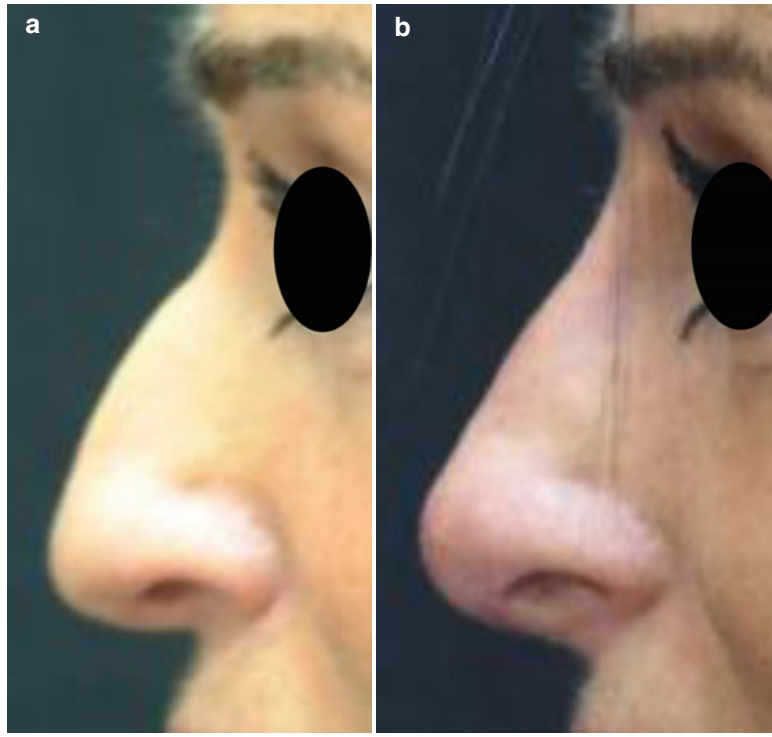

Fig. 119.11 (**a**) Medical rhinoplasty. Before filler treatment. (**b**) Medical rhinoplasty. After filler has been implanted at the bridge of the nose and at the nasal tip (Courtesy of Dr J-P Amsellem)

Temporal injection fills the temporal fossa. The convex temporal fullness of youth imperceptibly gives way to a concave temporal skeletalization that characterises old age. The point of maximum hollowness at the temple is selected. A perpendicular 'pistol shot' injection is made. The periosteum is reached. Using the aspiration-bolus technique, 0.2–0.5 ml is injected slowly.

The eyebrow injection raises the eyebrow 1–2 mm and so also raises the upper lid fold. If a cushion is put behind a curtain, the bottom of the curtain rises (i.e. the distance between the bottom of the curtain and the floor increases). The eyebrow injection is made deep to the eyebrow. If HA is used, the injection is a threading injection along the length of the eyebrow. The filler is deposited either just subdermally or on the periosteum. Between the two planes there are many vessels and nerves. If SMDS is used, the microdroplets are best placed subdermally or within the layer of the subcutaneous tissue where the roots of the eyebrow hairs lie. The eyebrow lift is much appreciated by the patient who will notice an opening of the orbit and hence a brightening of the face. After this injection there may be a temporary post-injection oedema.

Ear lobe injections reflate the ear lobes and efface ear lobe rhitids.

Prejowl bolus injection masks the mandibular line (Verner and Rowland Payne 2009).

Retromandibular injection (Rowland Payne) helps improve jowls by drawing them back posteriorly which also improves the prejowl

sulcus somewhat. By aspiration-bolus technique, 0.2–0.5 ml HA is placed on the periosteum of the posteroinferior aspect of each mandibular ramus.

Injection Technique for Full Face Treatment

In any particular patient, any or all above site specific techniques can be employed piecemeal, according to aesthetic good taste. Alternatively, a more global approach may be employed alone or in combination with the site specific technique.

Lipostructure. Coleman (2006) developed the principle originally espoused by Fournier (1986), in which tagliatelle-like threads of fat are intricately transplanted all over the face to restore the smooth and softly rounded curves of youth. This is a major procedure usually performed under general anaesthetic.

SoftLift. Luigi Polla's SoftLift (Fig. 119.12) employs the principles of Coleman's lipostructure technique in an ambulant outpatient procedure that is virtually painless. A microcannula delivers superficial subcutaneous retrograde threading injections of HA. These radiate out, like the spokes of a wheel, from each skin puncture in a clock face fashion: 1 o'clock, 2 o'clock, 3 o'clock, etc. Multiple puncture points enable the threads to cross-cross one another to produce a very even and smooth result.

Extrafacial Uses for Filler

Other non-facial sites can be treated by filler, including the hands, breasts and external and internal genitalia. Filler can also be used in the feet to treat corns and metatarsalgia.

Complications

Filler-Induced Arterial Occlusion

In the absence of a sufficient collateral circulation, intra-arterial injection of filler will result in distal ischaemia. The first sign is an immediate and transient greyish discolouration, often accompanied or followed by pain. Some minutes later, there may be a phase of reactive hyperaemia. A couple of hours later, reticulate livedo supervenes (Fig. 119.13). If the collateral circulation has not taken over, next comes scattered pustules followed by an eschar and/or ischaemic ulceration and later cicatrisation (Lazzeri et al. 2012). Vulnerable sites on the face include the glabella and the ala nasi.

Ala nasi or nasal tip necrosis may be caused by vascular embolization into the lateral nasal artery, which is a branch of the angular artery. This complication has also been reported after injection into the upper nasolabial area (Kang et al. 2011). Patients after nasal surgery have a higher risk of this complication due to their

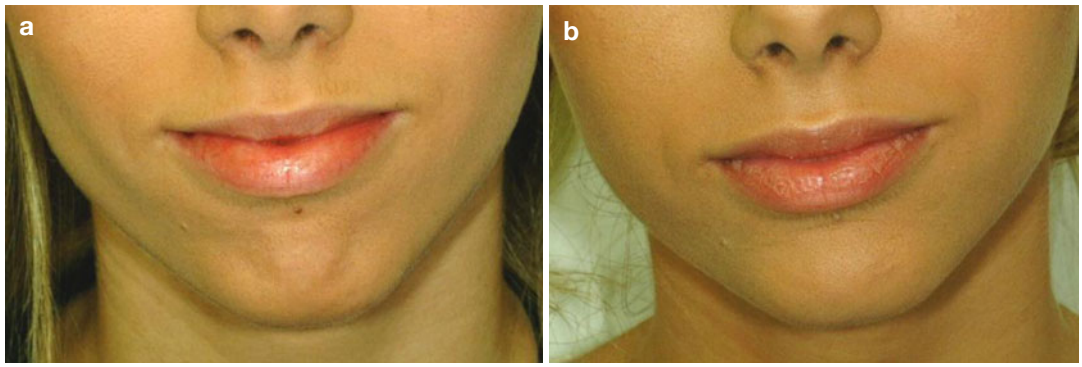

Fig. 119.12 (**a**) SoftLift. Before filler treatment. (**b**) SoftLift. After filler treatment (Courtesy of Dr L Polla)

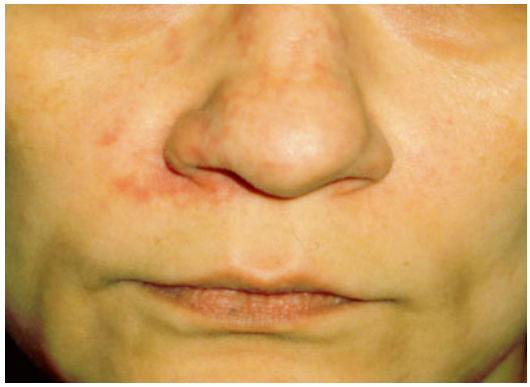

Fig. 119.13 Filler-induced occlusion of the facial artery at the ala nasi fossa. This reticulate livedo resolved spontaneously over the next week

compromised blood supply (Grunebaum 2009). Injection of hyaluronidase (in the case of HA injection) as soon as possible after the filler injection is the first treatment whether the HA is believed to be intra- or peri-arterial. Attempts should also be made to increase blood flow to the area to assist the collateral circulation both physically and pharmacologically. Physical methods include warm/hot compresses and massaging or tapping the affected area. Pharmacological methods include application of nitroglycerine ointment and oral glyceryl trinitrate spray. An oxygen mask may be helpful. In severe cases, hyperbaric oxygen therapy may be considered. Some authors also advise aspirin and/or low-molecular-weight heparin.

Filler-Induced Pulmonary Embolism

Barlow's group have had one death from fat embolisation after lipotransfer (Gleeson et al. 2011).

Ocular Embolisation

A particularly feared complication of filler treatment is embolisation of the retinal artery or one of its branches with consequent retinal ischaemia. Like the brain's circle of Willis, the face has a circular network of arteries that are in direct communication with one another and through which blood can flow in either direction. The major phylogenetic advantage of these circular networks is that blockage at any particular point is not disastrous, as the direction of blood flow in the residual network has the capacity to reverse. Consequently ischaemic necrosis of that part of the brain or face is avoided. Unfortunately, the corollary of this safety system is that filler injected inadvertently intra-arterially may travel, by retrograde flow, from any of the smaller arteries of the face into the arteries of the facial circle and thence into the central retinal artery before the embolus lodges in the retinal circulation resulting in ischaemic damage to that part of the retina with consequent loss of that part of the visual field of that eye.

To help protect against this possibility, cannulae are preferred, which are practical over needles; where possible, the syringe should be aspirated before injection; injection pressure should be as low as possible; injections should be performed slowly; volumes used should be as small as possible, and the patient's eyes are usually best kept open during injections. Retrograde and antegrade threading injections by needle are best avoided in the danger zones. These zones include the subcutaneous and muscle layers (but not the dermal, immediately subdermal or immediately submucosal layers), especially at the glabella, the ala nasi and the modiolaris. These parts of the face carry a greater risk, but no part of the face can be regarded as truly exempt of this risk.

Fortunately this complication is extremely rare. Between six and 40 cases of partial or complete loss of sight in one eye are believed to have occurred worldwide over about 10 years. In that time, approximately about 20–40 million filler treatments have been performed. It is deduced that the risk of ocular embolisation is of the order of one in a million.

If ocular embolisation does occur, attempts should be made to help shift the embolus more distally, so reducing the ultimate size of the field of ischaemia and the consequent size of the area of visual impairment. This is attempted by vasodilatation. Vasodilatation can be induced directly

by pharmacological means. Vasodilatation can be induced indirectly as a consequence of reducing intraocular pressure. Immediate ophthalmological help should also be sought.

Vasodilatation can be induced pharmacologically. This can be achieved by increasing the partial pressure of CO_2 through rebreathing and also by administration of glyceryl trinitrate.

Vasodilatation can be induced by reducing intraocular pressure. This can be achieved by bidigital orbital compression and by acetazolamide.

The role of oxygen is more debatable. Oxygen is a vasoconstrictor, but it is oxygen that the retina needs. Hyperbaric oxygen therapy (HBOT) facilitates increased partial pressure of oxygen, such that not only haemoglobin but also plasma oxygen saturation rises. Oxygen carried by plasma better penetrates marginally perfused areas. The benefits of HBOT may outweigh the unwanted vasoconstrictory effects of oxygen. HBOT can only be regarded as a temporary measure but may provide time for some collateral circulation to take over. Some authors also advise aspirin and/or low-molecular-weight heparin (Box 119.1).

Box 119.1. Emergency Treatment for Filler-Induced Ocular Arterial Embolisation

1. Rebreath into a bag for 20–30 min.
2. Firm and repeated bidigital compression of the eyeball for 20–30 min.
3. Glyceryl trinitrate spray 800 μg sublingually.
4. Acetazolamide 500 mg by mouth.
5. Seek ophthalmological assistance.
6. Consider oxygen mask.
7. Consider hyperbaric oxygen therapy.
8. Consider aspirin.
9. Consider low-molecular-weight heparin.

Fibrosis

Fibrosis is a physiological aspect of wound healing. A filler treatment is, in a certain sense, a wound, and some fibrotic reaction would not therefore be unexpected. Indeed the fibrogeneic fillers, such as silicone, rely upon this tissue response for their therapeutic activity. Nodules may develop due to fibrosis arising from a stimulatory filler as PLLA, CHA or silicone. Fibrosis is very rare after HA injection (Lemperle et al. 2003). Fibrosis responds well to SILS.

Granulomas

Any foreign bodies, and thus all fillers, may sometimes elicit a foreign body reaction in human tissue. In this kind of reaction, macrophages and foreign body giant cells surround the implanted material.

Granulomas mostly have a late onset, are tender and swollen and occasionally may suppurate or ulcerate. It has been proposed that granulomas may occur due to protein impurities in the product, irregularities of filler particle surface or biofilm activation (Hall-Stoodley et al. 2009).

Any filler may induce a granuloma. Indeed, the mode of action of fibrogeneic fillers, such as silicone or polylactic acid, is by deliberate induction of a controlled and limited host fibrosis-granuloma response.

A granuloma is a host tissue response. It is part of the physiological repertoire of the inflammatory reactions of the innate immune system. The capacity to form granulomatous inflammation varies from one individual to another and varies within an individual over time. This is best illustrated in tuberculosis or leprosy. Some patients readily entrap these bacilli in tuberculous granulomas. Other less lucky patients, in the absence of treatment, develop disseminated tuberculosis (‘galloping consumption’) or lepromatous leprosy. Changes in the general health or nutrition of a patient can result in a major modification to their capacity to form granulomas.

Granulomatous inflammation may also occur as a physiological inflammatory response to a foreign body. The intensity of this response may also vary over time. It also varies with disease. For example, longstanding silica foreign body granuloma reactions may later become more

severe if the patient later develops sarcoidosis (Rowland Payne et al. 1983).

In the same way, *unwanted* granulomatous reactions around filler implants may occur 4–6 weeks after injection or at any time, even many years later. At their worst, such granulomas may be complicated by calcification. Factors favouring the development of unwanted filler granulomas can be divided into host-related factors and filler-related factors.

Host-related factors include genetic factors and probably the development of sarcoidosis.

Filler-related factors include the nature of the filler and any microbial contamination. The mechanism of the therapeutic action of fibrogeneic fillers harnesses their capacity to induce fibrosis and granulomas, e.g. silicone. When silicone is used as SMDS, *unwanted* granulomas are most exceptional. If silicone were injected as a bolus (or 'lake') or as a thread (as HA might be injected), then unwanted granulomas would be very likely. This 'lake' method of injection of silicone is entirely outdated and is now merely of historical and theoretical note. Paraffin is no longer used as a filler, and so paraffin granulomas ('paraffinomas') are also fortunately now no longer seen. In recent years, some particular fillers have been notorious in having induced unwanted granulomas. These include New-Fill, now reissued as Sculptra with altered product preparation and usage advice. Microbial contamination of filler implants also increases the risk of subsequent granuloma formation. This can occur by contamination of the injection by skin flora or possibly by haematogenous spread from a focus of injection elsewhere, such as dental caries or sinusitis.

If granulomas occur, SILS injections are almost always successful in controlling them. In rare cases, intralesional bleomycin or oral agents, such as prednisolone or methotrexate, may be needed. Surgery, even biopsies, should in most cases be avoided as granulomatous material, especially if complicated by microcalcification, is not only likely to be difficult to remove in its entirety but also any residual elements have a high likelihood of continuing to discharge to the surface by way of a non-healing sinus. The ostium of such a sinus so often remains situated at the very point of the surgical incision, where it persists as a lasting reminder to the patient of the name of the surgeon whose well-meant incision is now the portal of a chronic weeping sinus, a sinus which remains open as long as the body attempts unsuccessfully to discharge the remains of the granuloma.

Infections

Cellulitis may result from contamination of filler by pathogenic bacteria and is associated with the appearance of red, painful swelling around sites of injection. This is extremely unusual and responds to antibiotics with or without incision and drainage of any contaminated lake of filler. A 10- to 14-day course of antibiotics, such as penicillin V 500 mgs with flucloxacillin 500 mg qd or erythromycin 500 mgs qd alone, will usually suffice. Moreover, as HA is slightly acidic, bacterial infection is relatively rare. Good aseptic technique makes cellulitis an unlikely hazard.

Subacute cellulitis is more common than frank acute cellulitis. It is characterised by tender lumps, which may be reddish, at sites of injection. Injections in the subcutaneous plane require careful aseptic technique to avoid this. Deep in the subcutaneous fat layer, the body's immune defences are less efficient than in the subdermal layer. Sometimes antibiotics are required. If penicillin V with flucloxacillin or erythromycin is not successful, a prolonged course of minocycline may be considered.

Subacute inflammatory reactions may occur when filler is used in the deeper fat. These are probably caused by contamination of the injection by skin commensal microbes. In most of these cases, an oral antibiotic will solve the problem, indicating that imperfect aseptic technique may be the cause of this subacute cellulitis.

Biofilm is the development of a microbial coating of the surface of a bolus of filler. It is most likely to occur with deeper subcutaneous injection as the host immune defences are less strong at this level owing to its poorer blood supply. A biofilm may induce the host inflammatory

response, sometimes causing erythema or a fibrotic shell around the bolus of filler. A biofilm may lie relatively dormant, potentially flaring up when the patient's general health becomes impaired. A biofilm or other subclinical infection may cause delayed or late reactions. Many complications that, on the basis of negative bacterial cultures, were previously assumed to be foreign body granulomas or allergic reactions are now thought to be due to biofilms (Nusbaum et al. 2012). Careful aseptic technique is required to avoid this complication (Hall-Stoodley 2009, 2004). A biofilm is an aggregation of microorganisms that excrete an extracellular polymeric substance (EPS) matrix composed of polysaccharides (especially HA), proteins and extracellular DNA. This framework of EPS facilitates surface attachment and increased antibiotic resistance. A biofilm can form when a foreign body (e.g. a filler) is contaminated. It can happen days or weeks or even months after injection and may be due to inoculation during the procedure, direct spread from another focus or haematological spread (De Boulle 2004; Dayan et al. 2011).

Haematogenous cellulitis is a dubious entity. Patients with chronic dental problems, sinusitis or other infections may have a greater tendency to develop an infection after filler injection. They may present as cellulitis with redness, tenderness and swelling. Mostly, an oral antibiotic will solve the problem.

Other Complications

Minor injection site reactions. Injection site reactions are the most common adverse events. These include pain, swelling, redness, bruising, itching and tenderness. These reactions (mostly mild) may occur to some extent after any filler injection and mostly subside in less than 10 days. No treatment is necessary.

Injection-induced oedema may follow injection, especially into the loose adventitial tissue of the lips, eyebrows and infraorbital skin, exactly the same areas which are most susceptible to angiooedema. Some people are more susceptible at certain times and to a variable degree to angiooedema from a variety of causes. Multiple needle punctures are one such cause. This post-traumatic angiooedema may develop in minutes or hours, even up to 24 h after injection. Typically, it lasts 2–20 min, occasionally 2 h to 2 days.

Deep ecchymosis may follow deeper injections. Typically, a day or two after the procedure, the patient will notice a deep and slightly tender nodule or a degree of asymmetry. There may be no colour change if the ecchymosis is deep. It resolves within 2–3 weeks. No treatment is required.

The Tyndall effect describes the apparently bluish hue of colourless transparent material (e.g. HA) seen through a thin layer of skin. It occurs after too superficial injection of filler. Needle puncture and expression will express the excess filler.

Beading describes small papules of filler near the surface of the skin. Needle puncture and expression will express the excess filler.

Visible lumps. Overcorrection or too superficial placement of a filler may lead to visible lumps under the skin. This problem is mainly seen in areas of thin skin with a lot of movement, such as around the lips or the eyes or in the nasolabial grooves. These lumps may be treated either by firm compression between finger and thumb or by aspiration or, in superficial cases, by puncture incision and expression. Injection of hyaluronidase (an enzyme that breaks up hyaluronic acid) may be used when the problem arises after injection of HA. When a temporary biodegradable filler is used, any unwanted lumps are usually temporary and treatable.

Prolonged infraorbital swelling is a result of water absorption by HA. It is a particular risk in the infraorbital skin. It may last a year. It can be avoided by using HA in only small quantities at this site and by choosing less hydrophilic preparations of HA.

Inert filler lakes may sometimes be unsightly. They respond to incision and expression.

Migration may occur if lakes of filler are implanted. It requires incision and expression. It is extremely unlikely if filler is threaded into the host tissues.

Facial lipoatrophy is a rare complication of filler use (Andre et al. 2002).

Conclusions

The use of soft tissue fillers is increasing rapidly. In part this is due to the development of fillers with better longevity and a higher safety profile. Now there are different fillers for different indications. Any former social pressure against fillers has been replaced by a peer pressure that encourages their use.

Though the complication rate with most fillers is very low, it is usually preferable to begin by using an inert biodegradable soft tissue filler of temporary duration, such as HA. Moreover, in due course most HA-related complications resolve spontaneously.

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Hair Examination

120

Bianca Maria Piraccini, Francesca Bruni, and Michela Starace

Key Points

- The methods for the study of hair include noninvasive and invasive techniques, with different difficulty of execution.
- A correct assessment of the patient requires a good knowledge of the physiology of the hair to correctly interpret the results.
- The new diagnostic instruments, such as the videodermatoscope, permit to reduce the necessity to utilize invasive techniques.

General Principles

The hair is formed by two parts: a visible part, the shaft, and a non-visible part, the hair follicle. The latter is further divided into upper segment, or permanent, and a lower segment, or dynamic, for the changes they have during the follicular cycle. The follicular cycle causes the production of the hair from the follicle, and it is not continuous but cyclic, with a succession of the three stages: growth (anagen), regression (catagen), and resting (telogen).

The daily "normal" hair loss is 50–70 hairs a day. These percentages vary in different periods of the year. In our climate, the peak of hair loss occurs between August and September. The follicular cycle is the result of a complex interaction of signals between epithelium and mesenchyme. It is influenced by environmental factors, such as the duration of the day that acts on the hypothalamus-pituitary axis with the production of melanin and prolactin and by systemic and local factors largely unknown.

Diagnostic methods in hair diseases are:

1. Pull test
2. Trichogram
3. Videodermatoscopy
4. Wash test
5. Modified wash test
6. Biopsy of the scalp

Hair diseases can be divided into two categories:

1. Associated with diffuse hair loss with no hair thinning
2. Associated with patchy hair loss

This classification is very important for the choice of the method to make a diagnosis. In fact, according to the clinical manifestation of diseases, it is possible to choose the instrument and the position where to perform the diagnostic method.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_120, © Springer-Verlag Berlin Heidelberg 2015

Pull Test

The pull test allows to evaluate the phase in which the hair is located at the time of fall. It is simple to perform, and it allows an immediate assessment of the phase. Using the thumb and index, the physician exerts a pull, slight but steady, of a tuft of 10–20 hair and evaluates the type of the root and the number of hairs that are extracted. Once the hairs are extracted, they are mounted on a slide with a gel or oil solution, covered with a cover glass, and analyzed by light microscopy.

In cases of diffuse hair loss, the test is usually performed in four to six areas of the head: the frontal, parietal, and occipital part of the scalp, and usually it detaches some roots in telogen. In case of patchy hair loss, the test is performed at the margin of the alopecic area.

The hair can be extracted in various stages of the hair cycle:

1. Anagen: it shows a pigmented dark bulb, often with a triangular shape. It's possible to identify both the external and internal epithelial sheaths.
2. Catagen: extracted very rarely, are similar to the hair in telogen with some pigment and a tiny epithelial "tail."
3. Telogen: typically club shaped and more or less pigmented. The presence of a lot of transparent epithelium around the bulb identifies a telogen hair extracted before the end of the cycle.

In normal conditions, the pull test extracts hairs in the telogen phase, and the number is the equivalent of the daily fall that is about 50–70 hairs/day and becomes 100–150 during washing. The extraction of more than six hairs in the telogen phase, from 4 to 5 days after the last washing, is considered pathological.

It is important to remember that the result of the pull test can be influenced by many external factors, such as the frequency of brushing, the distance from the last wash, and the traction force of the physician. The number of hairs that is extracted with the pull is in fact reduced by shampooing, brushing, and combing. We prefer to perform the pull test the same day or 1 day after shampooing.

Fig. 120.1 Dystrophic hair roots in alopecia areata

- A pull test revealing too many telogen hairs or hair in another phase of the hair's cycle is considered abnormal.
- Pull test extracting anagen roots with thickened sheaths is typically seen in cicatricial alopecia.
- Pull test extracting anagen roots devoid of sheaths and with rugged cuticles (loose anagen hair, LAH) is typical of the loose anagen hair syndrome (LAHS).
- Pull test extracting dystrophic anagen hairs (broken at the level of the keratogenous zone and present a fractured proximal end) is diagnostic for alopecia areata. These hairs correspond to the distal part of the exclamation mark hairs. They are also typical for anagen effluvium (Fig. 120.1).

Trichogram

The trichogram is a technique now disused, because it's not easy, it does not give objective data, and it is painful for the patient.

The trichogram is a forced tear of about 50–100 hair of a scalp area with klemmer forceps with the ends covered with rubber pads: it extracts by plucking all the hair in that area. You have to "clamp" the hair between the forceps ends 1 cm from scalp emergency and make a firm tug, pulling in the direction of hair's emergency from the scalp. Once extracted, the hairs are positioned side by side with the roots at the

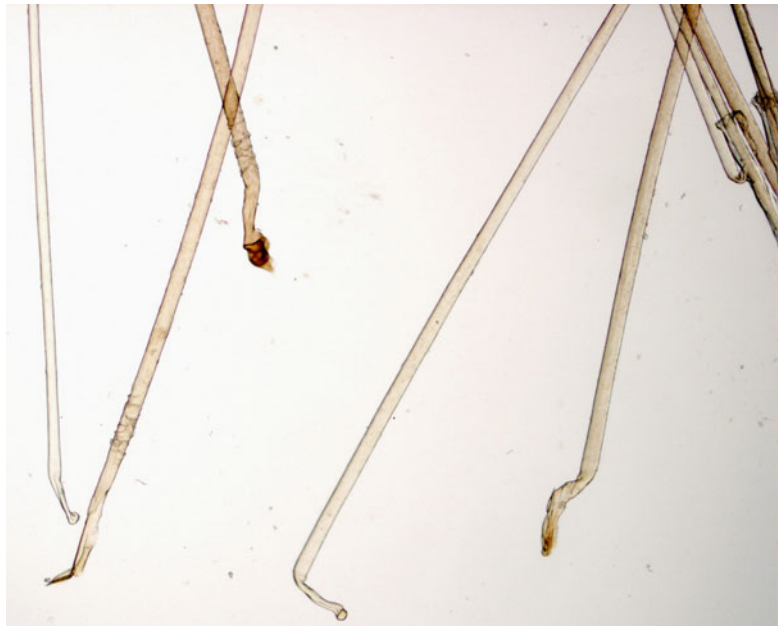

Fig. 120.2 Trichogram in an LAHS

center of the slide. The different hair roots are then counted. The normal percentage of telogen hair is less than 15 %.

The trichogram is important if you suspect a loose anagen hair syndrome, even if the pull test is negative (Fig. 120.2). Both the absence of pain during trichogram and the presence of more than 70 % of hair in the anagen phase with cuticles "ruffled" are diagnostic. In all the other hair disorders, the trichogram can only give information on anagen to telogen ratio but is not diagnostic.

In hair shaft diseases, the hairs analyzed are not extracted with plucking, but they are directly cut with scissors from the emergency of the scalp and then observed with a light microscope at high magnification and/or with an electronic microscope.

Videodermoscopy

Dermoscopy and videodermatoscopy (VDS) are useful techniques for the evaluation of the physiology and pathology of the hair and scalp. Several videodermatoscope devices, at different magnifications (from 20× to 70×), are available. The images are digitized, stored, and observed in a high-resolution monitor in real time.

The technique has been applied to the scalp, in order to study its skin, vessels, and hair shaft, and allows a noninvasive diagnosis, often avoiding the biopsy. Because of its complexity, however, this methodology is reserved for experienced dermatologists.

VDS allows to evaluate several basic parameters such as the density, the diameter, the diversity of the diameter of the hair, the appearance of the skin, and other specific signs of hair disorder (Fig. 120.3).

- Hair density (number of hairs per cm^2) is classified on a scale ranging from 1 (less than 4 hair) to 6 (more than 40).
- Hair diameter that indicates the size of the hair is classified as 1 (thin), 2 (medium), and 3 (large).
- The diversity of the diameter of hair indicates the presence of hair with varying diameter. A normal scalp has hairs of similar diameter and thinner hairs, which are less than 20 %. In androgenetic alopecia there is more than 20 % variability in the hair shaft diameter.
- Peripilar sign, which appears as brown halos around the follicular ostia, is a sign of perifollicular inflammation which is often associated with androgenetic alopecia.

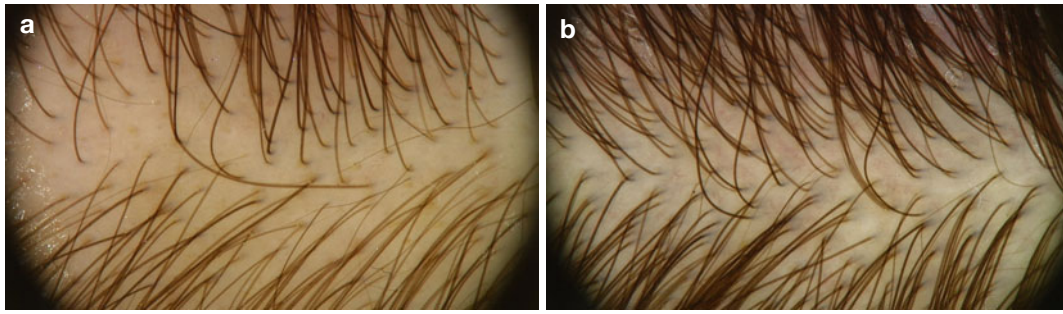

Fig. 120.3 Dermoscopy of the scalp in androgenetic alopecia: comparison of hair density (anterior lower than 20 % (**a**) vs posterior more than 20 % (**b**)) in central part line

- "Empty follicles" are the follicles that have already lost their hair in telogen but have not started to produce a new hair (kenogen stage) yet, as they have an abnormal hair cycle.
- Loss of follicular ostia is a diagnostic sign of cicatricial alopecia.
- Scalp vessels: dermoscopy permits to distinguish psoriasis and sebopsoriasis from seborrheic dermatitis. In psoriasis and sebopsoriasis, dermoscopy shows tightly coiled capillary loops.
- Hair shafts: the hair shaft abnormalities are easily recognized in vivo at high magnification.

Wash Test

The wash test is a noninvasive procedure, proved to be a reliable and useful tool for monitoring hair shedding. The wash test consists in weekly counting the hair that remains in the sink after washing. Washing must be performed at a distance of 5 days from the last shampooing. The test consists in the washing of the head in the sink with the drain hole covered with gauze and then counting the hair lost. In order to obtain an average of the situation, it is necessary to perform two washes at 15 days from each other (with always a 5-day interval).

Modified Wash Test

The modified wash test is a noninvasive and nonexpensive procedure, which can be employed with confidence in the office. It permits to distinguish telogen effluvium from androgenetic alopecia and patients with both diseases. The modified wash test also provides an estimate of the severity of the three conditions. In telogen effluvium the shed hairs are increased in number, but longer than 3 cm (hair with the tip of hair not previously cut) hairs; instead in the case of androgenetic alopecia, the hair count includes a prevalence of vellus and intermediate hairs, shorter than 3 cm. The test reveals the presence of both patterns when telogen effluvium and androgenetic alopecia occur. This technique allows the dermatologist to decide which condition is actually prevalent and which should be treated first.

The modified wash test is based on the wash test technique, added by the observation of the type of hair. In this simple way, it is possible to do a differential diagnosis between telogen effluvium and androgenetic alopecia.

Histology

Scalp biopsy is indicated in all cases of suspected cicatricial alopecia, in diffuse hair loss diseases, and in all cases of diagnostic doubts. When performing a skin biopsy in hair diseases, the choice of the place plays a key role. It depends on the disease involved and on the stage of the disease itself: an active inflammation area with hair follicles is better. A wrong choice may not be diagnostic and also requires the repetition of the biopsy.

The scalp biopsy requires a punch of 4 mm, which scans an area of 12.6 mm^2; the 4 mm piece

Table 120.1 Evaluation of hair's diseases

<table>
<tr><td rowspan="5">Widening of the central hair part</td><td rowspan="4">Yes</td><td rowspan="4">Dermoscopy</td><td>>20 % diversity</td><td colspan="4">Androgenetic alopecia</td></tr>
<tr><td rowspan="4"><20 % diversity</td><td rowspan="4">Pull test trichogram hair tip observation</td><td>LAH</td><td colspan="2">LAHS</td></tr>
<tr><td rowspan="2">Telogen roots</td><td>Dermoscopy</td><td>Telogen effluvium</td></tr>
<tr><td rowspan="2">Biopsy</td><td>AA incognita</td></tr>
<tr><td colspan="3">No</td><td>Anagen with roots</td><td>Cicatricial alopecia</td></tr>
<tr><td colspan="3"></td><td>Dystrophic roots</td><td colspan="2">Anagen effluvium</td></tr>
</table>

LAH loose anagen hair, *LAHS* loose anagen hair syndrome

is then divided longitudinally into two identical parts: one for the vertical sections and the other for the horizontal ones.

Whiting studied the normal parameters of a healthy scalp, studied with a 4 mm punch biopsy:

1. Terminal hairs: 33; 2 in telogen (6 % with a range between 0 and 15 %), 31 in anagen, and 0 in catagen
2. Telogen terminal units: 5
3. Vellus hair: 5
4. Follicular count: 38 (range 19–59)
5. Follicular unit: 1/mm^2 that is made up of about 12 2/5 terminal hairs and 0/2 level hair, similar to each other in size and number
6. Anagen/telogen ratio: 85 %:15 %

The best way to do a diagnosis of hair diseases is presented in Table 120.1.

After collecting a good personal history, the physician approaches the patient with the scalp examination. In case of diffuse hair loss, the first step is to look for the presence of widening of the central hair line; if it is positive, it's possible to suspect androgenetic alopecia and perform a videodermoscopy that observes more than 20 % variability in the hair shaft diameter. This confirms the diagnosis.

If there is the absence of widening of the central part, it's possible to perform a pull test in all the scalp. The pull test is positive when you extract more than six hairs and then observe the roots under the microscope.

In case of dystrophic roots, it's possible to suspect alopecia areata and perform the videodermoscopy in order to observe the activity of the disease. With dermoscopy it's possible to view dystrophic hair, exclamation hair, and black dots during the acute phase and yellow dots in the chronic phase.

In case of telogen roots, the diagnosis can be directed to telogen effluvium but not forgetting alopecia areata incognita, a type of alopecia areata with a diffuse hair loss and not a patchy pattern. In this case videodermoscopy shows diffuse yellow dots, and a scalp biopsy is mandatory to confirm the diagnosis.

Otherwise, when you have a patchy hair loss, you perform a pull test at the patch margin to understand the activity of the disease; in these diseases the hair's extract can be dystrophic in case of alopecia areata or anagen with sheaths in case of a cicatricial alopecia. In this last case, a scalp biopsy is mandatory.

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Lasers: Ablative

121

Leonardo G. Marini and Aleksandar L. Krunic

Key Points

- Ablative lasers are, without any doubt, the mainstay of laser technology in dermatologic surgery today.
- A relatively simple, touch-free, highly modulable tissue photothermal vaporization can be generated, either in full-beam or fractional mode with conventional surgical infrared lasers (CS-IRL).
- When performed properly, using the right laser equipment and delivery accessories, setting the appropriate parameters, and last, but not least, selecting the patients to be treated, ablative laser procedures will produce excellent clinical results with few contraindications and low complication rates.

Abbreviations

AFR	Ablative fractional resurfacing
CS-IRL	Conventional surgical infrared lasers
HSP	Heat shock protein
IR	Infrared
MMP	Matrix metalloproteinase
PIH	Postinflammatory hyperpigmentation
PRL	Platelet-rich plasma
QS-IRL	Q-switched infrared lasers
RTD	Residual thermal damage
TRT	Thermal relaxation time

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General Principles

Ablative lasers are, without any doubt, the mainstay of laser technology in dermatologic surgery today. A relatively simple, touch-free, highly modulable tissue photothermal vaporization can be generated, either in full-beam or fractional mode with conventional surgical infrared lasers (CS-IRL). This effect is based on the well-known physical process where light energy is absorbed by tissue chromophores resulting in heat formation leading to local temperature increases (Table 121.1). Intraoperative immediate results are clearly visible, and final clinical improvements – after wound healing – are quite predictable. Recently another type of tissue ablation has been introduced focusing on nonthermal photomechanical effects produced by Q-switched infrared lasers (QS-IRL) (Fig. 121.1). Modern laser systems can consistently rely on effective and efficient technical solutions able to facilitate operators in the performance of otherwise complicated surgical procedures, thanks to a better spatial control on degree and extent of tissue

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_121, © Springer-Verlag Berlin Heidelberg 2015

Table 121.1 Terminology used to describe ablative laser effects in biology and medicine

Cold photothermal ablation	Photothermal effects obtained by short pulse (≤1 ms) and relative high fluence on living tissue
Hot photothermal ablation	Photothermal effects obtained by long pulse (≥1 ms) and relative low fluence on living tissue
Photoacoustic nonthermal ablation	Photomechanical effects obtained by extremely short pulse (≤10 ns) and relative high fluence on living tissue
Full-beam ablation	Effects of intact laser beam produced on the surface of living tissue
Fractional beam ablation	Effects of micro-fragmented laser beam produced on the surface of living tissue

injury. Today ablative lasers can be effectively used to rejuvenate skin and mucous tissues through careful modulation of cellular destruction and tissue regeneration (Fig. 121.2), improve scars through precise severing of thick collagen bundles leading to their subsequent qualitative and quantitative regenerative rearrangement (Fig. 121.3), increase transcutaneous penetration of topical actives, precisely eliminate epithelial growth, and finely "sculpt" dermal irregularities (Fig. 121.4). Ablative lasers can be effectively combined with other technologies like radio frequency and different non-ablative light sources besides being integrated with more complex combined treatments as advanced PDT (Fig. 121.5) and regenerative platelet-rich plasma (PRP).

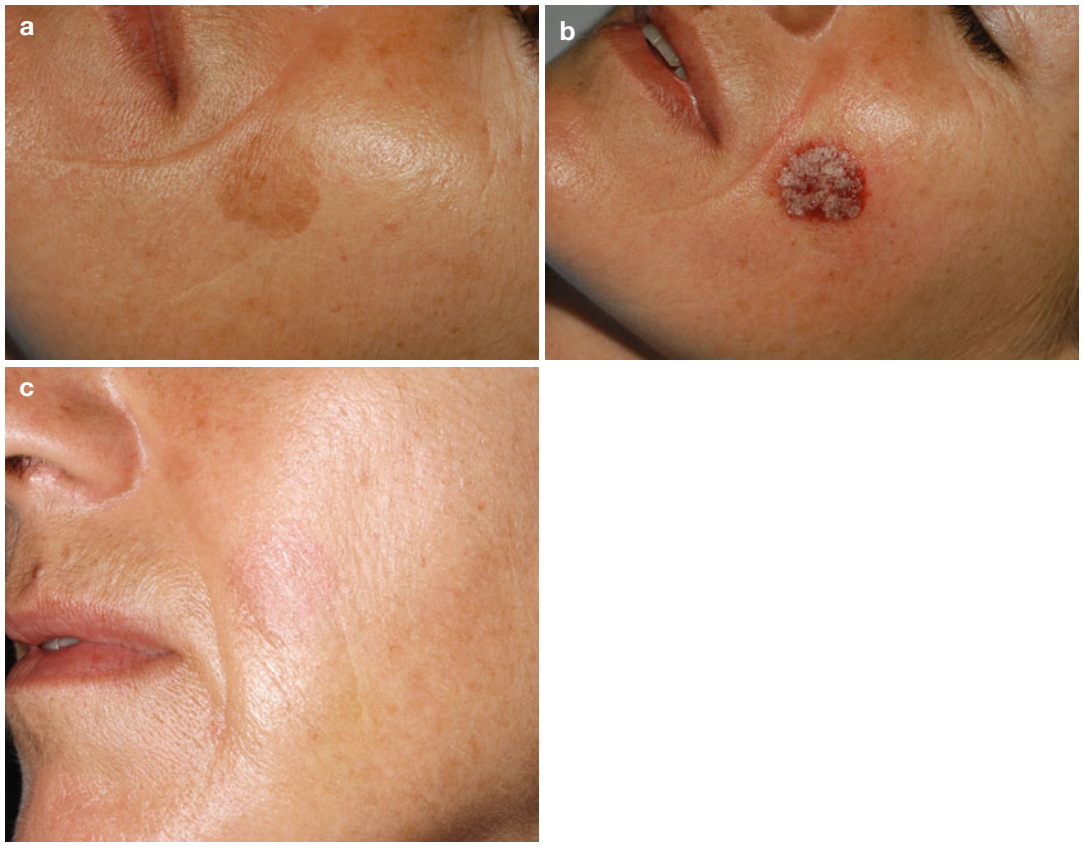

Fig. 121.1 Controlled Q-switched photoacoustic ablation: (**a**) pre-op, (**b**) immediately post-op, and (**c**) 1 month post-op

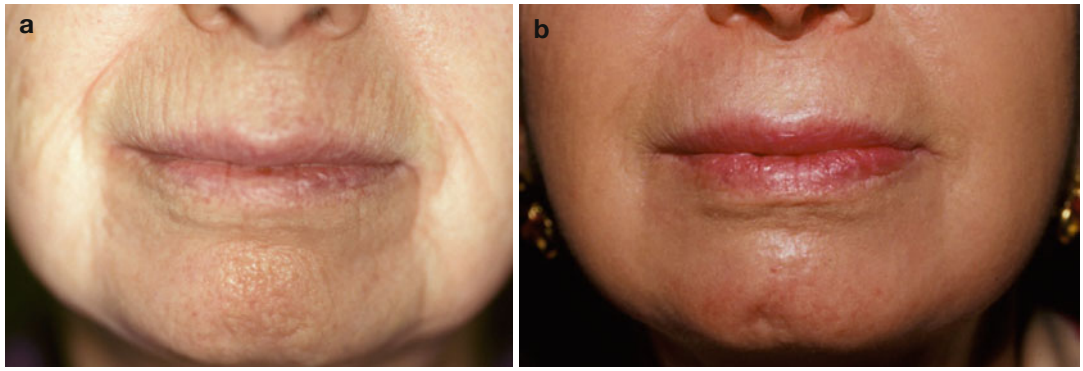

Fig. 121.2 Skin rejuvenation – full-beam CO_2 laser resurfacing: (**a**) pre-op and (**b**) post-op

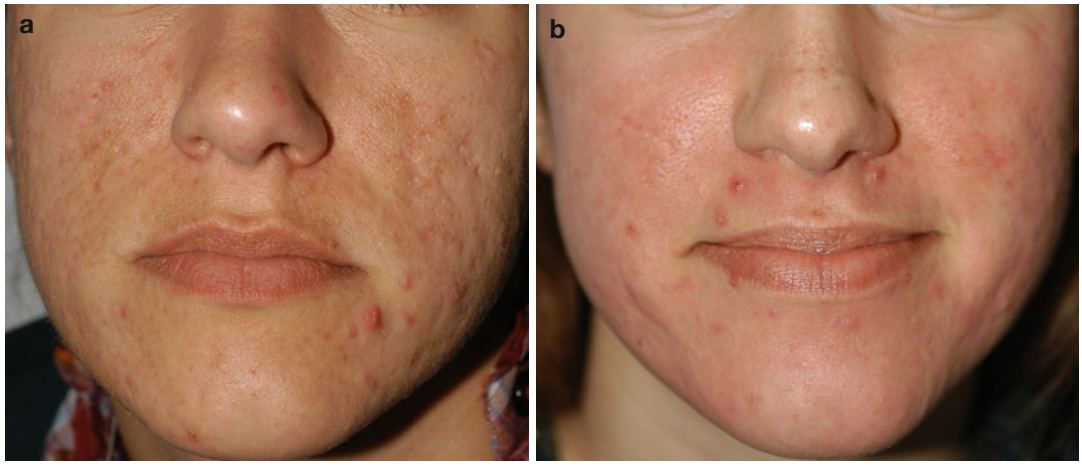

Fig. 121.3 Post-acne hypotrophic scars – fractional + full-beam 2940nm Er:YAG laser remodelling and resurfacing: (**a**) pre-op and (**b**) post-op

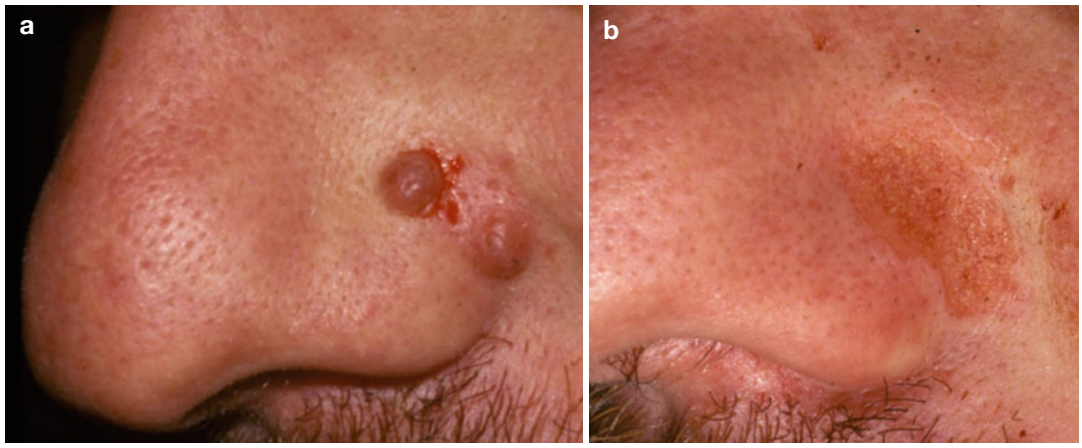

Fig. 121.4 Dermal nevomelanocytic nevi – post-shave biopsy full-beam Er:YAG laser resurfacing: (**a**) pre-op and (**b**) post-op

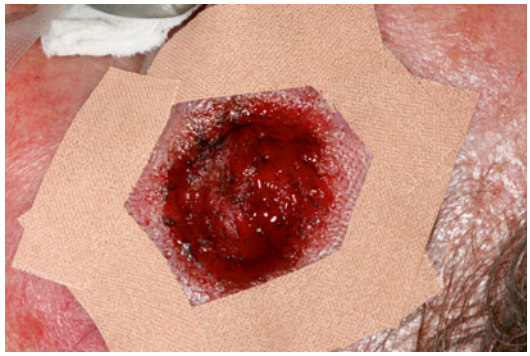

Fig. 121.5 Ablative laser-assisted transepidermal pharmacologic actives penetration: Er:YAG fractional preliminary to advanced PDT procedures topical application

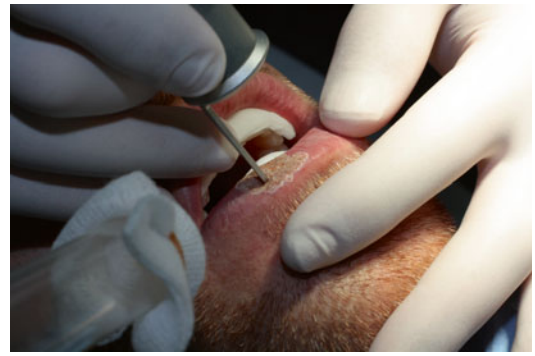

Fig. 121.6 CW CO_2 laser focused beam controlled-speed scanner-assisted ablation

History

The history of laser ablation begins with the birth of laser itself. The discovery of unique light-tissue interaction induced by lasers led to confirm that high-density light energies were able to spatially confine tissue heating resulting in controlled thermal injury, tissue removal, and coagulation. It became immediately evident that the choice of light wavelengths and their specific tissue interactions were fundamental in determining their optical penetration depth and thus their ability to influence the interplay between tissue removal and haemostasis. Throughout the 1960s, a surprisingly rich array of studies appeared in the scientific literature which presaged most modern applications of ablative lasers. The number of studies grew linearly in the 1970s but exploded around 1985 with the reinvigorated diffusion of laser applications in medicine and surgery, as well as in other biological fields, due to the publication of the theory of selective photothermolysis presented by Rox Anderson and John Parrish in 1983. Medical laser companies constantly struggled to provide dermatologists with progressively more sophisticated technologies aiming at efficiently controlling photothermal tissue effects and modulating tissue destructive vaporization and coagulation (Fig. 121.6). The development of short-pulsed, high-energy carbon dioxide laser systems in the 1990s led to the emergence of

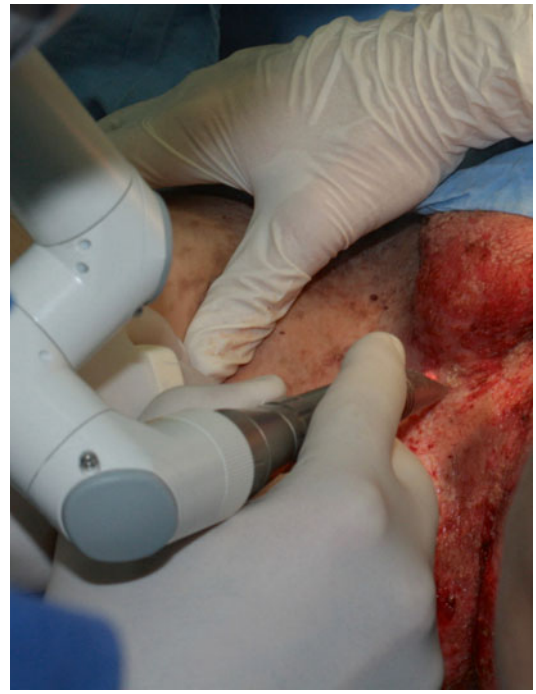

Fig. 121.7 Variable pulse modulation 2940nm Er:YAG laser-controlled photothermal ablation

precise laser skin resurfacing, clearly improving clinical outcomes from those induced by previously available continuous and pulsed laser mode (Hobbs et al. 1987). In the same timeframe, the advent of pulse modulation technologies allowed 2,940 nm Er:YAG laser systems to reach an optimal compromise between vaporization and coagulation previously unthinkable for this highly water-selective wavelength

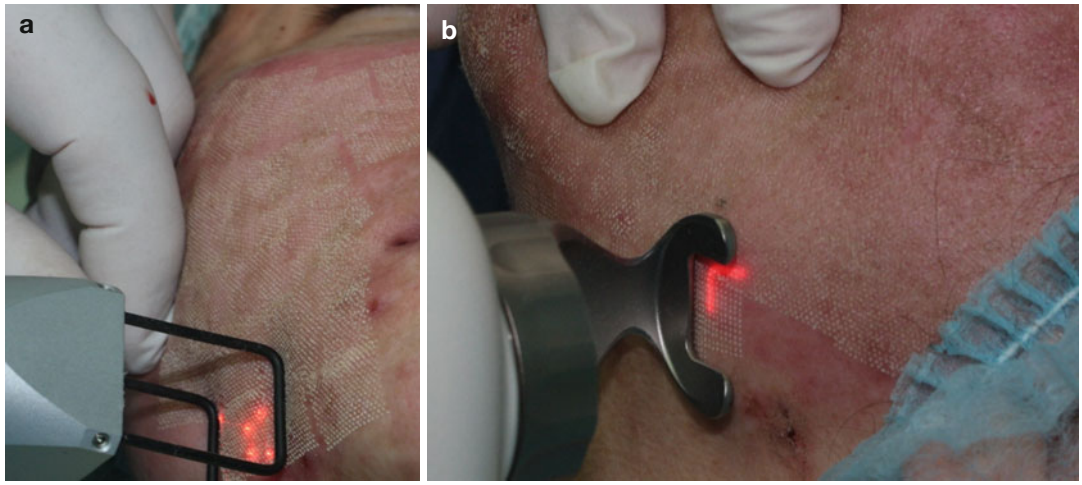

Fig. 121.8 Scanner-assisted ablative fractional remodelling/resurfacing: (**a**) random-pattern CO_2 variable pulse modulation photothermal micro-drilling and (**b**) sequential-pattern Er:YAG variable pulse modulation photothermal micro-drilling

(Fig. 121.7). Pulse modulation was immediately adopted also by CO_2 laser systems improving their biological interactions. Dieter Manstein and the group of Rox Anderson introduced the innovative concept of fractional thermolysis, originally applied to non-ablative lasers in 2003, with the specific aim of decreasing post-operative downtime and side effects produced by ablative full-beam skin resurfacing procedures. This technology, allowing controlled thermal destruction of microcolumns of epidermal and dermal tissue, in regularly spaced arrays over a fraction of skin surfaces, was successfully applied to ablative laser systems in 2007, changing forever the operative approach of ablative skin resurfacing (Fig. 121.8).

Short-pulsed, high peak power QS photoacoustic skin microablation was described by Leon Goldman and co-workers in 1965 after tattoo pigment removal using a 695 nm ruby laser. Randall Lane and Roy Geronemus further described the microablative properties of QS lasers on skin tissues using a 193 nm Ar:fluoride and a Kr:fluoride systems working at 14 ns pulsewidth in 1985. This nonthermal type of ablation has proven effective in skin rejuvenation as well as in controlled destruction of skin alterations such as xanthelasma palpebrarum.

Mechanism of Action

Conventional photothermal ablative lasers are confined within the mid-IR spectral band light emission. Their specific wavelengths are able to be selectively absorbed by water which is ubiquitously distributed within biological tissues. Photothermal effects induced by mid-IR lasers are mostly independent from the presence of other chromophores such as haemoglobin, melanin, and dermal cytochromes. Ablative lasers can be therefore considered virtually colour blinded. As in all kinds of light-tissue interactions, clinical effects are produced only when proper light absorption is guaranteed. Laser radiation generates heat precisely and selectively only where light absorption takes place. At least two processes occur during laser irradiation of biological tissues: the first is a thermodynamic heating process which results in a local temperature rise. The second is a complex chemical process whereby heated proteins reversibly or irreversibly modify their tertiary structure resulting either in biomodulational rearrangements or progressive loss of integrity within involved tissues. The rate of protein functional response is a complicated function of temperature, time, local pressure, and various different environmental parameters. Slow

Table 121.2 Photobiological light-tissue interactions in photomedicine

Photothermal mode	Photothermal effects obtained by short pulse (≤1 ms) and relative high fluence on living tissue (cutting, vaporization, coagulation)
Photobiological mode	Photobiological effects obtained by long pulse (≥1 ms) and relative low fluence on living tissue (photobiological effects)
Photomechanic (elecromechanic) mode	Photomechanical effects obtained by extremely short pulse (≤14 ns) and relative high fluence on living tissue (highly spatially confined nonthermal destruction)

Table 121.3 Sensitivity of tissue proteins to temperature and relative biological consequences

Temperature (°C)	Tissue proteins effects
43–45	Proteins conformational changes – retraction – hyperthermia (slow cell mortality after prolonged exposures)
50	Enzyme activity reduction
60	Protein denaturation – coagulation
80	Collagen denaturation – cell membrane permeabilization
100	Vaporization – ablation
>100	Desiccation – carbonization

heating will cause progressive reversible or irreversible tissue alterations below water boiling point (<100 °C), while rapid heating (>100 °C) immediately destroys tissue within confined microanatomical areas (Table 121.2). Thermally induced structural and functional modifications of human cells start at temperatures as low as approximately 43 °C (Table 121.3).

Ablative lasers are named so since their photothermal effects are evident immediately at their primary impact on biological tissue. Their optical penetration depth is confined to the first water-containing layers encountered by their light beams. Their specific secondary thermal action continues to be produced beyond the primary site of light impact, at its immediate or distant periphery, as long as tissue water is available. Ablative lasers are also known as "surgical lasers" since they are able to cut, photovaporize, and coagulate biological tissues. They can produce different photothermal effects on the skin depending on the particular absorption characteristics peculiar to their specific wavelengths as was clearly demonstrated by Kaufmann in 1994 (Table 121.4). 10,600 nm CO_2 lasers, for example, have a water absorption coefficient of 800 cm^{-1}. With a pulse duration of less than 1 ms and a fluence of 5–7 J/cm^2, its light penetrates approximately 20–30 μm, and peripheral residual thermal damage (RTD) is confined between 100 and 150 μm of peripheral tissue. 2940 nm Er:YAG lasers have a better water absorption coefficient, very close to the peak absorption for this chromophore, which is 16 times than CO_2 lasers. Its penetration depth is limited to 1–3 μm per J/cm^2 of fluence. Its estimated RTD is 10–40 μm. Laser skin ablation typically induces four concentric micro-zones of thermal damage. Starting from the centre, corresponding to the core of laser irradiation, it is possible to recognize an area of missing tissue ablation – maximal thermal effect (1), progressively surrounded by a variable thickness of tissue necrosis – direct protein thermal damage (2), an adjecent micro-zone of coagulation – indirect irreversible protein thermal damage (3), and a peripheral hyperthermia-related photo-thermal biomodulation (4). When ablative fractional photothermolysis is considered, well-defined histologic findings have been clearly documented. Ablative microcolumns are associated with eschar layers confined within corresponding micro-cavities. Annular coagulation zones are evident at their immediate periphery. Re-epithelization occurs rapidly, within 48 h.

Table 121.4 Ablative photothermal lasers commonly used in dermatology

Laser	Wavelength (nm)	Absorption peak of water (nm)
Nd:YAG (Q-switched)	1,064	3,000
Tm:YAG	1,927–2,010	
Ho:YAG	2,100	
Er:YAG	2,790	
Er:YAG	2,940	
CO_2	10,600	

The biological changes occurring during mid-IR laser-tissue interaction can be divided into three phases: (a) direct tissue injury, (b) photothermal biomodulation of perilesional cells due to residual thermal damage (RTD), and (c) inflammatory response.

(a) **Direct tissue injury** – the initial rise of temperature by rapid heating (100 °C), produces an immediate vaporization of intracellular and extracellular water associated with irreversible proteins denaturation within skin layers exposed to laser irradiation.
(b) **Photothermal biomodulation** of perilesional cells is mainly due to RTD insufficient to induce tissue vaporization (43–80 °C). Cellular dehydration induces an upregulation of aquaporins, special channels located within cell membranes to improve water balance, as well as more or less reversible structural modification of proteins.
(c) **Inflammatory response** induces selective release of biologically active cytokines able to initiate and modulate wound healing response within, and immediately around photothermally exposed tissue (increased production of collagen III, heat shock protein HSP70, and alpha smooth muscle actin).

Recently gene expression analysis performed 2 h after CO_2 ablative fractional resurfacing (AFR) has shown threefold upregulation on 38 genes including CYR61, HSP90, aquaporin 3, HSP27, and HSP40, whereas 68 revealed a threefold or more downregulation. The same analysis performed 24 h posttreatment confirmed an upregulation of 53 genes including Wnt5a, matrix metalloproteinase (MMP)-19, and histone deacetylase 7A (Kim et al. 2013).

Given that targeting skin with colour-blinded mid-IR lasers induces a sudden increase of tissue temperature, it is very important to remember that thermal surge starts always at its primary impact site and spreads subsequently to deeper layers. When laser parameters are properly selected, cells and extracellular matrix can be immediately and precisely vaporized. Modulation of laser parameters is crucial to produce different immediate photothermal tissue modifications and delayed thermally induced biological effects. Power density (irradiance: W/cm^2), fluence (J/cm^2), spot size, pulse duration, pulse "shape", and pulse stacking are extremely important parameters to be chosen by operators. Each of them should be precisely tailored according to the photothermal and photobiological effects useful to treat different skin alterations located on selected anatomical areas. The main goal of ablative laser treatments is to attain effective clinical results without excessive heat production at the immediate periphery of treated targets. Modern laser dermatology applications are based on the fundamental theory of "selective photothermolysis" originally proposed by Anderson and Parrish in 1983. According to this theory, each biological target has a specific thermal relaxation time (TRT, the time taken for a heated tissue to lose 50 % of absorbed heat through diffusion). Should laser irradiation last longer than target-specific TRT, heat diffusion will be inevitably conducted to surrounding tissue, leading to extended thermal effects and thermally induced biological alterations. Surgical lasers usually operate within continuous and millisecond light emission range. Longer laser exposures lead to tissue desiccation (complete subtraction of biological tissue water) and eventually to carbonization. Short exposures allow precise tissue destruction with controlled thermal effects within peripheral tissues. Lower fluences subtract water from biological tissue without reaching a thermal threshold sufficient to induce vaporization. Higher fluences reach water vaporization threshold immediately. Ablation depth depends on **fluence**; coagulation thickness is related to **pulse duration**. Modulating laser energy and pulse duration influences tissue vaporization efficiency and peripheral coagulation zones thickness, allowing "simulation" of photothermal tissue interactions produced by different IR wavelengths.

Nonthermal QS laser ablation is relatively independent from optical penetration depth of laser wavelengths since it mainly relies on the propagation of photoacoustic waves typically generated by short-pulsed ($\leq$14 ns) lasers within biological tissues. Cellular and extracellular tissue damage is immediate and not associated with any significant "thermal" tale. Penetration of photoacoustic waves is proportional to laser pulse intensity and not to the total energy dose accumulated in residual tissue.

Equipment

Ablative lasers consist of a main laser unit and its accessories: laser case, delivery systems, control panel, electric wires, activation switches, and key (Fig. 121.9) (Table 121.5). Further laser-independent accessories consist of a properly filtered smoke evacuator and primary eye and respiratory individual protections. Laser beams can travel a long distance and can be reflected by polished surfaces; therefore, laser rooms and surgical tools should be designed to prevent inadvertent photothermal effects on biological tissue different from the ones being treated. Laser room access should be restricted to authorized staff

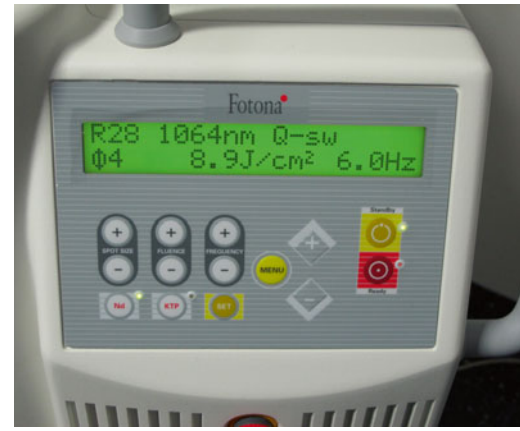

Fig. 121.9 Operational control panel of a modern laser system

Table 121.5 Ablative laser accessories

Laser accessories	Specifications	Ergonomic/functional efficiency
Laser case	Wheeled container hosting laser unit and its primary accessories	Compact, highly movable, sturdy, smooth angle frame, handy positioning of electric switches and key, easily cleanable
Delivery systems 1	Articulated arm	Sturdy, highly movable, weight balanced, effortless return to resting position, smooth hand-piece change operation, position as close as possible to operating area, easily cleanable
Delivery systems 2	Full-beam hand-pieces and spacers – focused or collimated	Sturdy, smooth hand operational, non-slip surface, easily cleanable
Delivery systems 3	Fractional beam hand-pieces (focused or collimated), pixel or stamping mode or true fractional mode	Sturdy, smooth hand operational, non-slip surface, easily cleanable
Delivery systems 4	Full-beam scanners	Sturdy, smooth angle frame, built-in digital controls, easily cleanable
Delivery systems 5	Fractional beam scanners	Sturdy, smooth angle frame, built-in digital controls, easily cleanable
Control panel	Full function or hybrid touch screen to interact with laser unit	Sturdy; easily accessible operation; standardized colour-coded operational settings, acoustic warning, and operational signals; position as close as possible to operating area; easily cleanable
Electric wires	Wires connecting laser case to electric sockets	Built-in plug-socket securing system to avoid accidental interruption of electric supply during operation, relatively long, colour coded, easily cleanable
Activation switches 1	Primary and secondary operational switches, built-in laser case	Easily accessible, colour coded, smooth operation
Activation switches 2	Foot pedal activation of operational laser emission	Remote control (wire independent)
Activation key	Laser system activation	Easily accessible, colour coded

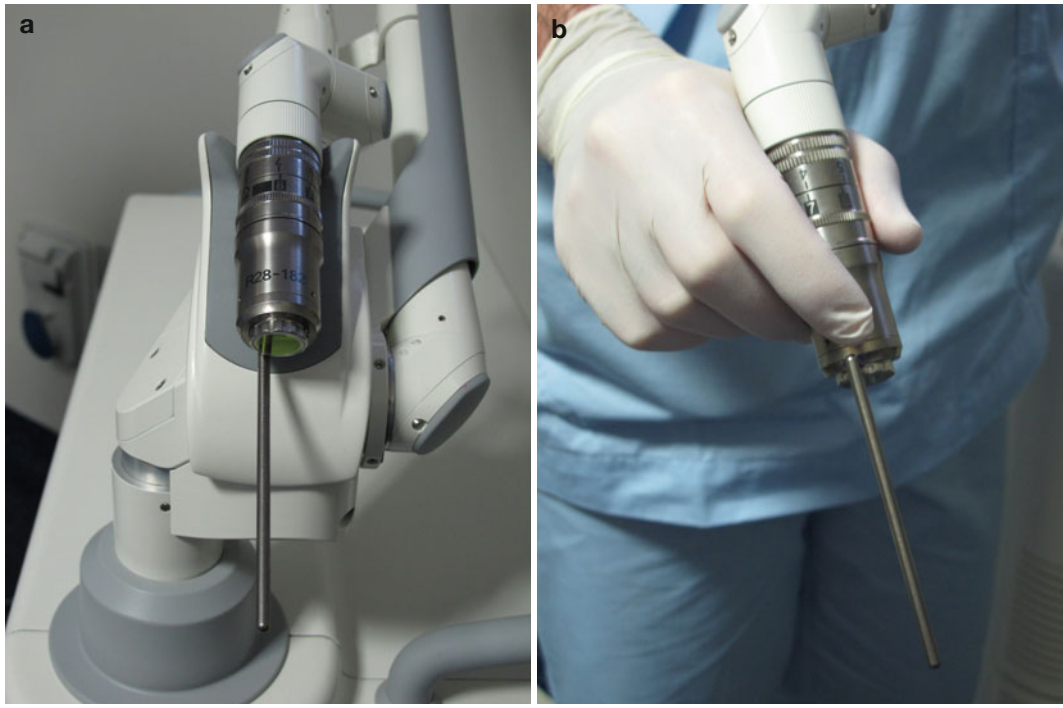

Fig. 121.10 Free-hand ergonomic hand-piece of a Q-switched laser system: (**a**) hand-piece in its protected resting position with articulated arm at rest and (**b**) hand-piece perfectly adapting to surgeon's hand

only, and warning signs should be placed outside the entrance door. Controlled door locking systems should be activated during laser operation in order to avoid unauthorized access to laser room without proper primary eye and respiratory individual protections.

Choosing the right accessories when performing ablative laser surgery is very similar to choosing proper surgical instruments when planning to perform an invasive procedure. Anatomical location, type, and extension of surgical procedures imply specific selection of scalpel shapes and sizes, as well as all necessary instruments to fulfil all operating requirements. Ablative laser accessories should be selected according to the same general requirements. Well-designed, ergonomic, relatively small focused beam hand-pieces should be chosen for precise photothermal cutting and small spot full-beam photovaporization. Collimated beam hand-pieces should be chosen when planning relatively large full-beam resurfacing to be performed on complex anatomical areas. The choice of fractional beam hand-pieces should follow the same criteria. Full-beam (Fig. 121.9) and fractional beam scanners (Fig. 121.10) should be used when large anatomical areas are to be treated (Fig. 121.11).

Techniques

The choice of primary photothermal and secondary bio-thermal thermal actions induced by conventional ablative lasers depends on the size and depth of lesions to be treated, as well as on specific tissue characteristics related to anatomical locations. Mid-IR lasers can be used either in full-beam mode (all irradiated surface is thermally affected) or in fractional beam mode (partial irradiated surface is thermally treated). Photothermal and thermal tissue interaction varies according to pulse shape (energy distribution during ablation time), total energy delivered per pulse (mJ/pulse – J/cm^2 irradiation dose), pulse

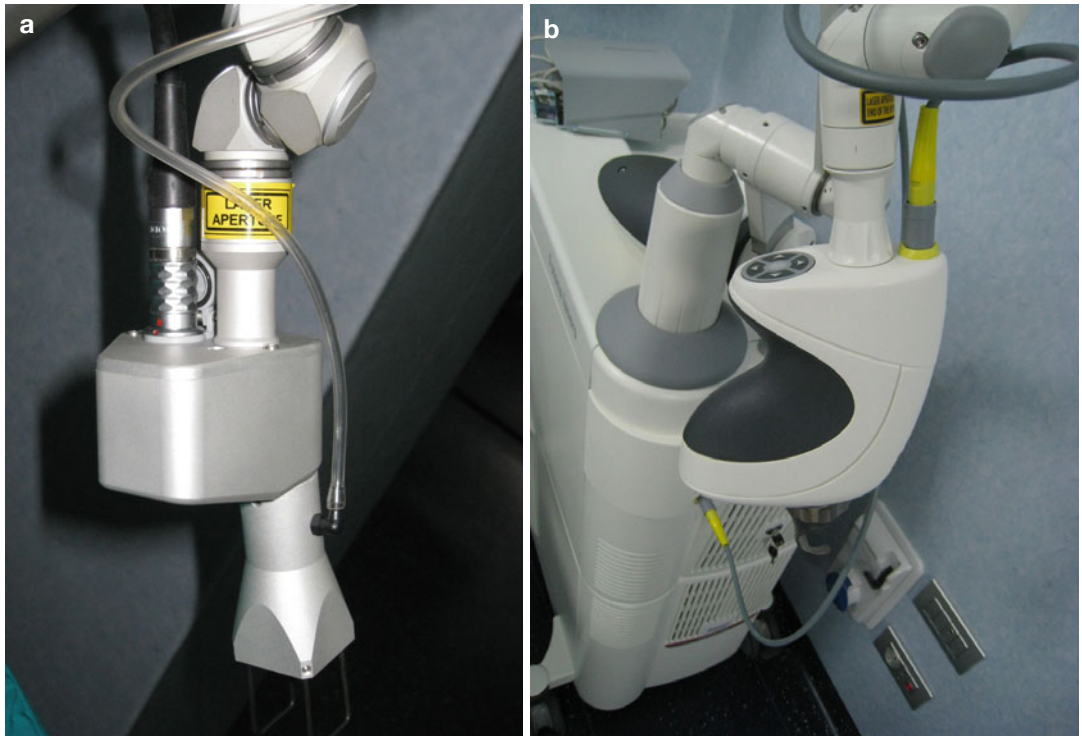

Fig. 121.11 Examples of ablative fractional laser scanners: (**a**) CO_2 laser scanner and (**b**) Er:YAG laser scanner

duration or action time, pulse diameter, pulse density (percentage of laser spot overlapping in full-beam mode or micro-spot spacing in fractional mode), pulse stacking, pulse layering, and sequential or random spot/micro-spot delivery. Full-beam mode was the first option available to operators and can be used either in a continuous emission (CW) or pulsed emission (chopped pulse, superpulse, ultrapulse, variable pulse) allowing variable degrees of thermal control on irradiated tissue. Full-beam delivery is usually performed free-hand and can be used according to a micro-focused mode (Gaussian energy distribution with maximum concentration of laser irradiation on the centre of laser spots – useful for cutting and vaporization resurfacing of small areas), variable spot size collimated mode (square pulse energy distribution evenly covering full laser spot surfaces – useful for full-beam resurfacing of variably sized anatomical areas) (Fig. 121.12), and defocused mode (diluted laser

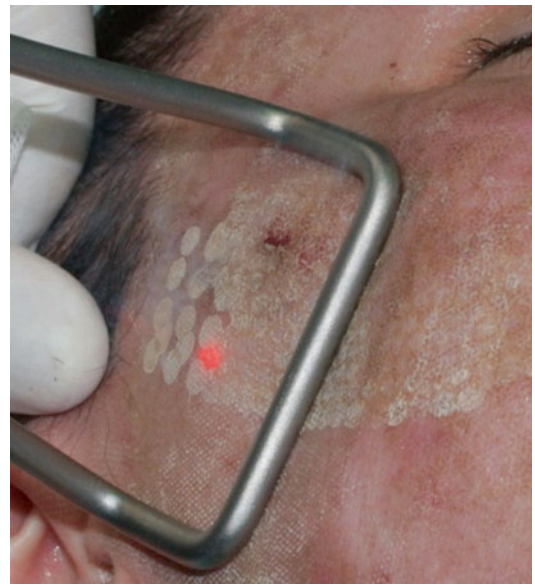

Fig. 121.12 Full-beam random-pattern, variable pulse modulation Er:YAG laser-controlled photothermal resurfacing

irradiation insufficient to induce vaporization, useful for tissue coagulation). Fractional beam delivery can be technically divided in two beam-splitting modes: (*a*) pixel or stamping mode and (*b*) true focused fractional mode. In the first case, laser beams are split by metal grids located along their paths within specific surgical hand-pieces – resulting microdots carry just a fractional part of the pulse energy selected on the control panel. True fractional mode implies the generation of complex sequences of focused microdots, each carrying the same energy selected on the control panel. When scanners are used, different photothermal effects can be achieved with proper selections of scanning sequences of microdots. Higher localized temperatures can be reached when uninterrupted sequential linear patterns are selected, while more gentle heating can be produced when interrupted, random-pattern microdot sequences are chosen. Maximum localized thermal effects are achieved when laser beams are directed perpendicularly to the skin surface, while variable thermal effects are produced when angling laser beams at different degrees. This simple manoeuvre can be quite useful in producing "feathering" effects to avoid demarcation lines in complex anatomical areas. Partially overlapping, full-beam spots can avoid skip areas when planning a full, conventional resurfacing, while stacking fractional microdots allows to reach deeper ablation depths – particularly useful in complex scar remodelling procedures. Anatomical tissue thickness variations should be taken into proper account when selecting ablative parameters, particularly when working on the face. Combinations of fractional and full-beam laser modes can be used either sequentially, according to more or less complex laser layering techniques, or fragmentally, according to different photothermal clinical end results planned for specific patients (mosaic resurfacing). Sequential combinations of photothermal ablative fractional resurfacing and Q-switched photoacoustic destruction have been successfully used in advanced tattoo removal procedures (Fig. 121.13). Q-switched photoacoustic ablation can be achieved according to both full-beam and fractional mode (Fig. 121.14). Due to the extremely high energies delivered by Q-switched laser systems, a flat-top beam, which allows an almost uniform laser energy distribution over the entire spot area, is highly recommended.

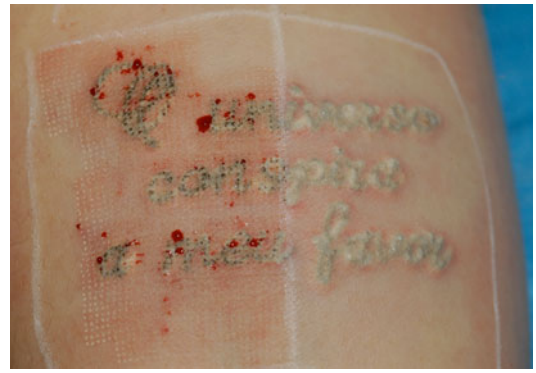

Fig. 121.13 Er:YAG ablative fractional resurfacing immediately performed before Q-switched photoacoustic destruction of tattoo pigments – note the transepidermal escape of photoacoustic-induced tissue vapour on Er:YAG laser treated side (*left*) compared to vapour "entrapment" in pure Q-switched laser treated side (*right*)

Clinical Applications

Most benign and superficial precancerous and cancerous lesions can be treated successfully with any of the several treatment modalities available to modern dermatologic surgery (excision, cryosurgery, electro-assisted destruction and curettage, dermabrasion, chemical peels). The choice depends on many different factors including aesthetic and economical considerations and including patients' specific attitude to accept or refuse specific treatment modalities. In any case patients should be informed about all treatment options and should be allowed to choose from the reasonable alternatives. Ablative lasers, even if more expensive and technically demanding, have specific advantages over other treatment modalities. Touch-free laser treatments allow to reach any anatomical area of the body, including the most delicate. Precise "deposition" of laser energy allows to finely modulate surgical ablation providing excellent visual control of surgical field. The risk of infection depends on the size and

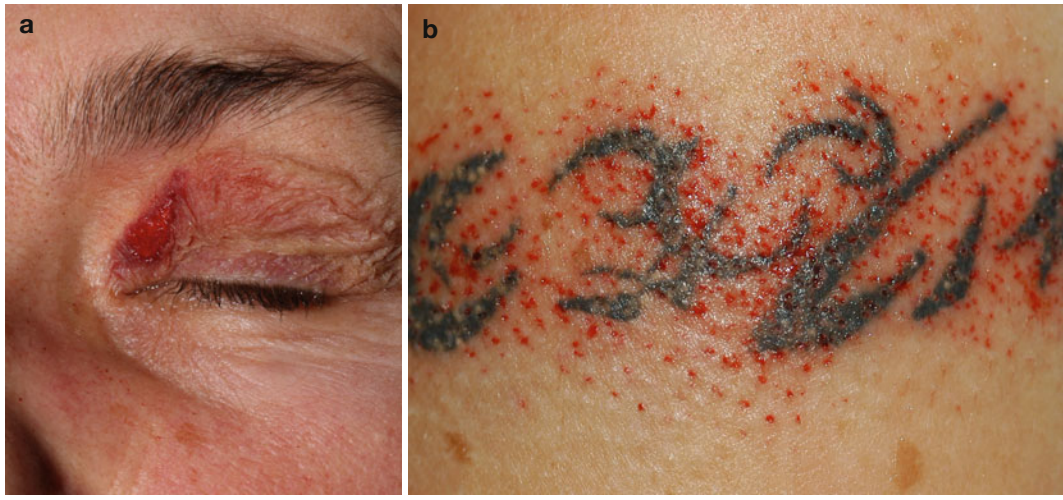

Fig. 121.14 Q-switched photoacoustic ablation: (**a**) full flat-top beam Q-switched photoacoustic ablation of xanthelasma palpebrarum and (**b**) fractional beam ablation as a "priming pass" before multiple full-beam photoacoustic passes in tattoo clearing

Table 121.6 Ablative laser techniques

Indications	Ablative laser mode	Technique
Benign epidermal growths[a]	Full-beam ablation	Free-hand painting or stacking
Precancerous lesions[b]	Full-beam/fractional beam ablation	Free-hand painting or stacking
Cancerous lesions[c]	Full-beam ablation	Free-hand painting or stacking
Hypertrophic scars	Fractional beam ablation	Scanner assisted
Hypotrophic scars	Fractional beam ablation	Scanner assisted
Keloids[d]	Fractional beam ablation	Scanner assisted
Topical drug delivery	Fractional beam ablation	Scanner assisted
Enhanced PDT	Fractional beam ablation	Scanner assisted
Enhancer PRP	Fractional beam ablation	Scanner assisted
Tattoo pigment removal[e]	Fractional beam ablation	Scanner assisted
Facial rejuvenation	Fractional/full-beam ablation	Free-hand/scanner assisted
Surgical incisions	Full-beam ablation	Free-hand linear

[a]Preliminary shave biopsy and histological analysis are advised for nevomelanocytic and not clear-cut clinical diagnosis
[b]Preliminary shave biopsy and histological analysis are always advised – associated curettage is advised
[c]Preliminary biopsy and histological analysis are always advised – associated curettage is advised (older patients, superficial lesions)
[d]Adjuvant topical or intralesional pharmacologic treatment usually associated
[e]Indicated for allergic reaction to tattoo pigment or ablative "priming" before Q-S laser photo-ablation (Ibrahimi et al. 2011; Marini and Crisman 2013)

site of treated areas; post-operative wound care is reasonably simple. Proper clinical diagnosis and lesion selection are as critical as the choice of laser parameters and light delivery systems in producing a favourable outcome. Considering that each patient is different and each lesion is unique, there are many variations to the so-called "standard" treatment protocols (Table 121.6).

Both conventional surgical infrared lasers (CS-IRL) and Q-switched infrared lasers (QS-IRL) trigger dermal nociceptors, inducing a pain response during ablative procedures. Proper topical and locoregional anaesthesia should be

Table 121.7 Stabilized Kligman's formula

Hydroquinone 5 g
Retinoic acid 0.1 g
Dexamethasone 0.125 g
Stabilizing excipient 100 g (vit. C 20 g)

performed before every ablative laser procedures in order to provide a comfortable experience for both patients and operators. Topical skin antisepsis should be performed without alcohol-based solutions in order to avoid possible explosive ignition. Ablative laser procedures can induce activation or deactivation of skin melanocytes; therefore, proper preoperative preparation and post-operative skin care should be implemented, particularly when sun-exposed skin is to be treated. Usually a modified Kligman's formula is prescribed 2 weeks prior to laser procedures (one application every day at bed time), associated with a balanced, high-SPF sunscreen during daytime (Table 121.7). The same formula is resumed 1 week post-treatment and continued for two more months. Darker skin types (Fitzpatrick 3–4) are at major risk for postinflammatory hyperpigmentation (PIH); therefore, it is strongly advisable to use class 1 topical steroids during the first 4–5 days after ablative laser procedures. Steroids should be continued according to a personalized pulsed regimen to be continued following a pulsed regimen usually (one application, two consecutive night per week) during the subsequent 2–4 months.

Complications, Side Effects, and Contraindications

Contraindications

The relatively few contraindications to ablative laser procedures are generally related to concomitant pharmacological regimes and selected skin alterations which may delay or jeopardize wound healing (Table 121.8).

Complications and Side Effects

Common complications and side effects of ablative laser procedures are listed in Table 121.8.

Table 121.8 Contraindications to ablative laser surgery

Absolute contraindications	Relative contraindications
Oral isotretinoin treatment	Pregnancy
Impaired vascular supply	Anticoagulant use
Agammaglobulinemia	Blistering disorders
Active bacterial/viral infection	Dark skin (Fitzpatrick 5–6)
Immunosuppression	Diabetes
Unexplained blood dyscrasia	Melasma

Table 121.9 Complications of ablative laser surgery

Complication type	Adverse effects
Immediate	Bleeding, edema, pain, vasovagal syncope
Delayed	Prolonged erythema, infection, altered sensation
Temporary	Postinflammatory hyperpigmentation (PIH), milia, acne reactivation, textural changes
Permanent	Hypopigmentation, demarcation lines, textural changes, and hypertrophic scarring

Moderate skin discomfort, generally a hot, burning sensation, occurs immediately after ablative laser procedures. Intensity varies according to extension and anatomical location of laser treatments. The most sensitive areas are the face, genitalia, and digital extremities. Postinflammatory hyperpigmentation (PIH) is quite common but improves within several months with proper topical treatments. Postinflammatory hypopigmentation is rare and maybe sometimes permanent. Textural changes associated with hypertrophic or hypotrophic scarring may occur after too aggressive ablative treatments. Reactivation of herpetic infections may be triggered by ablative procedures. Proper antiviral prophylaxis can effectively control this kind of complications (Table 121.9).

Conclusions

When performed properly, using the right laser equipment and delivery accessories, setting the appropriate parameters, and last, but not least, selecting the patients to be treated, ablative laser procedures will producing

excellent clinical results with few contraindications and low complication rates. Constant technical innovations surely contributed to expand the use of ablative lasers in modern dermatologic practice including procedures never thought before. Enhanced topical drug delivery, enhanced PDT, advanced tattoo pigment removal, and hypertrophic scar remodelling are just some of them. The future of ablative lasers is quite bright, and dermatology will certainly be at the forefront of its further developments.

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Mohs' Surgery

122

António Picoto, Jose Manuel Labareda,
Rui Themido, and Fernanda Coelho

Key Points

- Micrographic surgery is a method where a skin tumour is excised in horizontal successive layers followed by immediate preparation of frozen sections for histological examination.
- For the treatment of skin cancer, Mohs' micrographic surgery is currently the method that achieves the best cure rate.
- Preservation of healthy tissues is another great advantage of this method.
- Mohs' surgery is not indicated for multicentric tumours, patients unable to follow post-operative rules and cope with local anaesthesia and cases with bone invasion or invasion of natural cavities of the human body.

General Principles

Mohs' micrographic surgery was created in 1930 by Dr. Frederic Mohs, a North American surgeon working on his thesis in Madison, Wisconsin. He found that if a paste of zinc chloride was applied to tumours in vivo, for 24 h he would have a slice of "controlled" necrosis. "Controlled" because after separation of the necrotic tissue with a scalpel, histological slides could be prepared because the typical architecture was preserved. This method involved successive in vivo fixation followed by a deeper horizontal layer being taken from the patient each time. The fixation in vivo was painful for the patient and in certain locations could not be used because of the risk involved. If used on the eyelids, a spillage of the paste onto the eyeball could lead to serious lesions of the cornea. Therefore when treating the eyelids, Mohs did not use the paste but made the excisions similarly in horizontal succession under local anaesthesia. Then he made the histological preparations using a cryostat to obtain frozen cuts. He realized that this "fresh tissue technique" enabled him to reach the tumour-free plane much faster so that immediate surgical reconstruction was possible. He published his preliminary results in the book *Skin Surgery* edited by Epstein in 1956.

In 1970, Dr. Tromovitch showed his results with the "fresh tissue technique" applied to the treatment of tumours in different locations other than the eyelids in a Meeting of the American College of Chemosurgery. Dr. Tromovitch and Dr. Stegman promoted the diffusion of this technique that became widely used.

Another important step in the dissemination of this therapeutic modality for the treatment of skin cancer was the initiation by Professor Perry Robins in New York of the first 1-year chemosurgery education programme in the USA.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_122, © Springer-Verlag Berlin Heidelberg 2015

In 1990, the authors and other European doctors founded in Estoril (Portugal) the European Society for Micrographic Surgery. This Society gets together Mohs' surgeons from Europe and Israel and tries to make the method familiar to European doctors. In a so-called millennium paper, Brodland et al. (2000) write about the American history and evolution of Mohs' micrographic surgery.

Technique

Mohs' micrographic surgery is a method where a skin tumour is excised in horizontal successive layers followed by the immediate preparation of frozen sections for histological examination. Because a thin and horizontal piece of tissue is controlled, the bottom and lateral borders are controlled, and theoretically if the tumour persists, it will show in the histological slides. Simultaneously a map is drawn where the division of the tissue is marked and the anatomical orientation is indicated. At each stage, the tissue provided by the surgeon's excision, with the scalpel held at approximately 45° in relation to the skin plane, is divided into pieces preferably not more than 1 cm in diameter. The pieces are marked on faces opposing the skin edge with ink markers, normally black and green or red. Each stage is repeated until a plane free of tumour is reached. After that, immediate reconstruction can be done (Figs. 122.1, 122.2 and 122.3).

Because there are many methods for controlling skin tumour excision, the American College of Mohs' Micrographic Surgery and Cutaneous Oncology published a "position paper" where the principles are very clearly stated. The uniqueness of the method and base of its excellency is the horizontal control of the tissue with all its margins included – lateral and bottom.

The mapping should be accurate and we use xerocopies of anatomical drawings and measure exactly the pieces of tissue extracted so that we can exactly situate the tumour nests that we find after microscopic examination. Joseph Alcalay described a very interesting way to do the mapping with extreme accuracy. He has called it digital computerized mapping in Mohs' micrographic surgery.

The pieces of tissue are embedded in OCT compound and cut in a cryostat. It is very important that the first or second cut is obtained in perfect condition; otherwise, we will be marching towards the surface and abandoning the real margins.

The cryostat should be able to keep a low temperature (between −26 and −30 °C), and the cutting blade should be very sharp – preferably using a disposable blade. After cutting the tissue, we move to the staining of the frozen sections. The most common method is haematoxylin and eosin (H & E) or toluidine blue. Recently a variation has been described using haematoxylin and safranin instead of H & E

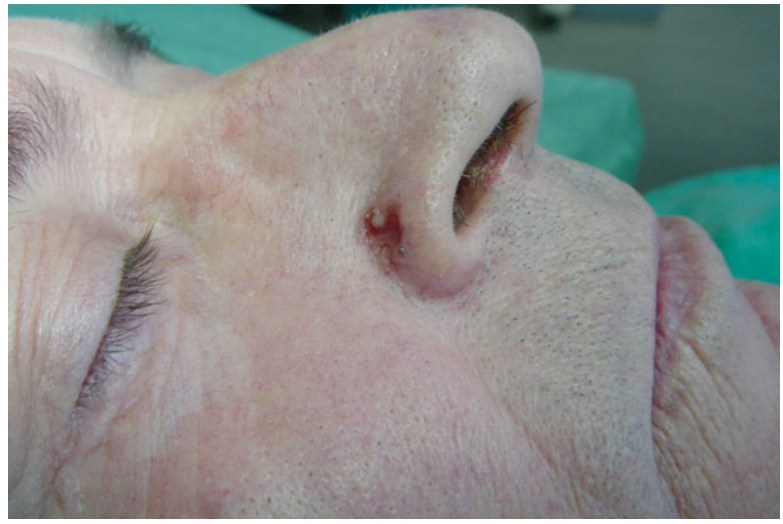

Fig. 122.1 A recurrent basal cell carcinoma

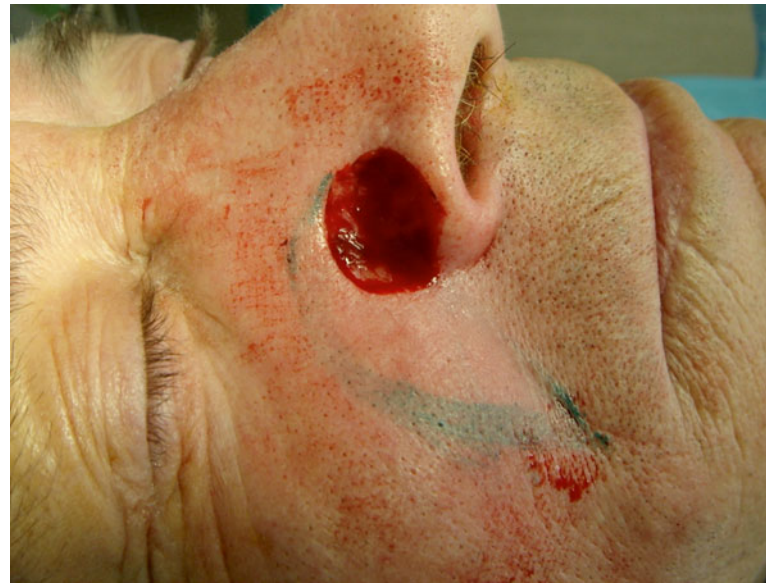

Fig. 122.2 The defect after Mohs' surgery

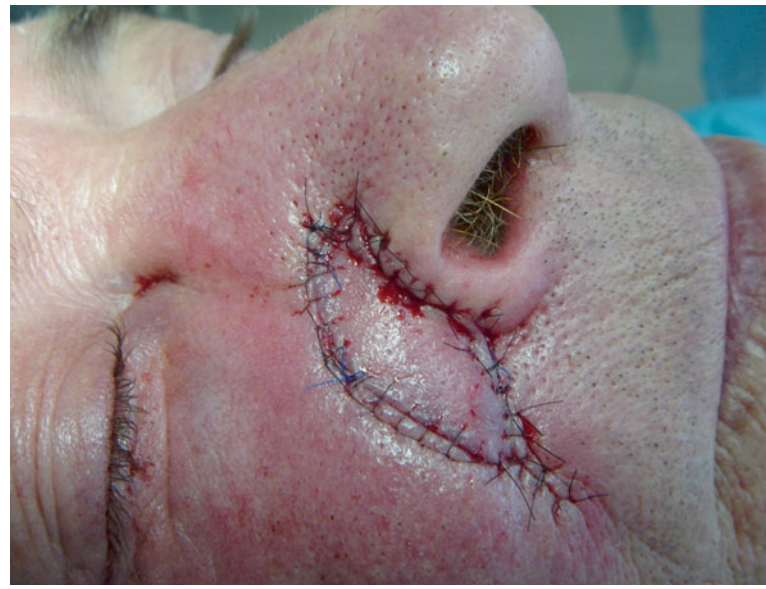

Fig. 122.3 Reconstruction done

apparently with superior results in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

In the last years, much investigation has been done on the use of special stains that could help detect tumour cells of difficult tumours among dense infiltrates or around nerves. One can use either immunohistochemical techniques as described by Jimenez et al. and Ramnarain et al. or immunoperoxidase techniques as described by Mondragon et al.

Indications for Mohs' Micrographic Surgery

For the treatment of skin cancer, Mohs' micrographic surgery is currently the method that achieves the best cure rate. Another advantage to consider is the preservation of healthy tissue because in Mohs' micrographic surgery, there is no "blind" margin of security. This can be of great value for the reconstruction of defects on the face, extremities and genitals.

Mohs' micrographic surgery is indicated for basal cell carcinomas and squamous cell carcinomas:

- That are recurrent
- That are more than 2 cm in diameter
- With histologically demonstrated perineural invasion
- With poorly defined borders
- That are persistent after previous surgery
- That are located near the orifices of the face, ears, scalp, extremities and genitals
- That are invasive histological types
- In immunocompromised host
- To check and ensure if excision was complete

Other cutaneous tumours:

- Bowen's disease and erythroplasia of Queyrat
- Dermatofibrosarcoma protuberans
- Merkel carcinoma
- Atypical fibroxanthoma
- Other uncommon tumours (microcystic adnexal carcinoma, sebaceous gland carcinoma, extramammary Paget's disease, angiosarcoma, malignant fibrous histiocytoma)

Some indications are debatable, in particular melanoma. In the case of melanoma, a complete excision block is the only sound basis for good histological examination as it is so important for establishing what further treatment and follow-up guidelines are required and to determine the prognosis. Difficulty in distinguishing melanoma cells from benign melanocytes in frozen sections was overcome with melanoma immunostaining techniques, namely, HMB-45, Mart-1 and Melan-A. Mohs' surgery may be useful for melanomas in areas where it is necessary to conserve tissue, namely, the head, neck and extremities.

The drawback is the increase in expense and time needed in between Mohs' stages.

It is also important to know what should not be referred for Mohs' micrographic surgery:

- Multicentric tumours
- Patients unable to follow the post-operative rules and to cope with the local anaesthetic in successive stages – cooperation of the patient in this is essential
- Patients with bone invasion or invasion of natural cavities

Conclusions

Mohs' micrographic surgery is a specific surgical method for the treatment of aggressive skin cancers and so far achieves the best cure rates with maximum spared tissue of all therapeutic modalities.

It is not an expensive method – the cryostat is the only expensive tool and most dermatology services have their own cryostat or easy access to one in general pathology. Proper training and appropriate referral of patients are essential elements for excellent performance; cooperation with other medical specialists is desirable.

Mohs' micrographic surgery should only be used when necessary, and recent studies have found that the referral rate for the treatment of nonmelanoma skin cancer will be approximately 20 % of all cases seen in a clinic.

In some rare cases, Mohs' surgery can be incomplete, either because the cancer has proved to be unresectable or the patient has been unable to tolerate further surgery. In a study published by Madaniet al. (2000), this happened only in 14 out of 10,346 procedures (0.15 %).

Asgari et al. (2009) compared patient short-term and long-term satisfaction before and after treatment of skin cancer with other therapeutic modalities and Mohs' micrographic surgery.

Patients treated with Mohs' surgery are more satisfied in the long term compared to patients submitted to other treatments.

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Mycological Examination

123

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Key Points

- Mycoses are diseases caused by fungi, present in the soil, air, contaminated food, animals, and humans. Fungi are classified according to the microscopy appearance and by the method of reproduction in culture. Therefore, laboratory testing is necessary to confirm the diagnosis in all conditions.
- Superficial localized infection can be diagnosed rapidly by taking fresh unstained material (skin, nails, hairs) to be examined by *direct microscopy* after potassium hydroxide (KOH) clarification. This procedure is usually rapid and easy to handle even in general practice, if provided with a light microscopy.
- *Fungal culture* is necessary to identify the fungus and to confirm the vitality of the strain. When a local or systemic antifungal treatment is performed, culture is necessary to assess effective recovery or current infection. It requires specific training and great expertise, reserved to specialized mycology laboratories.
- False-negative results are possible; therefore, *biopsy and histology* are indicated if direct microscopy and culture are negative and clinical suspicion is high.
- *Wood's lamp examination* has very limited indication, detecting the natural luminescence of only few pathogens, mainly *Microsporum spp.*, *Malassezia furfur*, and *Corynebacterium minutissimum*.
- *Molecular techniques*, such as DNA hybridization and PCR, are useful to prompt diagnosis, detecting even small amounts of fungi, but are expensive procedures, limited to the research or reference laboratories for the diagnosis of rare fungal infections, which are difficult or dangerous to cultivate in vitro.
- Great simplification of the fungal identification process is expected from the introduction of the *assay mass spectrometry* in routine laboratory.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_123,

General Principles

Mycological examination is the diagnostic procedure necessary to confirm a fungal disease, from the Greek word "mykes" meaning mushroom. The mycological test is also necessary to document the complete cure response to treatment, as clinical recovery is often followed by a relapse if the fungus has not been completely eliminated from the skin (mycological cure). The diagnosis of a fungal infection is considered simple from a clinical point of view, but the report of unusual presentations, misdiagnosed or sometimes neglected, has increased worldwide causing extensive and long-standing disease. General immunosuppressive treatment for inflammatory chronic diseases and acquired immune depression syndrome are frequently complicated with fungal superinfections, both from common strain and rare or opportunistic fungal species, such as cryptococcosis, histoplasmosis, sporotrichosis, blastomycosis, and aspergillosis. In the immunocompetent patient, dermatophytes are the main fungal infection, being the primary pathogen. Clinical presentation has also changed with time, from the classic ringworm appearance (tinea) to more veiled eczematous undefined patches, simulating more frequent diseases, such as atopic or contact eczema, seborrheic dermatitis, impetigo, rosacea, and lupus erythematosus. A general common attitude to prescribe combination treatments and/or corticosteroid topics before confirming the diagnosis ("ex adjuvantibus") is one of the possible causes of further dermatophyte pathomorphosis and misdiagnosis, named tinea incognita or tinea atypica.

The etiology of a fungal infection is rapidly proved with laboratory testing and possible in a general office if provided with very basic light microscopy. Besides, few dermatologists and laboratory physicians are trained to recognize dermatophytes. Final identification of the species requires culture facilities and further expertise, which should be referred to a mycology laboratory.

False-negative results are possible, especially if the specimen is not correctly taken, and more invasive assessment should be performed before ruling out the diagnosis of a fungal disease. Biopsy specimens for histopathology examination with PAS or silver staining are indicated when clinical suspicion is high. Sensitivity of culture alone is about 32 %, while histology reaches 85 %, especially in onychomycosis.

A specific fluorescent dye named calcofluor-white might be used, because it binds selectively to the fungal cell wall chitin (apple green fluorescence), but a fluoroscope is necessary.

A molecular approach has been proposed, but the tool is expensive; a plethora of different methods has been proposed without conclusive validation and therefore has never gained much popularity. Direct staining with monoclonal antibody labeled with fluorescent dyes has been proposed to detect rare and small amounts of fungi in the clinical specimens, mainly *Pneumocystis carinii* in bronchoalveolar lavage.

The perspective in clinical mycology laboratories is the fast fungal identification by assay mass spectrometry (matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer (MS)) from clinical cultures. Spectral databases (biotype library) of different fungal species have been realized by several independent researchers, and preliminary results confirm the usefulness of the tool, with a sensitivity of 91.9 % on skin isolates, which is hoped to become routine in the immediate future.

Biology and Morphology of the Fungi

Fungal microscopy identification requires an extensive knowledge of fungi biology as a whole, whose principles are magisterially described in the reference book by Grigoriu et al. (1987) and are somewhat synthesized as follows.

Fungi are classified with the lower plants (category, cryptogams; phylum, thallophytes), although devoid of chlorophyll and incapable of photosynthesis, and they are:

- *Heterotrophic*, meaning they subside on organic substances for survival and are unable to directly elaborate mineral elements, such as green plants. They are provided with several

enzyme systems able to digest organic substances (keratin) and to de novo synthesize toxins and antibiotics.
- *Aerobic*, developing at different temperatures varying from one species to another, but usually ranging between 20 and 37 °C, preferring neutral pH and several degrees of humidity, while dryness is poorly tolerated. Direct light exposure has different effects among species, fostering or inhibiting growth.
- *Eukaryotes*, with well-differentiated cytoplasm and nuclei. They consist of a thallus or aerius mycelium, which is a matted network of branching tubes called hyphae, filled with the living substance, continuously expanding with growing tips. The thallus accomplishes both vegetative and reproductive functions: from the central starting point of the colony, the hyphae develop centrifugally in all directions obtaining nourishment from the environment, with the young elements at the periphery and aging dead elements at the center. When the vegetative expanding apparatus has accumulated sufficient nourishment and the environment is favorable, the reproductive phase might take place, which can be either sexual (*perfect fungi*) or asexual. A limited number of fungal species do not have a documented sexual way of reproduction and for this reason are called *imperfect fungi*.

A number of *classifications* have been proposed on the basis of the thallus' different characteristic and sexual reproduction ways, to consent a precise nomenclature and identification, whose simplest ones are illustrated in Table 123.1.

- On the basis of thallium morphology, it is possible to distinguish among septate and not septate fungi. A single cell generates a type of thallus with intercommunicating filaments (hyphae), named coenocytic filaments, without subdivision and therefore called aseptate hyphae. Other thalli are made of septated hyphae, which indicate the presence of regular periodical septal division in the filaments, provided with central pores allowing the passage of nutrients from one segment to the other. Another type of thallus consists of isolated cells, solely and elongated or attached one to the other, forming fragile, eventually branching chains but without intercommunication, therefore called pseudomycelium.
- The principal way of fungal reproduction in pathologic material is asexual, producing a variety of spores (Table 123.2) responsible for fungal dissemination in the environment. The aspect of pathogenic fungi might differ from the parasitic state to the culture optimal saprophytic state. In fact, mycelia fungi do not usually deserve fruiting bodies in the pathologic materials, and species identification is possible only in culture specimens. Yeasts might bud in vivo, while the so-called dimorphic fungi are typically found as yeast cells in pathologic material, producing mycelia filaments in cultures.

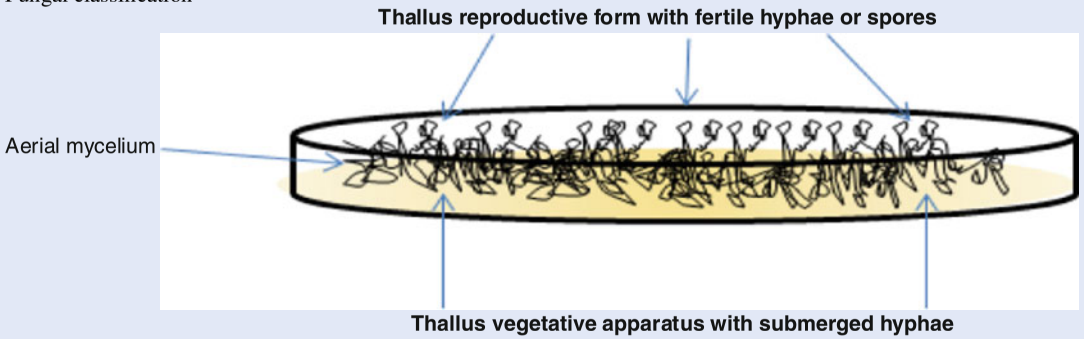
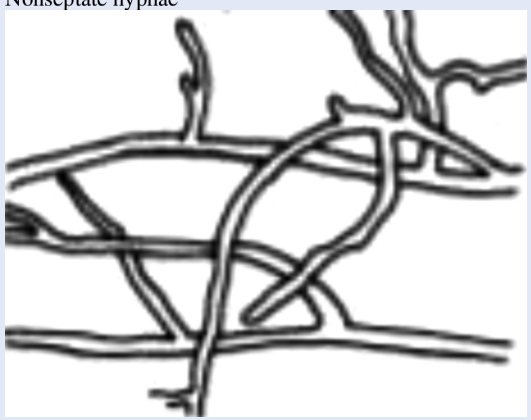
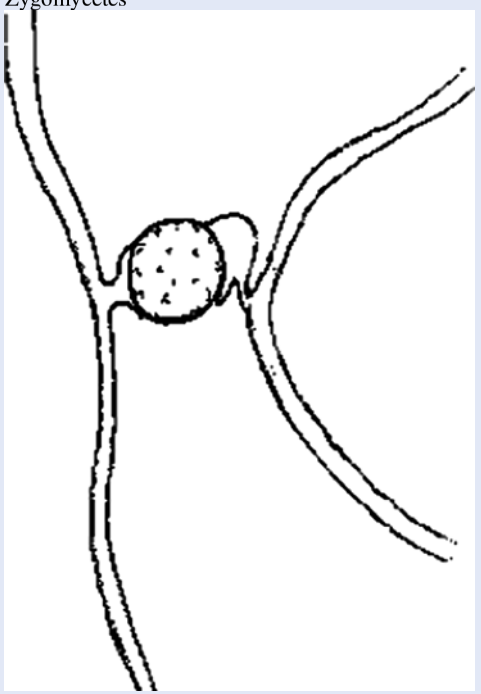
Basic Concepts Related to the Pathogens

From a practical medical point of view, the pathogenic fungi for humans are:
- Dermatophytes (whose mycological diagnosis is extensively treated in this chapter)
- Yeasts and yeastlike fungi (whose laboratory diagnosis requires specialized equipment and expertise, and only basic concepts are expressed in this chapter)
- Some dimorphic and opportunistic fungi, becoming pathogen under peculiar circumstances (whose diagnosis is not developed in this chapter)

Dermatophyte Infections

Dermatophytes are actually classified among the ascomycetes and represent a closely related group of fungi, whose main pathogens for humans are the *Trichophyton*, *Microsporum*, and *Epidermophyton* genera. They are ubiquitous and are characterized by the ability to use keratin as a nutrient source, therefore evolving a dependency on humans and/or animals for the survival and dissemination of their species. They are noninva-

Table 123.1 Fungal classification based on the thallus characteristics and type of sexual reproduction

Fungal classification		Type of sexual reproduction
		
Nonseptate hyphae  The thallus is characterized by continuous filaments, without any septa, forming the coenocytic thallus or coenocytes. The cellular multiple nuclear divisions are not followed by the cytokinesis, resulting in single coordinated unit composed of multiple cells linked structurally and functionally	Zygomycetes 	The name comes from the type of sexual reproduction, taking place in a specialized organ named zygosporangia, forming resistant spherical spores. They live in soil, on decaying plant, or on animal material

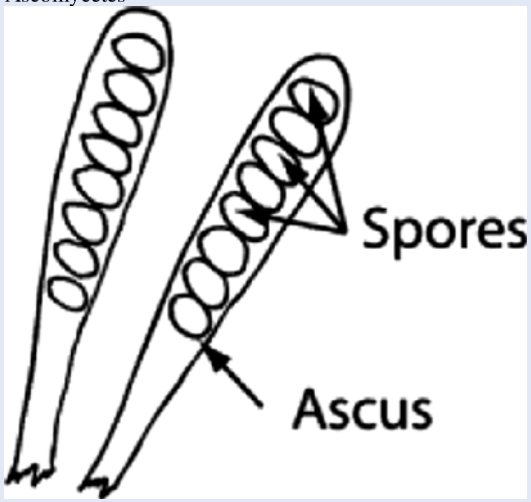
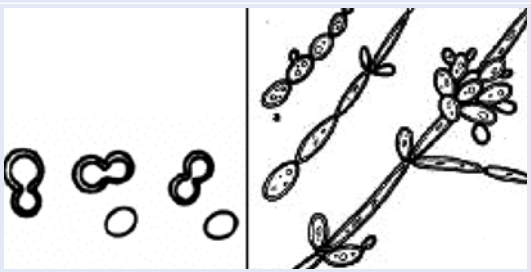
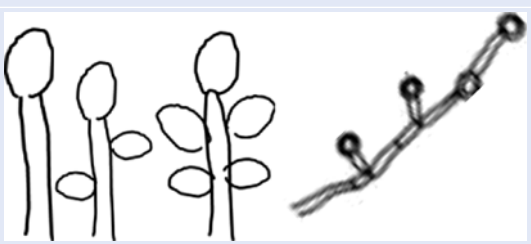
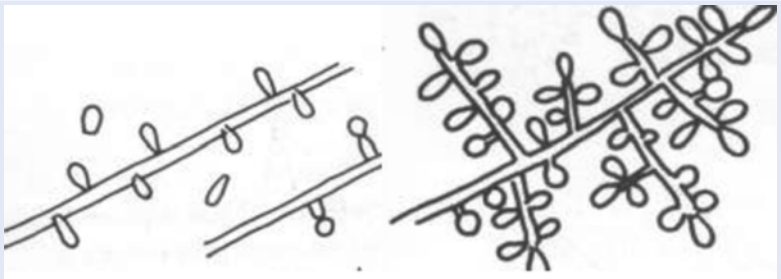
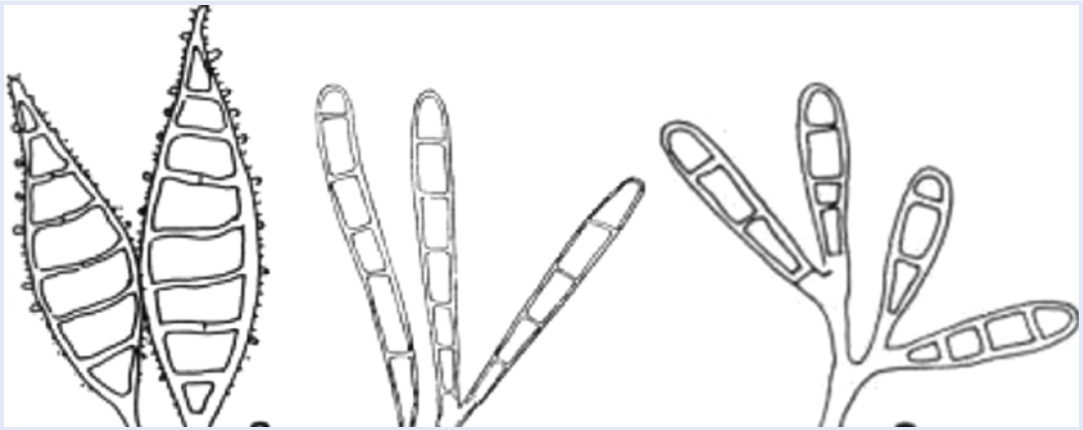
Septate hyphae  The thallus is characterized by regular interruption of the filaments (hyphae), called septate provided with central pores allowing the passage of nutrients from one segment to the other	Ascomycetes 	The sexual reproduction takes place in a specialized ovum structure (ascus), formed by the fusion of a male and female gamete, inside which successive divisions of the zygote produce unicellular endospores (ascospores)
	Basidiomycetes 	Similar sexual reproductive process, but the ovum makes peculiar extrusion towards the external space, called basidiospores, keeping them attached to the central core by minute arm called sterigmata
	Imperfect fungi	The thallus produces septate hyphae in the vegetative state, but the sexual reproduction modality has never been documented

Table 123.2 Distinctive morphological characteristics of fungal spores

Arthrospores	Formed by septated hyphae fragmentation, at the tip of the filaments, maintaining a rectangular shape	
Blastospores	Budding cells, the bud separating from the parent cell or keeping the linkage for a certain time and yet continue budding to produce extensive branching (pseudomycelia)	
Chlamydospores	Swollen portion of the hypha or pseudohypha, with a very thick double wall (intercalary or terminal), which ensures resistance to many adverse conditions	
Aleuriospores	Lateral budding of the hypha, disposed like a Cross of Lorraine or bunches, which remains attached to the hypha axis	

Microconidia	They are identical to aleuriospores but are deciduous and detach from the hypha immediately after their formation	
Macroconidia or fuseaux	Very voluminous and elongated septated budding, with the same significance of microconidia	
Dictyospores	Multicellular digitiform or globular elements	

sive, as they colonize the keratinized stratum corneum, which is a nonliving tissue. However, the presence of the fungus and its metabolic products usually induces an inflammatory eczematous response in the host, counteracting the parasitism. More severe reactions might be related to the species and strain of dermatophyte causing the infection, but also from host predisposing condition, such as skin barrier alterations or previous skin diseases.

- The superficial dermatophyte infections affect the outer layers of the skin, the nails, and hairs. Growing fungi produce typically branched and compartmented septate filaments (hyphae) and arthrospores, which break off from the hyphae at the septate level and represent the main ways of propagation and species conservation. Each segment forms a physiological unit.
- In culture, the characteristic morphology of the reproductive spores (micro- and macroconidia) and accessory features consent species identification.

Guidelines for Proper Specimen Collection in Dermatophyte Infections

Specimen collection is a delicate moment and is the first cause of false-negative results. It should be adapted to the site affected and type of material, including skin scrapings, broken hairs, nail clippings, corneal scraping, and body fluids such blood, CSF, urine, sputum, as well as discharge or pus from lesions.

All specimens must be transported to the laboratory without delay to prevent bacterial overgrowth. Some laboratories suggest refrigeration if a long delay is expected, especially for body fluids and discharged materials, but it is recommended only for a short period.

Skin scales scrapings are best taken from the leading edge of the rash, after the skin has been cleaned with soaks of 0.9 % saline solution to remove cream residuals. Disinfection with alcohol or ether is often advocated but is not necessary and might remove the upper scales which are the most infested. Gently remove the surface skin using a blade or curette and place the material in a sterile container or a black paper envelope (Fig. 123.1).

Hairs should be gently pulled out with a pair of tweezers, choosing those broken off at the surface (black dots) or few millimeters from the follicle, discolored and lusterless, surrounded by a whitish sheath, or covered by scales (Fig. 123.1). Parasitized hairs are removed easily and painless. A toothbrush can be used to collect scales from the infected scalp.

Nail clippings are usually taken from the ventral surface scaly deposits, using a blunt curette or a blade. If the nail plate is widely detached and full of debris, the distal end should be cut with a pair of scissors and discarded to find the fresh infected nail. Depending on the site of involvement, the lateral and/or proximal surface of the nail plate should also be scraped (Fig. 123.2).

Examination by Direct Microscopy

The most common and first step laboratory examination is to examine fresh unstained materials (*native preparation*), such as scales, hairs, and nails. Part of the material is placed on a clean slide and eventually split to very fine dust with the aid of a blade. Body fluids, content of vesicles, and pustules can be also directly placed on the smear. Keratinized material and cell walls are opaque at microscopy, and some chemical solutions (Table 123.3) must be added to dissolve keratinocytes and make the material transparent, a process that is called "clearing." Certain laboratories add glycerin to delay the preparation drying out and have more time to perform the slide lecture. One or two drops of the clearing agent is put on the collected material on the slide and then covered with a cover slip (Fig. 123.1). The most used clearing solution is potassium hydroxide (KOH) in 10–40 % concentrations. It is very cheap and stable on light and does not

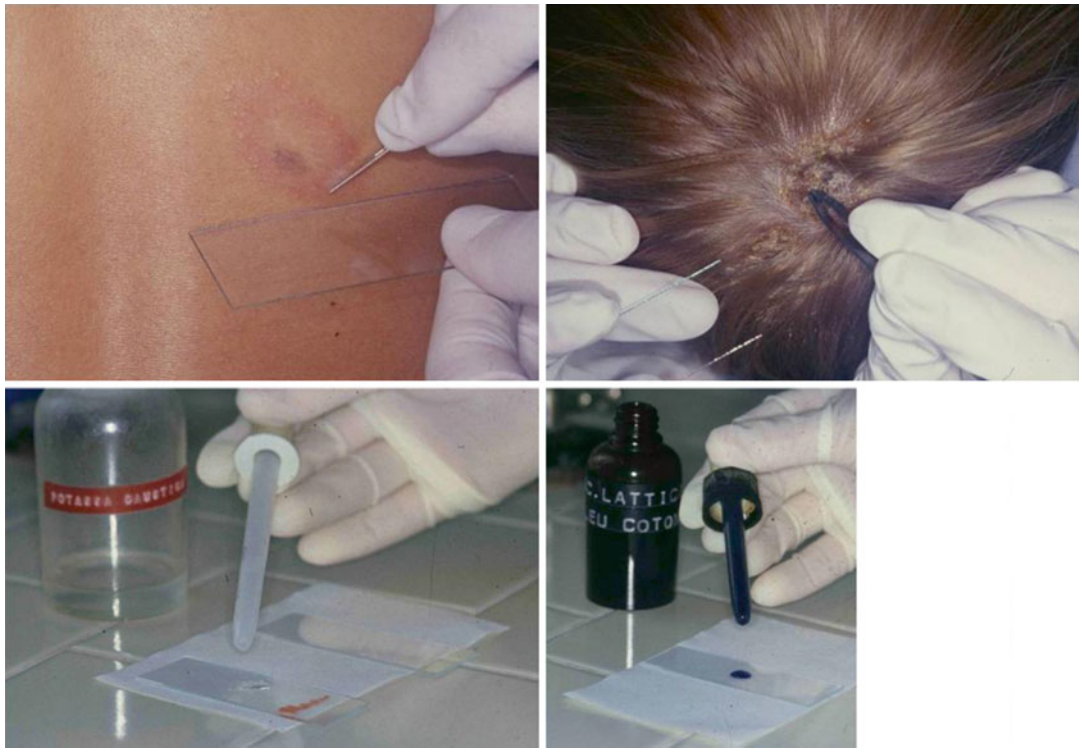


Fig. 123.1 Correct execution of the scales sample from the active borders of an erythematous scaling round-shaped lesion (*top-left* inset); correct execution of the hair sample from discolored and few millimeter broken-off hairs plucked with a pair of eyebrow tweezers (*top-right* inset). The native preparation is put on a smear and a drop of a clearing solution is added (*down-left* inset); staining with blue or black ink preparations might be useful to highlight hyphae and arthrospores or yeasts presence (*downright* inset)

need particular conservation or caution, and the preparation is rapidly ready. Time to clearing depends on the material type and thickness, the hairs being rapidly destroyed by KOH and therefore examined in 20 min, 1 h at most; the skin scales usually are examined within 3 h, while the nails are more resistant, sometimes requiring 24 h and addition of new clearing solution or physiologic solution, because one of the major disadvantages with KOH is precipitation and formation of crystals. Additional staining with methylene blue, Parker blue, or black ink do not replace direct examination (Fig. 123.1), but it is sometimes useful to highlight the chitin in the fungal cell walls. Fixation and staining with lactophenol cotton blue (LPCB) is preferred to observe yeasts, fungal accessories, and fruiting structures, especially from culture specimen.

The microscopic examination is first performed under a low-power lens (100×) run carefully along the slide to find fields of interests (Fig. 123.3). Once the fungus is detected, the high-power lens (200 or 400x) observation allows for true hyphae confirmation and distinction from pseudohyphae, as well as arthrospores selection from yeasts.

Fungal elements are sometimes difficult to find, and a negative result does not rule out fungal infection. Microscopy should be repeated, possibly with fresh material or giving more time to clearing and repeating the observation with great perseverance.

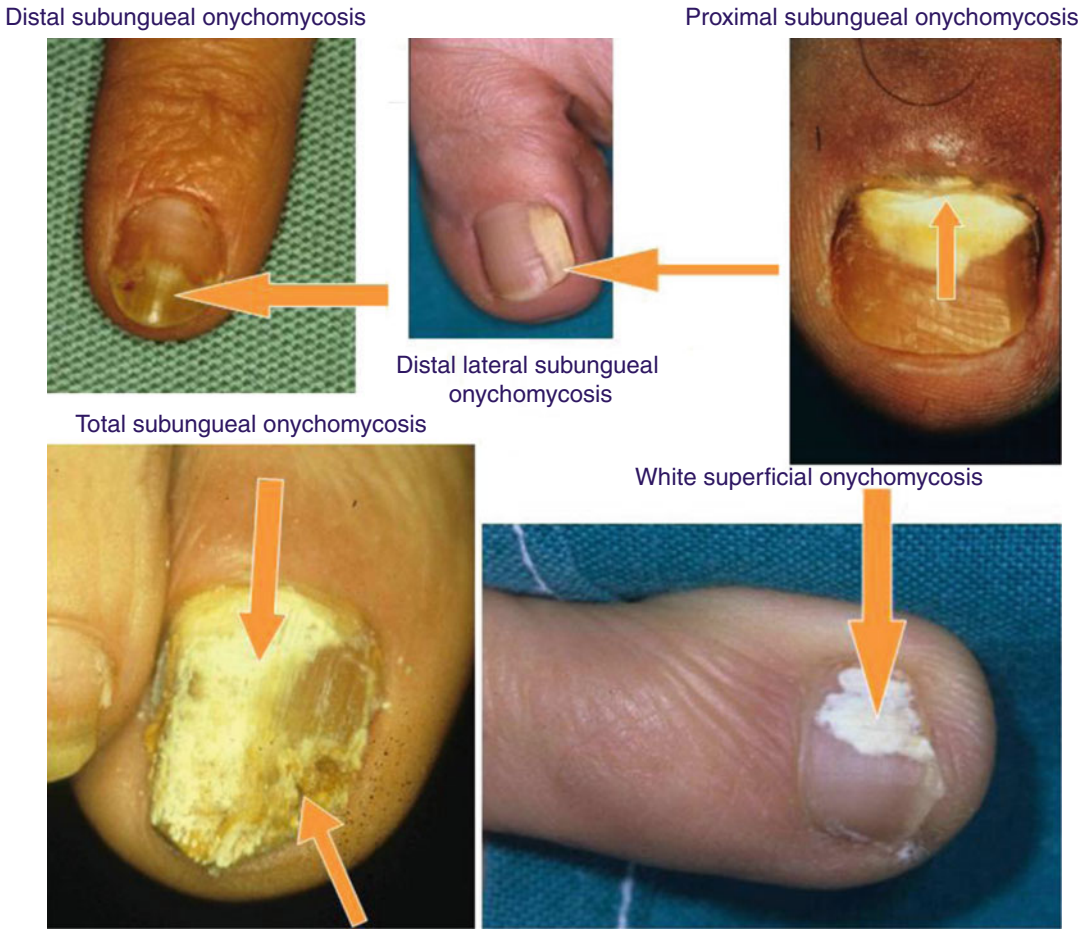


Fig. 123.2 Correct site of sampling depending on the clinical form of onychomycosis

Table 123.3 Clearing solutions for direct microscopic examination

Chemical solution	Preparation
KOH	Potassium hydroxide 10–40 % concentration
Amann's chlorallactophenol	Equal parts of chloral hydrate + lactic acid + phenol
Sodium sulfide	10 % sodium sulfide in a solution made of ¾ distilled water and ¼ 80 % alcohol
Sodium lauryl sulfate	5 % in distilled water

Direct Microscopic Examination Pitfalls

Specific training is necessary to avoid the many possible sources of errors in mycology, as in any other laboratory procedure.

- Mistakes in sample collection: insufficient material, inadequate site of sampling, and contamination.
- Insufficient clearing and hasty observation yield most false-negative results.
- Artifacts (Fig. 123.4): the mycelia filaments and arthrospores have to be distinguished from:
  - Fungus mosaics: a network made of refractive small filaments or crystals, irregular in shape and diameter, whose chain arrangement is very similar to the mycelia and might mislead a nonexpert investigator. They are cell debris containing cholesterol crystals due to a reaction of the intercellular substance with potassium hydroxide. Usually the mosaics are located at the limits of the cells and disappear if a drop of

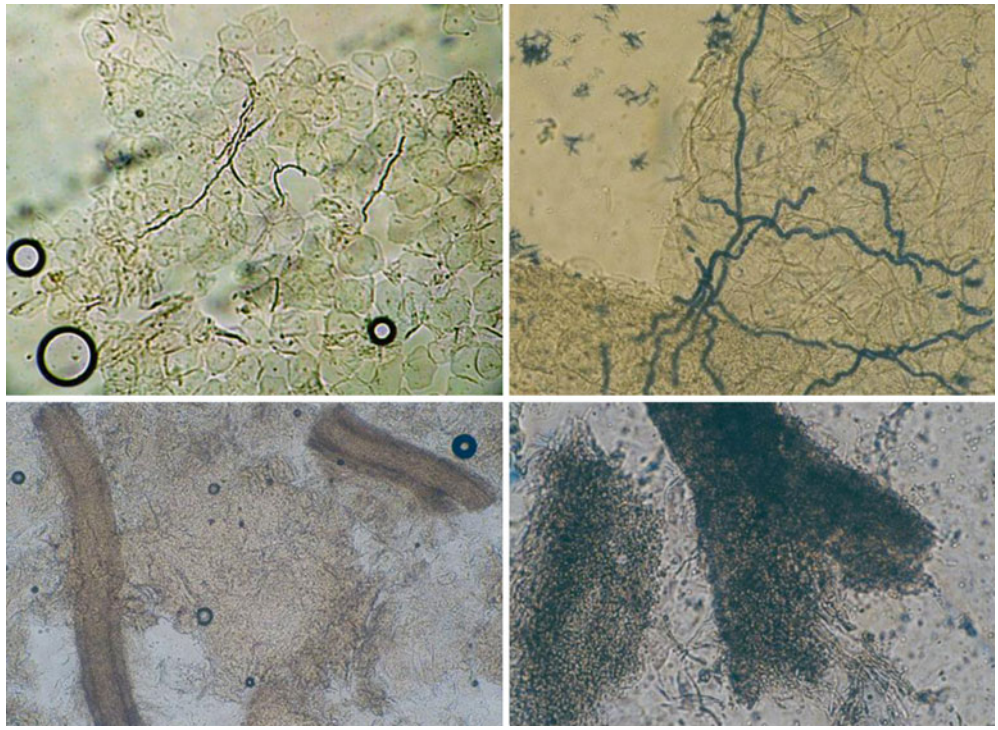


Fig. 123.3 Skin scraping: under low-power light microscopy, selection of a field of interest (*top-left* inset; 100×); major definition of hyphae and arthrospores characteristics at higher power observation (*top-right* inset; 400×). Parasitized hairs: sheath of arthrospores surrounding the hair shaft in an ectothrix arrangement and hyphae presence in the scales (*bottom-left* inset; 100×); hyphae and arthrospores inside the hair root and shaft in endothrix parasitism (*bottom-right* inset; 400×)

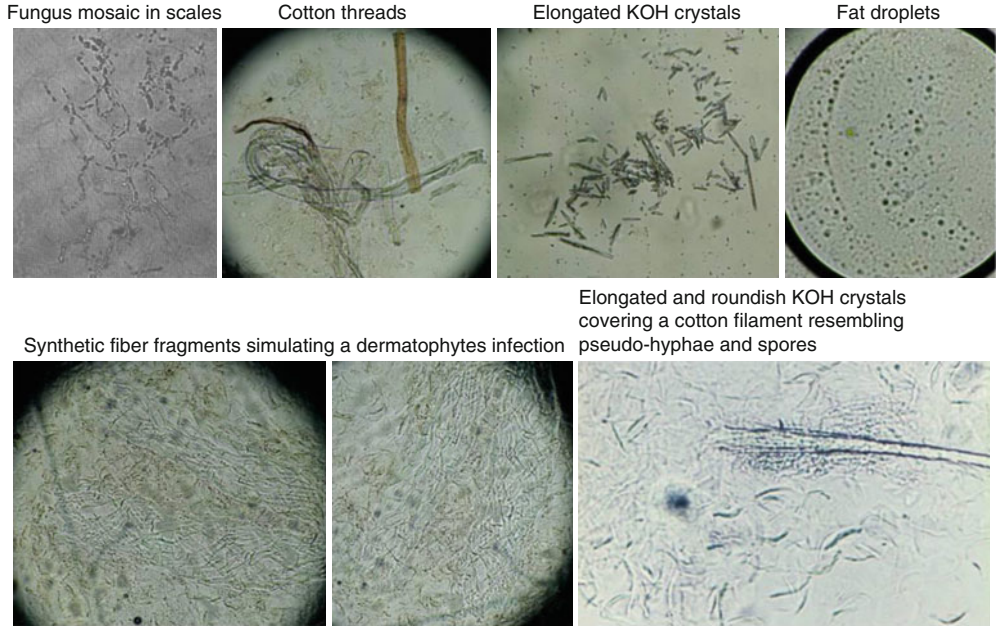


Fig. 123.4 Microscopic examination artifacts

glycerol or physiologic solution is added to the preparation. The higher-power observation (100×) enables the distinction from the fungal hyphae, which are regular in caliber and shape, septated, connected together continuously.
  - Cotton threads, other vegetal filaments and fur brittles, which are usually woven or twisted on their axis and irregular in caliber, tufted at the extremities.
  - Polyhedral or elongated crystals: refractive bodies differing in appearance one from the other and not connected together. It is the dehydrated clearing agent that usually causes this artifact, and a drop of distilled water added directly to the smear makes them to disappear.
  - Fat droplets, refractive roundish or oval bodies, enclosed by a double membrane frequently due to the previous use of cosmetic creams, persisting on the skin although disinfected. Cleaning with water and soap before examination is advisable.
- Filamentous bacteria: some *Actinomycetales* bacteria and particularly the *Streptomyces* genus are able to produce a network of branching filaments very similar to the fungal mycelia, but smaller in dimensions (0.5–0.8 μm).

Yeast Infections

Yeasts and yeastlike are a subtype of fungal species characterized by clusters of round or oval cells. They divide and propagate budding out similar cells from their surface. Some yeasts are capable of producing filaments, which remain part of the single original cell, not connected with other elements and called pseudohyphae. They are usually saprophytic, but a pathogenic potential might arise in the presence of several favoring conditions. The main yeasts causing human superficial skin infections, whose diagnosis might be confirmed in a general laboratory provided with a light microscopy, are:

- *Candida* species and *Torulopsis glabrata*
- *Malassezia* species

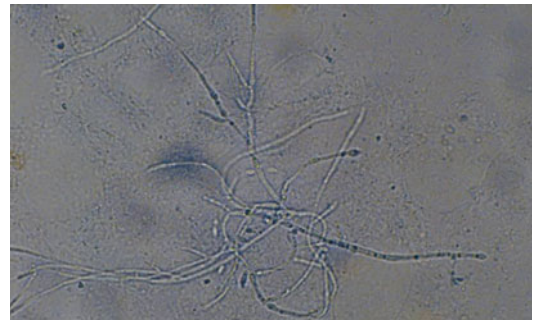


Fig. 123.5 *Candida* yeast cells and pseudohyphae in a groin intertrigo (400×)

Specimen Collection and Examination by Direct Microscopy

Basic concepts and procedures are similar to dermatophyte mycological examination, and only useful additional information for the general practice is addressed in the following paragraphs.

Candida spp. *infection* can be confirmed by swabs and by scrapings. The pathologic material (scales, pustules, white deposits, and secretions) is cleared with KOH between the slide and the cover slip. Urine can be examined without clarification, and blood is seeded directly on the medium for culture. Under the microscope, the presence of pseudohyphae and round, oval yeasts forms might be sufficient to confirm the type of infection (Fig. 123.5), but when dealing with opportunistic infections, culture execution is recommended to confirm pathogenicity instead of simple colonization. Detection of yeasts should be interpreted in close cooperation with clinicians, and equivocal or unusual findings should be verified by repeated laboratory tests. Superinfection of skin lesions in the course of several diseases is very frequent, and *Candida* detection is not sufficient to ascribe its etiologic role. Histology is sometimes necessary to distinguish primary infection from superinfection.

Malassezia spp. *infection* is better documented by stripping off the skin surface with an adhesive tape (scotch test), as the scales are very subtle and superficial. The scotch is then stuck on

a glass slide and examined using potassium hydroxide (KOH), eventually stained with blue or black ink preparation. The abundant presence of the fungal filamentous form budding from the yeast cells in a pattern called "spaghetti with meatballs" is very peculiar and diagnostic (Fig. 123.6).

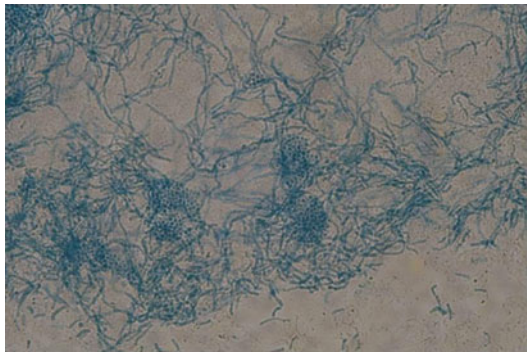


Fig. 123.6 *S*kin scotch test after KOH + Parker's blue clarification positive for *Malassezia furfur* pseudohyphae and clusters of yeastlike cells (400×)

Fungal Culture

General Principles of the Correct Procedure and Fungal Identification

Culture is necessary to correctly identify most of the fungal species but requires great expertise, and only very specialized laboratories are reliable.

Specimen collection is similar to the previously described technique for direct examination, but sterile materials should be used, because the transferring process of the pathologic samples (scales, hairs, nails) is a delicate moment, at high risk of contamination. Every subsequent passage should be performed under sterile conditions. The specimen must be placed on a sterile plate, subdivided into small particles with the aid of a sterile dissecting needle or a razor blade and collected with a previously flamed platinum loop to be seeded on the culture medium (Fig. 123.7). A distance of about 1 cm should be maintained

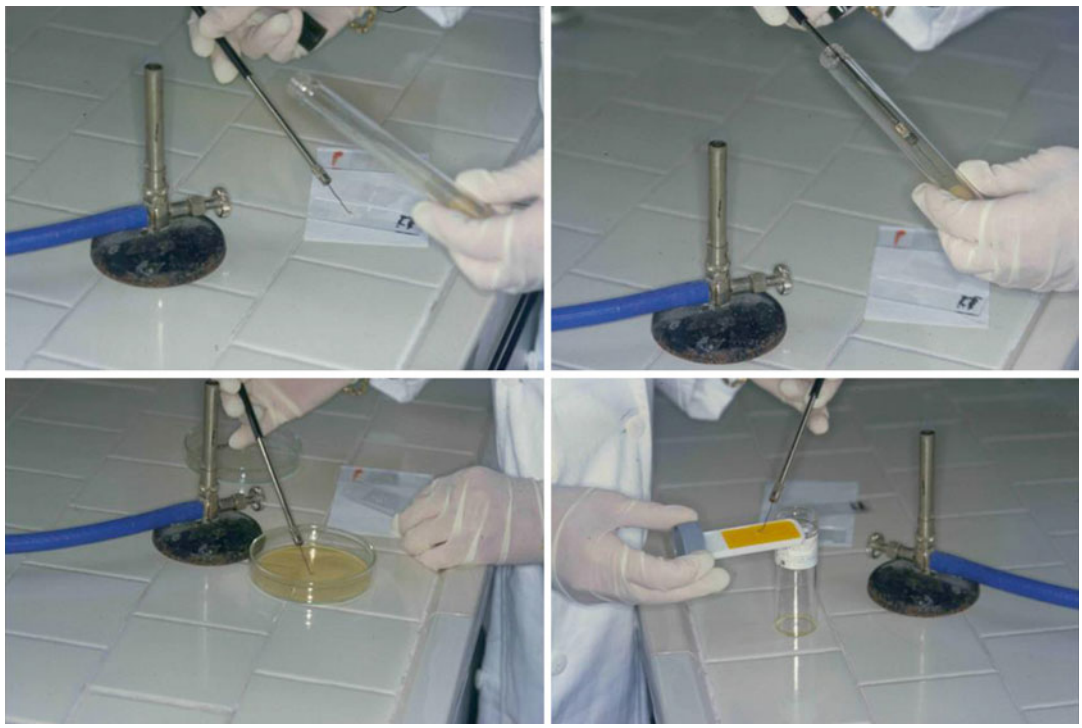


Fig. 123.7 Culture technique: transferring process of the pathologic material on different medium containers

between each inoculum on the medium surface. The test tubes or Petri dishes must be taken from fridge cool to room temperature, and the mouth of the tube or the dish plate must be flamed with a Bunsen burner to sterilize it.

The most commonly used culture medium is Sabouraud's dextrose agar added with cycloheximide and chloramphenicol to avoid mold contamination. Time to colony growth on Sabouraud's agar is a first discrimination of the type of fungus: filamentous fungi grow very slowly, along several weeks (3 weeks or more), incubated at 25–30 °C. Yeasts produce fast growing colonies (24–48 h). A number of other organic and synthetic culture media have been proposed (Table 123.4), whose laboratory preparation has been simplified by the use of prompt dehydrated media, which only need the addition of a fixed amount of distilled water, sterilization, and portioning on test tubes or Petri dishes.

A selective dermatophytes medium (DTM) is available for practitioner's use in the office, which does not require special conservation or care. Dermatophyte growth is indicated from the medium's color change to orange. Unfortunately, this kind of test is expensive and does not allow for subsequent fungal identification.

Table 123.4 Some examples of fungal culture media composition

Medium denomination	Composition	
Agar Sabouraud's medium	Crude glucose	40 g
	Granulated peptone	10 g
	Agar	20 g
	Tap water	1,000 ml
Emmons' variant	+ chloramphenicol	0.5 g
	+ cycloheximide (actidione)	0.5 g
Sabouraud's liquid medium	Same composition without agar	
Vanbreuseghem's variant	20 % earth + agar + tap water	
Rice medium (to favor dermatophytes fruiting)	Gelose	20 g
	Husked rice	20 g
	Peptone	2 g
	Tap water	1,000 ml
Potato-carrot medium (to favor *Candida albicans* chlamydospores formation)	Chopped potatoes 20 g	
	Chopped carrots 20 g	
	Macerated in 1 l tap water for 1 h; boiled for 5 min, filtered, and added with powdered agar g 20; the whole brought up to 1,000 ml	
Marcelou-Kinti's medium (used for the rapid sugar fermentation test)	Agar	9 g
	Peptone	10 g
	Bromocresol purple	0.04 g
	Chloramphenicol	0.5 g
	Tap water	1,000 ml
	+10 % sodium bicarbonate solution to adjust the pH	
	To this base, several sugars are added in separated 30 % solution: glucose, maltose, raffinose, galactose, lactose, saccharose, trehalose. Each sugar final solution is used to impregnate a disk of blotting paper, placed in hemolysis tubes and finally added with the fungal culture inoculum suspended in physiological solution. After 24–48-h incubation, the fermented tubes have discolored medium	
Lodder's medium (to study the assimilation of sugar and nitrogen)	Potassium dihydrogen phosphate	1 g
	Magnesium sulfate	0.5 g
	Ammonium sulfate	5 g
	Agar	20 g
	Distilled water	1,000 ml

Once the colonies have grown, identification relies on both gross and microscopic features. Colony morphology and growth dynamics may vary considerably with the culture medium used (type of glucose, peptone, pH) and other conditions such as the degree of humidity and temperature. It is therefore essential to maintain constant conditions in the laboratory and to use the same components for the media preparation. Well-established and reference features are based on Sabouraud's medium, and it is advisable to always perform at least one culture on that medium when other culture media are used.

Candida species cannot be identified either by direct microscopy or by culture macro- and microscopic features. The final species determination relies on the germ tube tests (rapid production of chlamydospores) and on sugar fermentation and assimilation tests, as well as nitrogen utilization (Table 123.5).

Candida strains resistant to antifungals have been detected (35–39); therefore, the antifungal susceptibility test should be performed, especially in nosocomial settings and in immunocompromised patients.

Culture of *Malassezia species* is not easy to obtain and usually not necessary. The Sabouraud's agar medium is added with a layer of olive oil to favor *Malassezia* caramel-colored colonies growth.

Gross Morphology Examination

The colony morphology examination has a relative value, because gross features are changeable and similar to related fungi (Figs. 123.8 and 123.9). Observation includes the reverse side of the tubes or Petri dishes, because some features may differ greatly.

Surface of the colony: convex or flat; elevated with a central button, convoluted with regular folds or vermiculate, with radial branching.

Aspect of the colony: plaster-like or waxy, glabrous or wooly, granular, dusty, creamy.

Color: grayish or creamy, orange, red, purple, pink, cafè au lait, dark brown, black, dark or olive green. The pigmentation density usually varies as it diffuses in the medium and might greatly change on the reverse side of the colony.

Consistency: soft and friable or so hard that it is difficult to detach with the platinum loop.

Culture Microscopic Examination

Once the gross morphology observation is completed, a specimen of the culture is taken with a platinum loop and put on a slide, cleared with one or two drops of KOH or stained with lactophenol cotton blue, which stains the fungal elements in blue, and covered with a cover slip.

The first step of the culture microscopic examination is to reveal if the specimen contains hyphal fungi (septate or not septate) or yeasts (pseudohyphae, budding cells). In the case of yeasts, it is not usually possible to complete identification under the microscope, and therefore a switch to other techniques is necessary, as previously mentioned (implantation on selective medium, sugar fermentation and assimilation test, nitrogen utilization).

The *second step* is the detailed description of the mycelia elements configurations (Tables 123.6 and 123.7). Some hyphae are very straight, others sinuous, slender, or thick, with periodical enlargement of single enchained elements and/or swelling at the tips of the filaments. These specialized, ornamental or accessory structures, arising from a single cell modification into a thick-walled resting cell, with a very peculiar morphology aid in species identification: spiral and racquet hyphae are commonly seen in *Trichophyton mentagrophytes*; pectinate body occurs in *Microsporum audouinii*; chandelier hyphae occur in *Trichophyton schoenleinii* and *Trichophyton violaceum* infections, and nodular organ characterize *Trichophyton mentagrophytes* and *Microsporum canis*.

Although suggestive, the accessory structures are changeable, and the most important elements to note are the presence of fruiting bodies (spores, chlamydospores, asci, aleuriospores, etc.). In the case of dermatophytes, the micro- and macroconidia configurations, arrangement, and shape make identification certain. Additional biochemical tests

Table 123.5 Additional tests to discriminate the main pathogen *Candida species*

	Fermentation test (zymogram)						Assimilation test (auxanogram)						
Species	Glucose	Galactose	Saccharose	Maltose	Lactose	Raffinose	Glucose	Galactose	Saccharose	Maltose	Raffinose	Trehalose	KNO_3
C. albicans	+	±	−	+	−	−	+	+	+	+	−	+	−
C. pseudotropicalis	+	+	+	+	−	+	+	+	+	+	−	/	−
C. parapsilosis	+	+	+	+	−	+	+	+	+	+	−	/	+
C. tropicalis	+	+	+	+	−	−	+	+	+	+	−	/	−
C. guilliermondii	+	±	+	−	−	+	+	+	+	+	−	/	−
C. stelloidea	+	−	−	+	−	−	+	+	−	+	−	/	−
C. krusei	+	−	−	−	−	−	+	−	−	−	−	−	−
Torulopsis glabrata	+	−	−	−	−	−	+	−	−	−	−	+	/

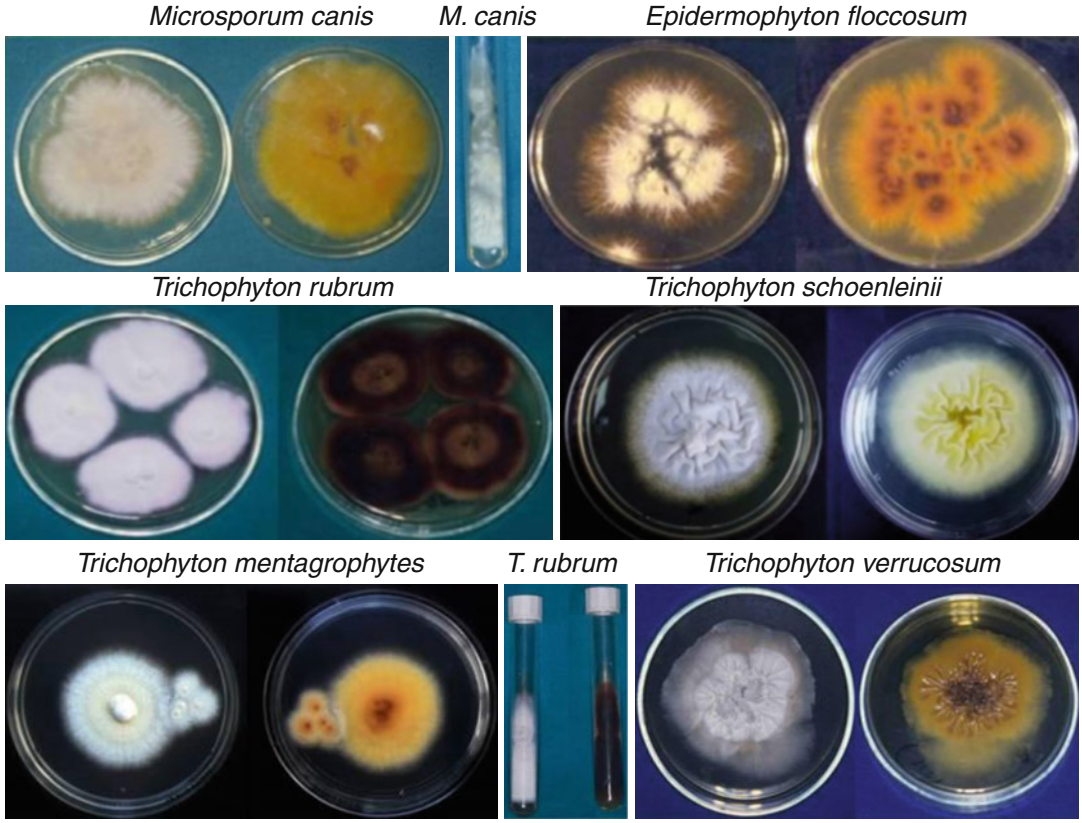


Fig. 123.8 Gross morphology of *dermatophyte* colonies

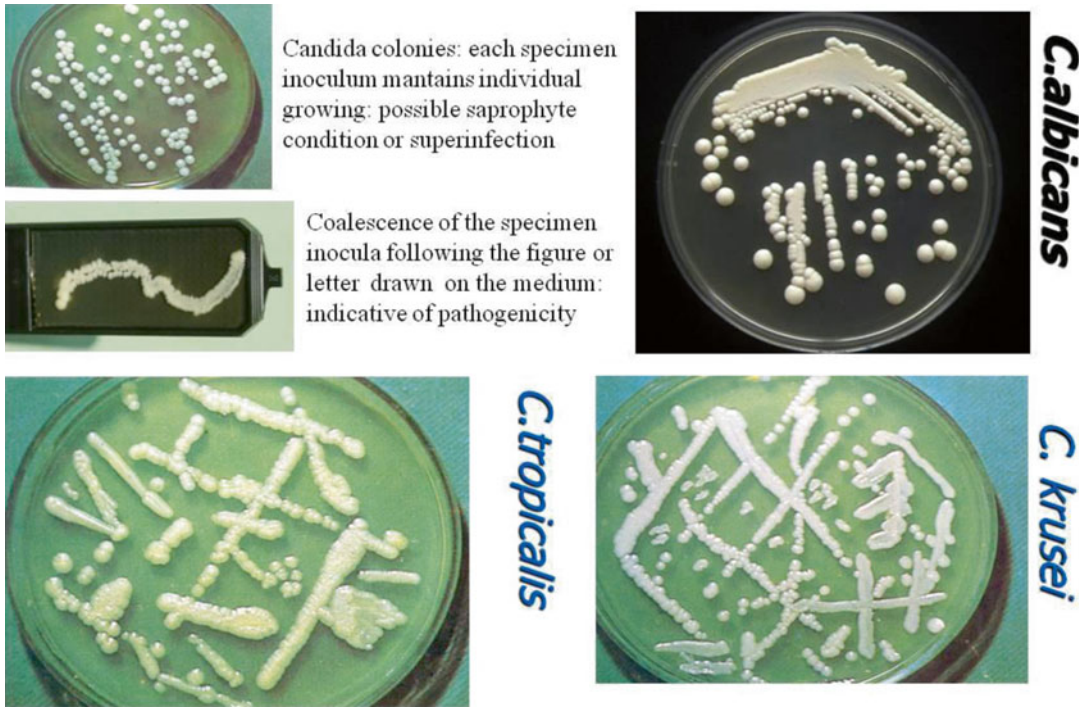


Fig. 123.9 Gross morphology of *Candida* colonies on Sabouraud's agar

Table 123.6 Some examples of the main dermatophyte species characteristics on culture identification process

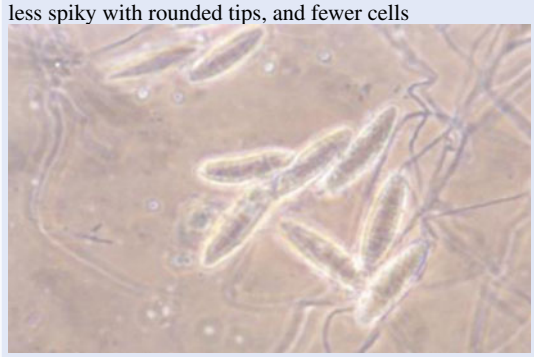
Dermatophyte	Culture morphology	Accessory structures and fruiting bodies
Microsporum canis (zoophilic fungus)	Colonies grow at moderate rates and are cottony or wooly with whitish center and lemon-yellow pigment at the periphery; radial grooves may also be present. The reverse is lemon-yellow, becoming yellow-brown with age	Few pyriform microconidia; numerous large macroconidia with thick rough walls, spiky, boat-like septate (navicular) with more than 6 cells (multilocular) 
Microsporum gypseum (geophilic fungus)	Colonies grow moderately rapidly with dusty granular to sugar texture, whitish surface darkening to cinnamon brown, especially on the reverse	Macroconidia are more numerous than *M. canis*, but ellipse-like shaped, less spiky with rounded tips, and fewer cells 
Microsporum audouinii (anthropophilic fungus)	Colonies grow at moderate rates and are gray-white, flat, or velvety, with a characteristic light pink to brown reverse	Usually no microconidia are present, but the presence of pectinate hyphae and terminal chlamydospores suggests the identification. Macroconidia are fusiform, beaked, and septated, with irregular intervals
Trichophyton mentagrophytes (zoophilic fungus)	Colony grow slowly, with variable appearance, usually white-creamy with a shielded center and dusty periphery; the reverse may be tan-brown, yellow, or red similar to *T. rubrum*	Numerous round or pyriform microconidia arranged in grape-like clusters, presence of spiral hyphae. Macroconidia are cylindrical and septate

Table 123.6 (continued)

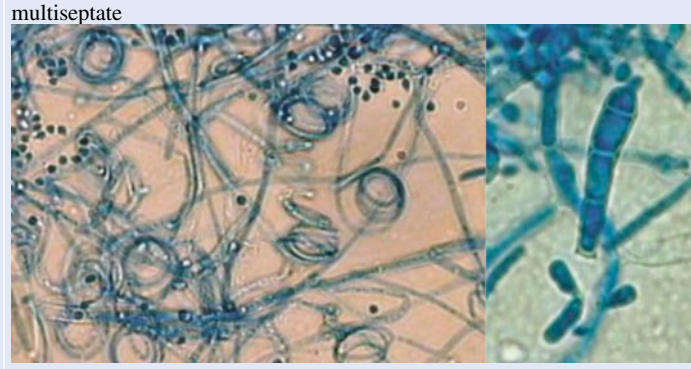
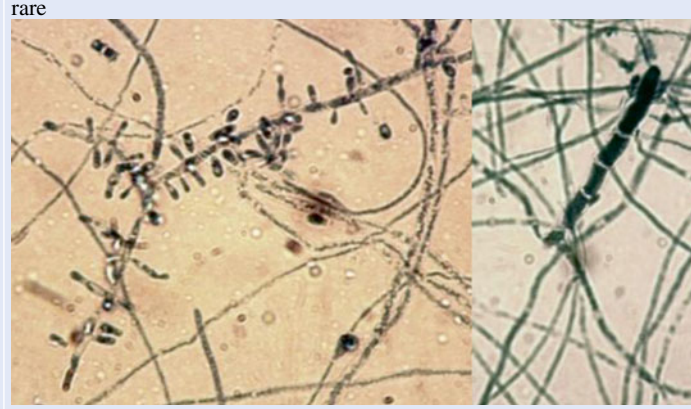
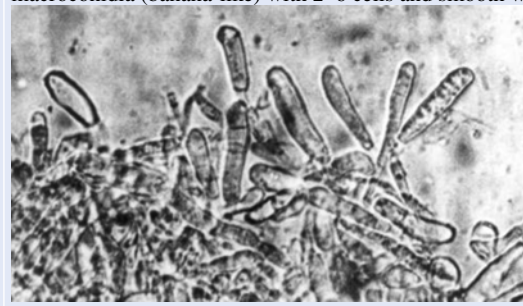
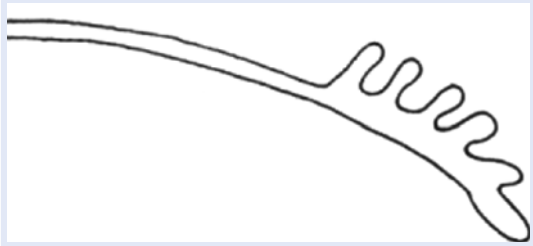
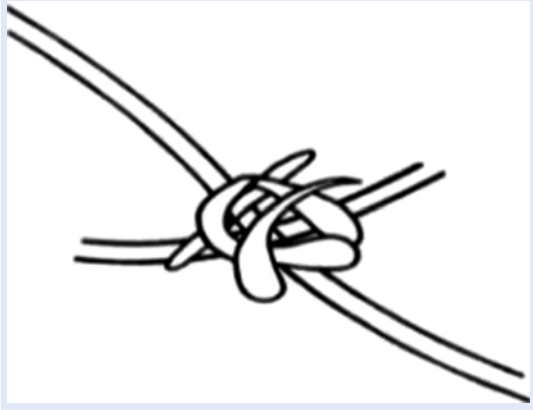
Dermatophyte	Culture morphology	Accessory structures and fruiting bodies
Trichophyton rubrum. (anthropophilic fungus)	Colonies grow slowly; with a convex central surface (like a shield boss or umbo) and dusty periphery; the colonies are white pigmented with a characteristic wine red reverse	Numerous grape-like microconidia and aleuriospores arranged along thick unbranched hyphae; macroconidia are rare, cylindrical or clavate, and multiseptate 
Trichophyton schoenleinii (anthropophilic fungus)	White shielded surface, with yellow pigment on the reverse	There are no micro- or macroconidia; divergent branching and swellings at the hyphae tips producing chandelier or favus accessory structures are useful for the identification
Trichophyton verrucosum (zoophilic fungus)	Colonies with a velvety convoluted surface, creamy to ochre in tan; the reverse may be colorless or yellow	Hyphae with swollen tips, and symmetrical arthrospores arranged like a string of beads. True pyriform microconidia and rattail macroconidia are rare 
Trichophyton tonsurans (anthropophilic fungus)	Colonies mature slowly and have variable color, texture, and shape; usually yellow-brown tan	Clavate to elongate microconidia; some are usually swollen and attached to conidiophores by short stalks. Macroconidia are rare
Epidermophyton floccosum (anthropophilic fungus)	Colonies are yellow-khaki or olive green with flat aerial surface conveying a soft leather appearance (suede)	Microconidia are absent; very numerous bunches of clavate or club-shaped macroconidia (banana-like) with 2–6 cells and smooth walls 

Table 123.7 Specialized accessory features help to further distinguish several dermatophyte species

Accessories structure	Morphology	Dermatophyte species
Spiral hyphae: subtle filaments coiled on their axis spirally		*Trichophyton mentagrophytes*
Pectinate body: short, unilateral projections from the hyphae that resemble a broken comb		*Microsporum audouinii*
Favic chandelier: hyphal tips grouped to resemble a chandelier or the antlers of the deer (antler hyphae)		*Trichophyton schoenleinii and Trichophyton violaceum*
Nodular organ: enlargement in the mycelium that consists of closely twisted hyphae		*Trichophyton mentagrophytes and Microsporum canis*
Racquet hyphae: regular enlargement of one end of each segment with the opposing end remaining thin		*Epidermophyton floccosum, Trichophyton mentagrophytes*

may be helpful in distinguishing *T. rubrum* from *T. mentagrophytes*: milk agar medium favors *T. mentagrophytes* growth, while *T. rubrum* is restricted; *T. mentagrophytes* is urease positive while *T. rubrum* is urease negative.

Culture Pitfalls

A negative culture may arise because:

- The condition is not due to fungal infection.
- The specimen was not collected properly, especially as regards sterile procedure and eventual bacterial contamination.
- Antifungal treatment had been used prior to collection of the specimen.
- There was a delay before the specimen reached the laboratory.
- The laboratory procedures were incorrect.
- The organism grows very slowly.

It is advantageous to collect several samples from the patient, to eventually repeat the cultural examination when a fungal infection appears likely, preferably prior to treatment.

Another major problem is false-positive results due to contamination, especially *molds development* in nail specimens. Molds are ubiquitous and their etiologic role in onychomycosis is very controversial. Onychomycosis due to opportunistic fungi, especially *Scopulariopsis brevicaulis*, have no specific clinical features, and simple isolation from the nails is not sufficient to assess infection. As a general rule, the suspected pathogen fungus must be detected at least in three different samples of the pathologic material, obtained from several different sites, plated out on at least three different media, including Sabouraud's agar + actidione.

Other Complementary Examinations in Mycology

Wood's Lamp Examination

This very simple examination introduced in medical mycology in 1925 by Margarot and Devèz is no more very popular in routine use, requiring a source of ultraviolet rays filtered with a 9–10 % nickel salt sheet of glass (366 nm wavelengths allowed to pass). The examination is performed in a dark room and natural luminescence phenomenon is limited to *microsporum species (*green fluorescence*)*, *pityriasis versicolor* (yellow green), and erythrasma (reddish fluorescence). It is otherwise useful to rapidly distinguish the malassezia infection from other skin coloring changes such as vitiligo and to detect tinea capitis during epidemics, especially in schools.

Histological Examination

Biopsy and histological examination does not replace native preparation and usually is unnecessary in superficial fungal infections, but it is sometimes performed to exclude major skin diseases and superinfections, especially if dealing with yeasts. Histological examination allows for primary candidiasis to be distinguished from superinfection, by the presence of a parakeratotic horny layer, stuffed with PAS-positive yeast cells and pseudohyphae.

It is otherwise mandatory to confirm the clinical suspect of rare deep-seated or disseminated fungal diseases, such as actinomycosis, cryptococcosis, histoplasmosis, and other infections. It is also effective to confirm a pathologic role of opportunistic fungi and their relation with the infected tissue. Histology is superior to the other methods in its negative predictive value. The combination of direct microscopy plus histology was 97.8 % sensitive with 98 % negative predictive value and remains the most sensitive diagnostic approach for onychomycosis.

The specific request must be clearly indicated to the pathologist, because simple hematoxylin-eosin stains give more information on the tissue reaction pattern than on the fungal presence and require a very careful examination. It rarely enables a more precise diagnosis than simple mycosis and the fungus cannot be identified as a rule. The most used stains are Hotchkiss-McManus stain (Periodic Acid Schiff reagent, PAS) in all conditions, May-Grunwald-Giemsa and Gram stain to visualize very fine Gram-positive filaments (actinomycosis, nocardiosis), and methenamine silver nitrate staining by Gomori's method, which is particularly useful to fungal membrane detection.

Electron Microscopy

The extensive use of both transmission and scanning electron microscopy is devoted to research on the morphology and physiology of the various pathogenic fungi. It does not play a role in diagnostic procedures.

Future Perspectives

Mycology is sometimes considered an obsolete assessment, because clinical diagnosis is usually simple and antifungal treatment highly efficacious. Laboratory exam has relied on direct examination for such a long time that interest on research and implementation has been limited for decades. The sensibility of the traditional mycological examinations is not very high and conditioned from the investigator's expertise. The diagnostic error accounts for about 30 % of the cases. Therefore, last decade's research has devoted a certain interest to faster, more sensitive, and culture-independent techniques. The molecular biology techniques, especially the *polymerase chain reaction (PCR)* and *in situ hybridization* for fungal identification, are highly sensitive but expensive and require complex post-amplification procedures to differentiate relevant fungal types. At the moment, research is limited to deep-seated and disseminated fungal infections (blood infections, drug-resistant *Candida* and *Aspergillus* species) or to severe special site infections (fungal keratitis). Preliminary data using real-time polymerase chain reaction high-resolution melting analysis (PCR-HRM) suggest the capacity to detect and differentiate yeasts from filamentous fungi and to discriminate among relevant species of yeasts.

Current limitation of the molecular assays is the lack of methodological standardization and validation, with continuous new method proposals whose results interpretation are not always clear and reproducible.

New impulse to collect samples and make correct fungal identification arises from the *assay mass spectrophotometry*, which seems to be a cost-effective rapid tool and will probably be largely adopted as routine laboratory determination in an immediate future.

Wide consensus and validation from large prospective studies are necessary to allow widespread adoption of these assays into the clinical setting, but the basic approach with direct microscopy remains the clue to the diagnosis of superficial skin fungal infections.

Acknowledgement The authors are grateful to Barry Mark Wheaton for the kind revision of the English text.

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Patch Testing

124

Anna Tagka and Alexandra Katsarou

Key Points

- Patch testing is a well-established practical method to diagnose and evaluate allergic contact dermatitis. The main indication is persistent eczema.
- The International Contact Dermatitis Research Group (ICDRG) contributed to the standardization of patch testing procedures and methodology.
- These guidelines include recommendations for the test systems, the site, the technique of patch testing, the concentration of allergens and vehicles.
- The method includes the application of a certain antigen in standard concentration under occlusion. We usually prefer the upper back and white petrolatum as a vehicle.
- It is necessary to give special instructions concerning to medication and activities of the patient in order to perform patch testing.
- The procedure to evaluate the relevance between the reaction to the specific allergen and the present case of eczema is usually the most difficult and interesting part.

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General Principles

Josef Jadassohn (1895) is considered as the first scientist who established the procedure of patch testing. He first reported a patient suffering from an eczematous reaction to mercury. Bruno Bloch later followed and expanded the clinical and experimental work of Jadassohn.

Patch testing is now a well-established practical in vivo method to diagnose and evaluate allergic contact dermatitis. According to Gell and Coombs classification, we study a type IV reaction of delayed-type hypersensitivity in patients previously sensitized and presenting clinical signs of contact dermatitis. In the past, because patch test techniques varied, it was difficult to compare results from different dermatology centers. Over the last few decades, much work has been done worldwide, in order to determine the optimal concentration of materials and to standardize allergens, vehicles, tapes, technique, and scoring of reactions. The International Contact Dermatitis Research Group (ICDRG) has set specific guidelines for patch testing that include recommendations for test systems, the test site, the technique of patch testing, the concentration of allergens, the vehicles, the components of a standard test series, and the interpretation of results.

This has greatly facilitated comparisons of patch test reactivity and conclusions about allergic contact dermatitis between centers in different geographic areas.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_124, © Springer-Verlag Berlin Heidelberg 2015

Indications

The patch test provides objective information about contact allergy. Without it, the diagnosis and management of contact dermatitis are based only on clinical criteria. The socioeconomic and medical consequences of contact allergy are so important that proving the presence or absence of allergy is essential. Thus, patch testing is indicated:

1. In patients with a recurring, eczematous, pruritic dermatitis that is clinically diagnosed as contact dermatitis. In these cases, patch testing can:

   Determine the actual allergens among many clinically suspected allergens. Detect relevant, but clinically unsuspected, contact sensitizers. Determine the safety of materials for the patient.
2. In patients with aggravation of other dermatoses, particularly psoriasis, endogenous eczema, or leg ulcers, where superimposed contact dermatitis needs to be excluded
3. As part of a thorough workup in a patient with a puzzling diagnostic problem

Test Systems

Two types of patch tests are used, the original system and the ready-to-use system, where only a covering membrane has to be removed before the test is performed.

Original System

In the original system, the allergens, patches, and tapes are supplied separately.

Allergens

Contact allergens are simple chemical substances with low molecular weights (<1,000 Da). The allergens should be as pure and well defined as possible. According to de Groot, more than 4,350 chemicals are identified as sensitizers. Of these, approximately 300 are commercially available from the various suppliers (Trolab/Hermal, Kurt Herrmann, Chemotechnique Diagnostics AB, Lofarma and others), and the most frequently encountered allergens are included in standard batteries. The present European Standard Series includes 28 substances. The choice of allergens in the standard series is based on the experience of the members of the ICDRG and on the frequency of positive reactions. If the incidence of positive reactions to an allergen falls to less than 1 %, it can be removed from the series. Therefore, the composition of the standard series is not constant.

Several additional series are available for patch testing patients with different medical histories and occupations. Thus, series are available for hairdressing chemicals, metal compounds, cosmetics, medicaments, antimicrobials, preservatives, plants, plastics, glues, and rubber chemicals, for example.

The most commonly used vehicle for allergens is petrolatum, although a few substances are incorporated in water or other vehicles (ethanol, acetone). White petrolatum has good occlusion, keeps the allergens stable, and is inexpensive. Commercially available allergens are dispensed in individual syringes. Packaging should protect against air, humidity, mechanical damage, and radiation. In general, test allergens should be kept in the refrigerator to minimize degradation.

The Patches

Commercially available patches have a test area that is circular with a diameter of 8–10 mm. The AL test has been a standard method for patch testing for several years. It consists of a filter paper disk of cellulose (10 mm) attached to a strip of plastic-coated aluminum foil and is available in rolls. The Finn Chambers is the most widely used method, and it employs 8 mm aluminum and polypropylene cups is an alternative option.

Large firm chambers (12 mm) may be useful for the detection of weak responses and are usually recommended for experimental studies.

The Tape

The modern polyacrylate-based adhesive tape (Scanpor) eliminates irritant and allergic reactions.

Concentrations

In textbooks of patch testing and suppliers' catalogues, the concentration of an allergen is given as a percentage. In TRUE test concentration is given in milligrams or micrograms per square centimeter.

Ready-to-Use Systems

The TRUE test is a system in which a measured amount of allergen is included in a gel printed on a polyester patch of 9×9 mm. These patches, containing different allergens, are mounted on acrylate tape covered with a siliconized protection sheet and packed in an airtight, light-impermeable envelope. Epiquick is another ready-to- use patch test system that consists of Finn Chambers, on Scanpor tape, that contain allergens of the standard series in petrolatum.

The advantages of these systems are the constant volume of allergen in the chamber, uniformity in materials and procedure, and savings in test performance time. However, the cost is higher. Ready-to-use systems are especially recommended for use in children.

Test Sites

The midportion of the upper back is the site of patch test application. The skin must be hairless and normal. If even a trace of dermatitis is present on the test site, the patient should not be tested at that time, in order to avoid false-positive reactions. If the skin is not hairless, shaving should be done with an electric razor in order to avoid abrasion, soap, and shaving cream. In certain instances, the upper, outer arm can be used to isolate a test allergen when a strong positive reaction is expected, as, for example, with nickel.

False-negative results can be observed on the lower back or on the volar arms.

Technique of Patch Testing

Patch tests should be applied to the upper back on intact skin, without prior use of alcohol or soap. The amount of test material used is an important point. Twelve to fifteen microliter of test material, or slightly more than half of the chamber area (for Finn chambers), should be applied. For materials in solution, it is sufficient to place one drop onto the filter paper disk, and this should be done a few minutes before applying the test in order to avoid evaporation. The physician or technician that is handling the allergen-filled syringes must wear a protective glove to prevent contact allergy.

The tape strips are applied from below with slight pressure so as to remove air bubbles and obtain uniform and complete contact. In cases of oily or hairy skin, sweating, or high humidity, the ends of the strips require additional tape.

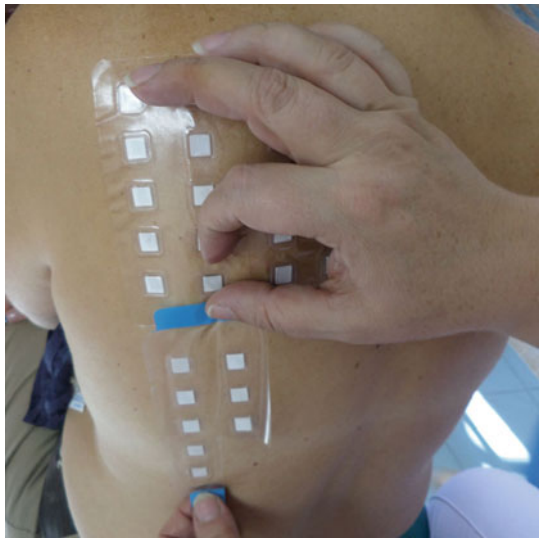
The type of series and representative (i.e., top) numbers of the set should be labeled on the tape. Before removing the patch tests, it is important to mark the skin outlining the test area using a water-resistant marking pen that will not stain clothing (Figs. 124.1 and 124.2).

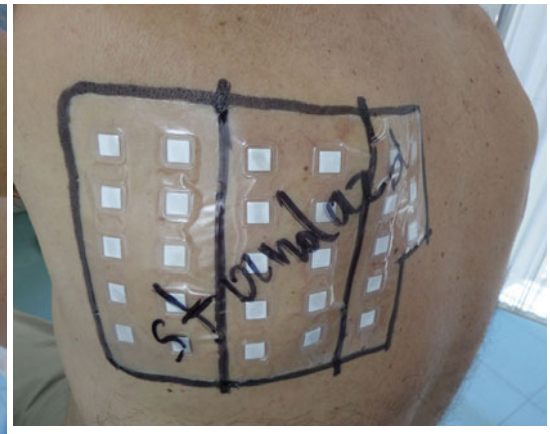
Instructions for the Patient

There is special recommendation to avoid washing the upper back and scratching the area.

It is inconvenient for the patient exposing to heat, the outside activities, and sports.

We strongly recommend avoiding systemic treatment that interferes or topical treatment, especially used on the upper back. Patients must be given written instructions to keep the patches dry, to diminish work activity, to avoid vigorous exercise, and to fix any area that becomes loose with additional tape. If excessive itching





Figs. 124.1 and 124.2 Application of patch test (standard series) usually on the upper back

or burning occurs at a certain area, the patch may be carefully removed, but all other patches should be left in place to be removed at 48 h.

Baseline and Additional Series in Patch Testing

There are four proposals concerning the baseline series in patch testing:

- The updated 2011 European baseline series from the European Society of Contact Dermatitis (ESCD) and the European Environmental and Contact Dermatitis Research Group (EECDRG)
- The updated 2011–2012 North American baseline series from the North American Contact Dermatitis Research Group (NACDG)
- The updated 2011 Japanese baseline series from the Japanese Society for Contact Dermatitis (JCDS)
- In 1997 the ICDRG (International Contact Dermatitis Research Group) group published a short list with 20 allergens used internationally performing the rule of 1 %. A new revised recent approach was lately published by Alikhan et al. (2011).

These series are in a dynamic status with several additions and removals according to the rules of ICDRG.

We perform the standard series and supplementary available additional series according to the medical history of the patient (Tables 124.1 and 124.2). There are available additional series for hairdressers, chemicals, metal compounds, cosmetics, medicaments, antimicrobials, preservatives, plants, plastics, glues, rubber, and other substances (Table 124.2). We choose the proper additional series on the basis of clinical relevance.

There is a list with chemicals that are not available in commercial lists of allergens and have been collected in de Groot's textbook, which proposes the proper vehicle and concentration of several allergens. It is of great importance to avoid patch testing with unknown products because of adverse effects.

Nickel is the most frequent allergen of baseline series among children and adults, remarkably high in young women.

Table 124.1 Standard series of allergens

	Allergens	ECDRG[a] (%)	NACDG[b] (%)
1.	Potassium dichromate	0.5	0.25
2.	Neomycin sulfate	20	20
3.	Thiuram mix	1	1
4.	*P*-phenylenediamine base	1	1
5.	Cobalt chloride ($CoCI_2$–$6H_2O$)	1	–
6.	Benzocaine	5	5
7.	Formaldehyde	1aq	1aq
8.	Colophony	20	20
9.	Clioquinol	5	–
10.	Myroxylon pereirae (Balsam of Peru)	25	25
11.	*N*-Isopropyl-*N*-phenyl 1-4-phenylenediamine (IPPD)	0.1	–
12.	Wool (lanolin) alcohols	30	50
13.	Mercapto mix	2	1
14.	Epoxy resin	1	1
15.	Paraben mix	16	12
16.	*p*-tert-Butylphenol formaldehyde resin (PTBP resin)	1	1
17.	Fragrance mix 1	8	8
18.	Quaternium-15	1	2
19.	Nickel sulfate ($NiSO_4$ $6H_2O$)	5	2.5
20.	Cl + Me-isothiazolinone	0.01aq	0.01aq
21.	Mercaptobenzothiazole	2	1
22.	Sesquiterpene lactone mix	0.1	0.1
23.	Budesonide	0.01	1
24.	Tixocortol pivalate	0.1	1
25.	Methyldibromo glutaronitrile	0.5	2
26.	Fragrance mix 2	14	14
27.	Hydroxyisohexyl-3-cyclohexene-carboxaldehyde (Lyral)	5.0	–
28.	Primin	0.01	–
29.	Imidazolidinyl urea	–	2
30.	Cinnamic aldehyde	–	1
31.	Carba mix	–	3
32.	Ethylenediamine dihydrochloride	–	1
33.	Black rubber mix	–	0.6

The concentrations refer to petrolatum (in any other case there is a specific note)
aq in aqua
[a]The updated 2011 European baseline series
[b]The updated 2011–2012 North American baseline series

Interpretation of Patch Tests

The optimal exposure time is 2 days (48 h). A first reading takes place 30–60 min after the removal of a patch test. At this time, many irritant reactions can be noticed, caused by occlusion and reactions to allergens or tape. If only a single reading at 48 h is performed, 30 % of positive reactions will be missed. Therefore, it is recommended that two readings are performed, the first after the removal of the patches (48 h) and the second 2–4 days later. A positive

Table 124.2 Additional patch test series

Trolab	Chemotechnique diagnostics
Antimicrobial, preservative, and antioxidant	Bakery
Cosmetics	Corticosteroid
Dental materials	Cosmetics
Hairdressing	Dental screening
Medicament (including corticosteroids, antibiotics, local anesthetics, and ophthalmics)	Epoxy
Metal compounds	Fragrance
Metalworking/technical oils	Hairdressing
Perfume and flavors	Isocyanate
Photoallergens	Leg ulcer
Photographic chemicals	Medicament
Plant	Adhesives, dental and other (meth)acrylate
Plastics and glues	Nails – artificial (meth)acrylate
Rubber chemicals	Printing (meth)acrylate
Sunscreen agents	Oil and cooling fluid
Textile and leather dyes	Photographic chemicals
Vehicles and emulsifiers	Plant
Miscellaneous	Plastics and glues
	Rubber additives
	Scandinavian photopatch test
	Shoe
	Sunscreen
	Textile colors and finish
	Various allergens

Table 124.3 Interpretation of patch test reactions according to the ICDRG (International Contact Dermatitis Research Group)

?+	Doubtful reaction
+	Weak positive reaction, non-vesicular; erythema, infiltration, papules
++	Strong positive reaction; erythema, infiltration, papules, and vesicles
+++	Extreme positive reaction; intense erythema and infiltration, coalescing
–	Negative reaction
IR	Irritant reactions (of different types)
NT	Not tested

reaction on day 2 that is negative on day 4 is usually considered to be an irritant reaction. Certain common allergens such as neomycin, organic dyes, and corticosteroids may only show late reactions.

The system for interpreting patch test reactions as recommended by the ICDRG is shown in Table 124.3.

The doubtful and weak reactions are the most difficult to interpret. Irritant responses can be characterized by erythema without infiltration, papules in follicular distribution, pustular reactions, wrinkling, bullae, or necrosis.

Reading only at 48 h may show irritant reactions that disappear within 24 h.

There are difficulties in distinguishing weak allergy and irritant lesion. In such cases we have to perform supplementary test with different dose and dilution of allergens, ROATS (repeated open application test), and get access to the clinical history of the patient (Fig. 124.3).

Accuracy of Patch Testing

Patch tests, like all biologic tests, have inherent errors. False-negative or false-positive reactions may occur, and the experience of the dermatologist is a very important factor that helps distinguish false reactions.

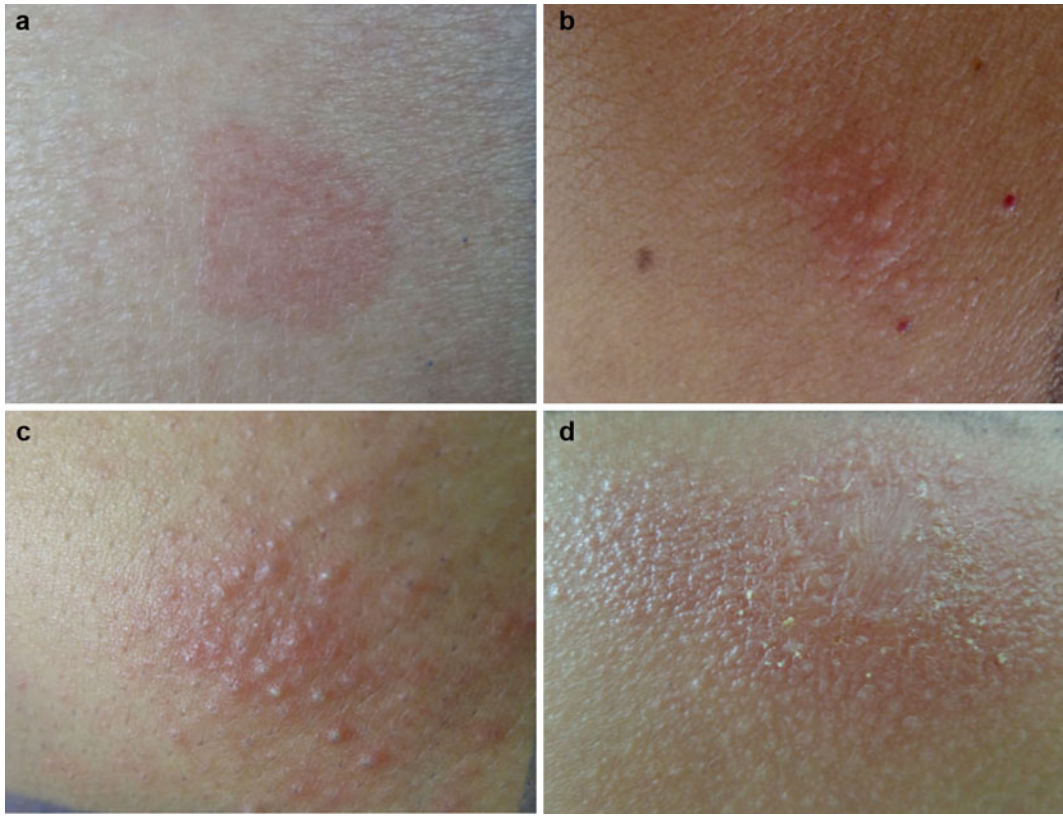


Fig. 124.3 Allergic Contact Dermatitis. Scoring of positive patch test reaction (72 h). (**a**) +, (**b**) ++, (**c**) ++, (**d**) +++

Causes of false-positive patch test reactions are:

1. *Test system factors*
   Test concentration is too high (i.e., with substances of unknown composition).
   Impure or contaminated test substances.
   Mechanical irritation (pressure, friction, soluble substances).
   Pustular reactions to metal salts.
   The vehicle is irritant (irritates the skin or enhances allergen penetration).
   Adhesive tape reaction.
   Reaction to the patch (pressure, friction, irritant or allergic reactions).
2. *Personal factors*
   Presence of dermatitis at test site, or elsewhere
   Lowered natural resistance
   High skin temperature, sweating
   Previous exposures to alcohol solvents, topical cosmetics

Causes of false-negative patch test reactions are:

1. *Test system factors*
   Test concentration is too low.
   Allergen is not in active form (i.e., degraded).
   Insufficient amount of occlusion.
   The vehicle prevents the substance from penetrating the skin.
2. *Methodology factors*
   Patch applied to site other than upper back (leg, lower arm).
   Test read too early (48 h); some substances give delayed reactions (i.e., neomycin).
3. *Personal factors*
   Prior treatment of test site with topical corticosteroids or UV irradiation (even 10–15 days earlier)
   Systemic medications: corticosteroids (prednisolone >15 mg/day), cytostatic agents, cyclosporine A
   Anergic phase (available T lymphocytes are involved in clinical reaction)

Complications

The most common complications of patch testing are irritant reactions from products of unknown composition brought in by the patient, active sensitization, aggravation of previous existing dermatitis due to percutaneous absorption of allergen (excited skin syndrome), alterations in pigmentation (hyperpigmentation, hypopigmentation), scarring, necrosis, bacterial and viral infection, and anaphylactic reactions (penicillin).

Excited Skin Syndrome The phenomenon is characterized by the presence of several strong positive reactions on the skin which is in status of hyperreactivity. These multiple strong reactions to several allergens are not reproductible. This situation is alternatively described by the use of the term angry back. The pathogenesis has not yet been evaluated. This occurs often in patients with active atopic dermatitis or other type of dermatitis. This status eczematicus makes reading impossible. The procedure has to be continued with additional tests.

Irritant Patch Test Reactions

This type of reaction is related to the chemical nature of substance and the high concentration of the allergen. It is often when we use an inappropriate procedure.

Irritant responses usually present as:

- Erythema without infiltration
- Papules in follicular distribution
- Pustular reactions especially in atopic patients (metallic salts)
- Wrinkling or bullae or necrosis

There are difficulties in distinguishing weak allergy from irritancy.

The clinical pattern of irritant reactions usually presents a number of clinical signs as an erythematous reaction, which is strictly limited to the site of application, usually not edematous (usually related to fragrance mix, parabens, thiuram mix). Purpuric reactions are common in some allergens like metals (particular in cobalt chloride), also in paraphenylenediamine, IPPD, and drugs. Soap-like effect reactions are often. Soap and detergents are involved in skin disease related to irritant reaction. The skin is red, wrinkled, usually with no vesicles. Blistering (or bullous reaction) occurs after testing with nondiluted or high concentrations of caustic substances as turpentine. Pustular reactions are mainly related to metallic salts (chromate, cobalt, nickel, mercury) in atopic patients. Necrotic reactions are often described as a sign of strong irritancy (caustic soda, kerosene).

In cases of irritancy, we have to perform patch testing again in order to reproduce the result, to use controls and serial dilution of the allergen with further investigation.

Cross-Reactions

Sometimes, the contact allergy of a primary allergen is connected with the allergy to another substance with related chemical structure. These patients who are sensitized to the first chemical are more likely to present contact dermatitis to the second allergen. Chemically similar materials may be immunochemically indistinguishable for the skin. Thus, cross-reacting substances (i.e., para-substances) may give a weaker reaction than the primary allergen. This is an indication to search for the responsible allergen.

Examples of cross-reaction are:

- *P*-phenylenediamine which is related to the amino group in para position, local anesthetics, azo compounds, and sulfonamides.
- Some antibiotics like neomycin, kanamycin, gentamicin, and framycetin.
- Nonsteroidal anti-inflammatory drugs, like ketoprofen and tiaprofenic acid.
- Plant dermatitis presents true examples of cross-reaction.

Relevance

The procedure to evaluate the relevance between the reaction to the specific allergen and the present case of eczema is usually the most difficult and interesting part. In order to decide about the relevance of our results and patient history, we are obliged to study the chemical properties of

Table 124.4 The relevance scoring system of positive patch test reactions (adopted from Lachapelle 1997)

Past relevance (PR)	
PR 0	Not traced
PR 1	Doubtful
PR 2	Possible
PR 3	Likely
Current relevance (CR)	
CR 0	Not traced
CR 1	Doubtful
CR 2	Possible
CR 3	Likely

the allergen, the aspects of patient's probable exposure to the substance during his/her professional and personal habits (hygiene, aesthetic procedures, clothing, etc.), and the course and recurrence of current episode of dermatitis.

A positive skin reaction can be related to an allergen that presents an etiologic relevance (present relevance) with the present episode of dermatitis (Table 124.4).

In some other cases, a positive skin reaction can be related to a previous episode of allergic contact dermatitis (past relevance) with no clinical significance concerning to the present case of dermatitis.

The most difficult part of evaluation is an unexplained positive skin reaction (unexplained positive) and lack of etiologic relevance, until the patient is able to recognize the allergen during his/her personal habits.

Medical history, clinical examination, accessing of exposure and chemical analysis of the substance may contribute to a detailed analysis of the clinical relevance between positive allergens and the current episode of dermatitis.

Considerations About the Effect of Systemic or Topical Treatment in Patch Testing

Corticosteroids

The oral administration of corticosteroids has an influence in patch tests results. Oral dose of 20 mg of prednisone has been acceptable and is considered as a safe solution in order not to miss any important allergies. Application of topical corticosteroids in the area of patch testing is not recommended. The interpretation of patch test results in patients with oral administration of corticosteroids is difficult. Sometimes in doubtful results, it is necessary to repeat patch testing after treatment discontinuation.

Antihistamines

Generally, it is recommended to discontinue antihistamines. Sometimes a low dose is acceptable.

Immunomodulators

It is unclear the effect of these drugs in patch testing. Generally we prefer to perform patch testing without the administration of these agents. Sometimes, cyclosporine is acceptable in dose of 25–50 mg/day. Topical immunomodulators (tacrolimus, pimecrolimus) could influence the results of atopy patch test.

Irradiation

There is an effect to patch testing related to treatment with UVB and Grenz rays. This is a result of the reduced number of Langerhans cells. We have to avoid performing the test in darkly tanned patients and directly after sun exposure, at least for 4 weeks.

Pregnancy and Patch Testing

There is no evidence that allergens could influence the fetus. The general rule indicated by the members of ICDRG is not to test pregnant women because in case of miscarriage or deformity it is likely to blame the doctor.

Patch Test in Children

There is the same indication for patch testing as in adults. The procedure is similar and it is considered to be safe for children. There is only a

technical problem related with the small surface for patch testing in children's back. It is usually advised to use 8 mm Finn Chamber. There is a general consensus of using the same concentration of allergens as in adults. Irritant reactions are not rare in children. Usually the classical standard and additional series are applied to the children according to their medical history. A number of authors propose to use limited number of allergens and specific series according to children's environment.

Photopatch Test (PPT)

Photopatch test is of main importance when we suspect photoallergic contact dermatitis for patients presenting dermatitis with distribution mainly in the exposed sites of the body in order to indentify the responsible allergen. Further indications for the use of PPT are photoallergic contact dermatitis, photoallergic drug reaction, photosensitive eruptions (lupus erythematosus), and idiopathic reaction (polymorphic light eruption, chronic actinic dermatitis).

This is patch testing with the addition of UV radiation in order to induce formation of photo allergens. It is necessary additional equipment of a light source for UVA. The method of application of the test and the scoring criteria are the same. The action spectrum for most photoallergies is included in UVA rays (315–400 nm). Allergens are applied to the upper back using standard series and photopatch series twice. The one set is removed after 24 h (or preferably 48 h) and is irradiated with ultraviolet UVA (5 J/cm^2).

We read the test according to the ACDRG scoring system in preirradiation, immediately postirradiation, and 48 h postirradiation. Further evaluation at 72 and 96 h postirradiation is recommended. PPT is positive when reaction is present only in irradiated area of allergens. A true positive photopatch test persists and increases the reaction between 24 and 72 h. Phototoxic (false-positive) reactions are common.

UV filters are the most frequent photoallergens, drugs like ketoprofen, diclofenac, ibuprofen, naproxen topical antihistamines like promethazine and others.

Atopy Patch Test (APT)

Patch test can reproduce of contact skin reaction using allergens that elicit IgE-mediated reactions, and the evaluation is performed after 24–72 h. The method is called atopy patch test (APT). This test represents a diagnostic tool for patients suffering from atopic dermatitis triggered by allergens. APT is indicated in children and adults. Positive reactions in APT are associated with allergen-specific T-cell responses.

APT results are graded according to ICDRG guidelines.

The performance of APT test has to identify aeroallergens and food allergens connected with the occurrence or exacerbation of atopic dermatitis (AD). The APT value in diagnosis of food allergy,associated or not with AD, is limited.

Positive reactions are frequent in patients with persisting dermatitis, increased total IgE, increased specific serum IgE, positive skin prick test reaction, and rhinoconjunctivitis. The main allergens identified include aeroallergens (with house dust mites and grass pollen) and food allergens, specially in children (cow's milk, eggs, soy, wheat flower). Allergen-specific avoidance strategies are recommended in certain cases of patients presenting positive APT reactions.

The diagnostic validity of APT in routine diagnosis of aeroallergen triggered atopic dermatitis has to be evaluated in further controlled studies.

Conclusions

Patch testing is a well-defined method to diagnose contact allergy.

Recognizing and avoiding the responsible allergens are of great importance for the prognosis of allergic contact dermatitis.

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Photodynamic Therapy for Benign Lesions

125

Marita Kosmadaki

Key Points

- Acne can be improved with long photosensitizer application and high fluences of light or with shorter application time and/or lower light exposure. Concentration of the drug, application time, and light fluence and wavelength need to be further studied to determine an optimum protocol. With longer photosensitizer application time and higher provided energy, the severity of side effects is increasing.
- PDT seems to improves signs of photoaging, fine wrinkles, mottled hyperpigmentation, roughness, and sallowness that appear to ameliorate after PDT sessions. Different light sources, energy fluences, different photosensitizers at varying concentrations, and shorter or longer application times are being used. It is not known which the optimum protocol for the improvement of photoaging is.

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General Principles

Topical PDT involves the application of a precursor of a photosensitizer on the skin (typically aminolevulinic acid (ALA) or its methylated ester, MAL) which are converted by the heme biosynthetic pathway mainly to protoporphyrin IX (PpIX). PpIX is the photosensitizing substance and is preferentially accumulated in rapidly proliferating tissues, such as tumors or sebocytes. PpIX is activated during illumination with visible light, and as a result reactive oxygen species are produced. They trigger apoptosis and/or necrosis of target cells and immunological changes in the target tissue.

Over the years, PDT has expanded to several off-label applications, most responsive of which appear to be acne and photoaging. The method probably offers improvement of different diseases like granuloma annulare, necrobiosis lipoidica, viral warts, onychomycosis, cutaneous leishmaniasis, leg ulcers, lichenoid dermatoses (the erosive and scleroatrophic variant). However, no well-controlled clinical trials have been performed to precisely assess the efficacy of PDT for off-label applications. Pretreating the skin with CO2 fractional laser or other ablative methods may increase ALA/MAL penetration and enhance the therapeutic results.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_125, © Springer-Verlag Berlin Heidelberg 2015

Acne

The photosensitizer precursor is applied for 1–3 h, then it is gently removed, and the area to be treated is irradiated with light of varying wavelength (blue to red) and of varying fluence. Lower drug concentrations, low light doses, short incubation, and less penetrating blue light are termed "low-dose" PDT. "High dose" involves long incubation times and delivery of more energy of deeper penetrating red light. There is no consensus about optimal light dosimetry and irradiance and no consensus about optimal photosensitizer, its concentration, and the time it should be applied for. High-dose PDT appears to have more long-lasting results but also is associated with more side effects and a longer-lasting phototoxic reaction that limits patient for several days. The ideal effective protocol for PDT treatment of acne must balance efficacy with tolerability. Interestingly, novel photosensitizers, like indocyanine green and indole-3-acetic acid, are also being tested for acne.

PDT for acne is often painful. The treated area should be protected from the sun for at least 24 h after treatment to avoid further exposure to photoactivating wavelengths. Sunscreens are usually of very little help for the initial post-treatment period (hours) since the action spectrum of porphyrins extends into the visible range. However, they should be applied later to avoid post-inflammatory hyperpigmentation.

Mechanisms

Photodynamic therapy is believed to have a role in acne treatment due to different mechanisms. Reactive oxygen species (ROS) produced with PDT cause a direct destruction of sebaceous glands (shown for high-dose red light ALA-PDT). PDT-produced ROS also induce immunologic changes: they promote inflammation increasing pro-inflammatory cytokines like TNF-alpha, IL-6, and IL-1. PDT may also decrease the expression of TRL-2, which is implicated in mediating inflammatory response in acne, and thus have an anti-inflammatory action. The precise mechanism by which PDT modulates inflammation and improves acne remains unknown.

Further, PDT probably enhances epidermal cell turnover, reduces the hyperkeratosis in the hair follicle, and thus blocks the triggering mechanism in acne formation.

Propionibacterium acnes involved in the pathogenesis naturally produce small amounts of porphyrins, especially coproporphyrin III. Topical photosensitizers may promote its accumulation and render the propionibacteria more sensitive to light. However, consistent reduction of propionibacterium acnes population has not been described after PDT of acne patients.

PDT for acne has not been optimized. It is not clear which is the optimal ALA/MAL concentration, for how long it should be applied, and which irradiation dose of which wavelength the patient should receive. Therefore, PDT may be used as an alternative treatment for selected cases. It seems to have little or no effect on non-inflammatory lesions.

Side Effects

Erythema that usually lasts 3–5 days, edema, blisters, and crusts may appear. A pustular sterile eruption may appear on the second to third day post-treatment that typically lasts 3 days (reported with high fluences of red light). Post-inflammatory hyperpigmentation and herpes simplex may also occur.

Photorejuvenation

Topical photodynamic therapy appears to be effective for the improvement of several aspects of skin aging. Fine wrinkles, mottled hyperpigmentation, tactile roughness, and sallowness appear to ameliorate after PDT sessions. Red light, blue light, pulsed dye laser, and high-energy flash lamps with different cutoff filters all appear to be inducing good results. However, there are no well-controlled studies comparing the efficacy of different light sources with each

other, so it remains unknown which is the most effective. Short pulse durations used with IPL and PDL have a role in reducing pain (in comparison to continual irradiation with red/blue light). Moreover, similarly to acne, no consensus exists regarding the optimal irradiance the light sources should deliver, the photosensitizer, its concentration, and time it should be applied for. Both ALA (concentration varying from 0.5 % to 20 %) and MAL (16 %) are being used with different incubation times (1–3 h). Lower MAL concentrations are being tested. A single treatment appears not to be enough for significant improvement of photoaging – a second or third treatment at intervals of 2–4 weeks is recommended.

Mechanisms

The mechanism by which PDT improves photoaging appears to be related to enhanced collagen production and remodeling after treatment. Specifically, biopsies taken before and 1 month after ALA-PDT with red light showed an increase of collagen and procollagen types I and III in the upper dermis. TGF-b, which stimulates fibroblast proliferation and thus increases collagen synthesis, was upregulated. The expression of collagen- and elastin-degrading matrix metalloproteinases (MMP-1, MMP-3, and MMP-12) was decreased. Increase of collagen fibers was also observed in biopsies taken 6 months after MAL-PDT.

There are no clear indications of when to use PDT for rejuvenation and no clear data on which protocol to use. However, patients with actinic keratosis seem to be good candidates for the unmodified protocol used for precancerous lesions. Patients with telangiectasias/erythema may benefit more from pulsed dye laser or IPL using appropriate filters.

Side Effects

Erythema that usually lasts several days or weeks, edema, blisters, crusts, and scaling may occur. A pustular sterile eruption may appear on the second to third day post-treatment that typically lasts 3 days (reported with high fluences of red light). Post-inflammatory hyperpigmentation and herpes simplex may also occur. Lower photosensitizer's concentration, shorter incubation time, and low fluences result in milder side effects.

Contraindications

Photosensitivity to visible light used for the procedure, to the photosensitizer, or photoaggravated dermatoses. PDT is not licensed for use during pregnancy or lactation.

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Photodynamic Therapy for Malignant Skin Lesions

126

Edidiong Celestine Ntuen Kaminska, Susan Pei, and Maria M. Tsoukas

Key Points

- Photodynamic therapy (PDT) is a form of phototherapy involving a photosensitizer, a light source, and tissue oxygen.
- Aminolevulinic acid (ALA) and its ester derivative methyl aminolevulinate (MAL) are commonly used photosensitizers acting as prodrugs for protoporphyrin IX (PpIX). PpIX accumulates in abnormal epidermis and upon subsequent exposure to and activation by the appropriate light source generates reactive oxygen species that selectively destroy diseased lesions.
- PDT has been established to be a safe and effective treatment for superficial skin cancers and premalignant skin lesions. Pain is the most severe adverse effect but can be effectively managed. Porphyria is an important contraindication.
- Common approved PDT protocols include Levulan 20 % solution ALA-PDT activation with blue light for treatment of actinic keratosis (AK) in the USA and Metvix/Metvixia MAL-PDT for treatment of AK, Bowen's disease, and basal cell carcinoma in Europe.
- Off-label, ALA-/MAL-PDT have been reported to treat invasive squamous cell carcinoma, cutaneous T-cell lymphoma, Kaposi's sarcoma, Paget's disease, and various benign inflammatory disorders and to prevent recurrence of squamous cell carcinoma in organ transplant recipients.
- Combination therapy of PDT with other treatment modalities such as cryotherapy, surgery, and field therapies is being explored with preliminary data suggesting improved efficacy, tolerability, and long-term results.
- In addition, PDT offers enhanced cosmetic outcome compared to cryotherapy or surgery. PDT can also be used for skin photorejuvenation.

General Principles

Photodynamic therapy (*PDT*) is a form of phototherapy using a light-sensitive compound that upon exposure to the appropriate light source will become activated. The byproducts of this activation produce targeted toxic effects on abnormal cell types (i.e., malignant and other diseased cells). Three necessary components are required

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_126, © Springer-Verlag Berlin Heidelberg 2015

for PDT applications. These include a photosensitizer, a light source, and tissue oxygen. The combination of these three components leads to the chemical destruction of tissue that has selectively taken up the photosensitizer and has been exposed to light. Activation of the photosensitizer requires a suitable wavelength of the light that will excite the photosensitizer to produce reactive oxygen species (ROS) and free radicals. These ROS are generated by the targeted tissue's oxygen supply through PDT. Specifically, cells become overloaded with the activated photosensitizer via light, and the activated molecule transfers energy to tissue oxygen in close proximity. This creates excited singlet state oxygen molecules and free radicals that accumulate within the affected tissue and ultimately result in lesion destruction by direct cellular damage by apoptosis or necrosis and indirect stimulation of inflammatory cell mediators. Therefore, PDT causes selective destruction of targeted abnormal premalignant or malignant cells with the simultaneous preservation of surrounding normal structures.

Photodynamic Therapy: Basic Concepts

Evolution

At the end of the nineteenth century, Oscar Raab, a student of von Tappeiner, observed a toxic effect of acridine dye on paramecia cultures and recognized that light was required for the killing of paramecia cultures to take place (Raab 1900; Kick et al. 1996). Von Tappeiner and colleagues further explored this concept and discovered, in addition to a photosensitizing compound and light, importantly that oxygen was also essential for the photodynamic effect (Jodlbauer and Von Tappeiner 1904). These scientists expanded the application of the photodynamic effect clinically by applying 1 % eosin solution as a photosensitizer to patients with facial basal cell carcinoma followed by exposure to either sunlight or to an arc-lamp light. Many of these patients demonstrated complete tumor resolution and a relapse-free period of 12 months (Jesionek and Von Tappeiner 1905). Almost a century later, Thomas Dougherty and colleagues used PDT with a hematoporphyrin derivative (HpD) as a photosensitizer to treat cutaneous and subcutaneous malignant tumors and observed a total or partial resolution of these tumors (Dougherty 1987; Dougherty et al. 1978). Thus, the first clinical applications of PDT were used for dermatology.

Kinetics

Topical exogenous porphyrin (aminolevulinic acid (ALA) and methyl aminolevulinate (MAL)) administration results in the stimulation of the heme synthesis pathway, thereby culminating in the accumulation of protoporphyrin IX (PpIX) in cells (Fig. 126.1). Normally, the rate of heme synthesis and the intracellular concentration of different porphyrin intermediates are under negative feedback heme control of the ALA synthase activity. This limits the concentration of endogenous ALA. By supplying the cells with exogenous porphyrins, the normal regulatory control is lost and overproduction of endogenous porphyrins results. Malignant tumor cells have abnormal porphyrin metabolism because of disturbed enzyme activity, and therefore the accumulation of PpIX is enhanced in these lesions (Orenstin et al. 1997). Although PDT is dependent on the concentration of photosensitizer in the tumor, adequate light irradiation is also important (Dougherty 1987; Dougherty et al. 1978). Incubation and irradiation times are discussed in the "General principles of treatment" section below.

Photosensitizers

In PDT, photosensitizers allow for the transfer and translation of light energy into a chemical reaction that produces ROS leading to tissue destruction. In clinical practice, photosensitizers arise from three major groups—porphyrins, chlorophylls, and dyes. Each photosensitizer needs to be reliably activated at a high enough light wavelength useful for therapy. Porphyrin species

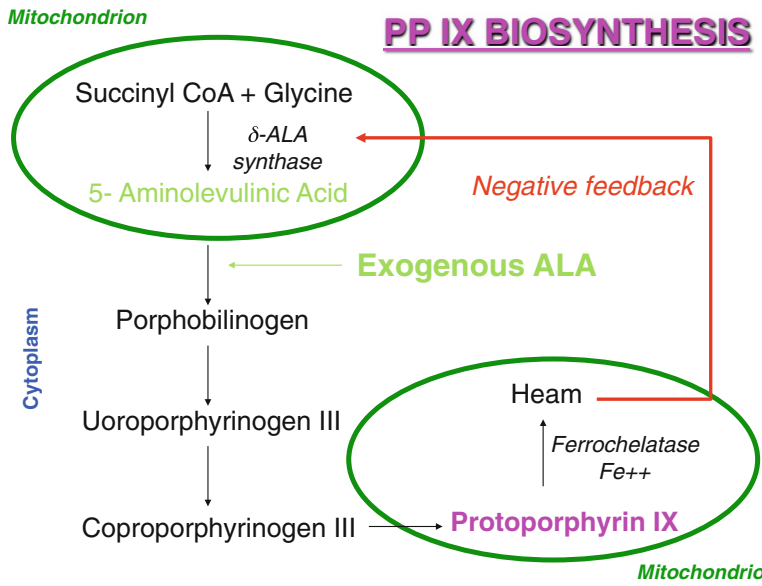

Fig. 126.1 Pathway of protoporphyrin IX (PPIX) biosynthesis. PPIX is produced in excess amounts in mitochondria as a result of exogenous photosensitization due to ALA topical application, utilizing the same cellular pathway for heme production

derived from hematoporphyrin have long been recognized as demonstrating preferential uptake by cancerous cells since these cells exhibit a significantly greater uptake and affinity for porphyrins compared to normal quiescent tissues (Lipson and Baldes 1960; Lipson et al. 1961). As such, refined topical exogenous porphyrin derivatives are currently used and absorbed by rapidly proliferating cells utilizing the heme synthesis pathway to produce PpIX, which is the photosensitizing agent. An additional benefit of porphyrin-derived products is that PpIX fluoresces during photoirradiation allowing for margin identification of human skin tumors. The most characterized and broadly applied in dermatology agents are 5-ALA and MAL. Other topical compounds will be briefly mentioned.

Aminolevulinic Acid (ALA)

In 1990, Kennedy and co-workers introduced 5-ALA with PDT for the treatment of skin disorders (Kennedy et al. 1990). ALA is the first compound in the porphyrin synthesis pathway, and it serves as a prodrug for the active photosensitizing compound, PpIX which is synthesized in vivo after exogenous application of ALA. Pp IX photosensitization is induced in cells of the epidermis and its appendages, but not in the dermis. Kennedy et al. found that ALA in aqueous solution passes readily through abnormal keratin, but not through normal keratin. Therefore, photosensitivity is restricted primarily to the abnormal epithelium (such as in nonmelanoma skin cancer and premalignant conditions like actinic keratoses (AK)). Subsequent exposure to photoactivating light selectively destroys such lesions. Several studies after these initial findings have confirmed the mechanism of ALA-PDT. ALA is presently available in the USA in the form of reconstituted hydroalcoholic solution (Levulan Kerastick) and in Europe as Alacare skin-colored patch facilitating occlusion, as well as BF-200 ALA nanoemulsion for increased stability and penetration.

Methyl Aminolevulinate (MAL)

MAL is a more recent ester derivative of ALA, with a similar mechanism of action. However, MAL may offer advantages over ALA including deeper skin penetration depths due to potentially enhanced lipophilicity and greater specificity for neoplastic cells (Peng et al. 1997, 2001). Although MAL was FDA approved in the USA, it is mostly applied in Europe (Metvixia).

Other Topical Photosensitizers

Although ALA and MAL are most commonly used, other porphyrin molecules such as benzoporphyrins and porphycenes may potentially play a role in PDT (Szeimies et al. 1996). Additionally photosensitizers from the chlorophyll and dye families may also be used for treating premalignant cutaneous lesions with topical PDT and have excellent photosensitizing properties (Allison et al. 2004). Chlorophyll-derived and degradation photosensitive products include temoporfins, purpurins, mono-L-aspartyl chlorin e6 (NpE6), LS11, and HPPH. Dyes have been used as early in the twentieth century as photosensitizing products (Raab 1900). The dyes most commonly reported to include phthalocyanines and their relatives are the naphthalocyanines. Although data is promising, there is still a need for comparative studies and standardized therapeutic protocols to define the place of these other agents and topical PDT in dermatology.

Fig. 126.2 Activation of PPIX during photodynamic therapy with BLU U light source (blue light, 417 nm). Eye protective goggles are utilized during exposure to visible light

Light Source

The administration of a photosensitizing drug and its subsequent activation by irradiation with a light source at wavelengths matching the absorption spectrum of the photosensitizer is important for clinical efficacy. The absorption spectrum of PpIX includes the blue light range (the main absorption peak) and the red light range; these are the most commonly used light sources for PDT. In the USA, Levulan 20 % solution ALA-PDT activation with blue light (417 nm Blu U, Levulan Kerastick, DUSA Pharmaceuticals, Inc) is FDA approved for the treatment of AK (Fig. 126.2). Whereas in Europe, practitioners frequently use 16.0 % cream Metvix/Metvixia MAL-PDT (Galderma) for the treatment of AK, Bowen's disease (BD), and basal cell carcinoma (BCC). Light activation is with red light (~630 nm) because it allows greater optical penetration depth (8–10 mm at 630 nm compared with 1–2 mm at 400–500 nm (Wolf et al. 1993)) and permits shorter illumination times.

Several small studies have investigated intense pulsed light (IPL) and pulsed dye lasers (PDL) as possible light sources for PDT in the treatment of AK (Peng et al. 1997; 2001; Haddad et al. 2011; Alexiades-Armenakas and Geronemus 2003). IPL emits a broad spectrum of visible to near-infrared light. Infrared irradiation causes hyperthermia, and it has been suggested that mild hyperthermia may act synergistically with PDT (Peng et al. 1997; 2001). The combination of ALA-PDT with an IPL source has been shown to improve AK clearance compared to IPL alone (Haddad et al. 2011). Long pulsed PDL (595 nm) in combination with ALA-PDT also has proven efficacy for eradicating AKs compared to PDL (Alexiades-Armenakas and Geronemus 2003). The advantages of using other light sources even with broad-emitting radiation spectrum are that (a) they eradicate the need to have a dedicated PDT light source, (b) they activate PpIX at different absorption maximal wavelengths, (c) they may increase PDT efficacy per each treatment, (d) they may require lower light doses, and (e) they can be better tolerated with decreased recovery time or discomfort.

Table 126.1 ALA-PDT vs. MAL-PDT

	ALA-PDT	MAL-PDT
Exogenous porphyrin	5-aminolevulinic acid	Methyl aminolevulinate
Strength and formulation	20 % alcohol-water solution[a]	16 % oil in water cream[b]
Indication	Actinic keratoses of face and scalp (USA)	Actinic keratoses of the face and scalp (USA and Europe), Bowens disease, superficial and nodular basal cell carcinoma (Europe)
Light source	Blue fluorescent light	Red and blue light
Incubation	14–18 h FDA approved[c]	3 h under occlusion
Efficacy	Reports vary ~80 % up to over 90 %	Same as ALA-PDT
Safety	Photosensitivity and dermatitis	Same as ALA-PDT
Pain	Variable	Unclear compared to ALA-PDT but more intense if red light used

[a]Metvix®/Metvixia®, Galderma
[b]Levulan Kerastick™; DUSA Pharmaceuticals
[c]Although many investigators are now using 1–3-h protocols, based on similar efficacy at these shorter incubation times

General Principles of Treatment

Pretreatment

Usually prior to treatment with ALA-/MAL-PDT, the superficial crust and scale of skin lesions, such as moderate thickness or hyperkeratotic AK, and nonmelanoma skin cancers (NMSC) are gently removed with light curettage or scalpel removal, occlusion with a keratolytic the night before treatment, tape-stripping, microdermabrasion, or laser ablation (Morton et al. 2013a). A topical acetone solution may also be used to decrease oils on the skin surface. These pretreatment techniques may improve efficacy of medication uptake and optical penetration.

Incubation and Exposure

Although Levulan ALA-PDT is approved for a 14–18-h incubation followed by activation with blue light (417 nm Blu U, Levulan Kerastick, DUSA Pharmaceuticals, Inc), expert consensus recommends shorter incubation times with intervals around 1–3 h (Nester et al. 2006). These were derived from the results of several studies demonstrating comparable efficacy with reduced incubation time. Patients are then treated with an appropriate light source. For Levulan ALA, a 1,000-s exposure to BLU U, 417 nm, is suggested (*Figure—consider image of patient sitting under blue u*). Repeat treatment may be performed after 8 weeks as clinically indicated. This protocol is generally accepted in the USA and Europe for the treatment of AK. Metvix/Metvixia MAL-PDT (Galderma) is typically applied for 3 h under occlusion, followed by red light irradiation (570–670 nm or narrower spectrum) for a total light dose of 75 J/cm^2. Two treatments separated 1 week apart for BD/BCC or one initial treatment repeated at 3 months, only if required for AK, may be performed (Morton et al. 2013a) (Table 126.1). Although these are the most common protocols, there are many off-label uses of ALA-/MAL-PDT for malignant skin lesions; please see section "Photodynamic therapy of malignant skin lesions."

Photodynamic Therapy of Malignant Skin Lesions

Several clinical studies have established PDT as a safe and effective treatment for superficial skin cancers and premalignant skin lesions. We review key studies below and as reported in the recent 2013 European guidelines for topical photodynamic therapy.

Actinic Keratoses

AK on the face and scalp tend to respond well to topical ALA-/MAL-PDT, with typical clearance rates of 89–92 % 3 months after therapy,

and 1 year clearance rates of 63–69 % (up to two treatments) (Piacquadio et al. 2004; Tarstedt et al. 2005; Morton et al. 2006a, b; 2008). Clearance rates of AK on acral sites are reduced by ~10 % likely because lesions tend to be thicker on these sites. Comparing MAL-PDT with cryotherapy for facial and scalp AK, after the initial therapy, PDT cleared more lesions (87 % vs. 76 %); however, the outcome was equivalent after nonresponders were retreated (89 % vs. 86 %) (Morton et al. 2006a, b), and for acral AK, PDT was less effective in clearing lesions, 78 % vs. 88 % at 6 months (Kaufman). Guidelines identify ALA-/MAL-PDT as an effective treatment option for focal and field AK. PDT may also serve as an alternative treatment option for patients that cannot tolerate multiple cryotherapy treatments or session, prolonged irritation from topical therapy such as 5-fluorouracil or imiquimod, or that may not respond to immunomodulators.

Squamous Cell Carcinoma

Bowen's Disease

ALA-/MAL-PDT clearance rates of 82–100 % have been reported for BD lesions. For the ALA-PDT studies, a single treatment or two treatments (separated by 1 month based on incomplete response at follow-up) were used (Dijkstra et al. 2001; Varma et al. 2001). In the MAL-PDT studies, clearance rates were determined at 3 months beyond one or two cycles (two treatments 7 days apart defined as one cycle). Sustained clearance rates of 68–71 % at 24 months were observed. These rates were similar to conventional therapy with cryotherapy of 5-flurouracil, but with superior cosmesis (Morton et al. 2006a, b; Calzavara-Pinton et al. 2008). Another study demonstrated a 76 % clearance rate of BD after two sessions of MAL-PDT and a median follow-up of 16 months (Truchuelo et al. 2012).

Similar to AK therapy, guidelines identify ALA-/MAL-PDT as an effective treatment option for BD. Some guidelines recommend PDT as the treatment of choice for BD on poor-healing sites and for large lesions (Cox et al. 2007).

Invasive Squamous Cell Carcinoma

Currently, MAL-PDT clearance rates of 57 and 26 % have been reported for microinvasive and nodular invasive SCC at 24 months (Calzavara-Pinton et al. 2008, 2013a, b). Cellular atypia and poorly differentiated keratinocytes are negative prognostic factors for invasive SCCs, and these cells may be less sensitive to PDT. Another potential concern is that PDT may not reach adequate depths to treat deeply invading tumors. Because of the metastatic potential and the reduced efficacy rates of invasive SCC, European guidelines do not recommend PDT use for these tumors (Morton et al. 2013a).

Basal Cell Carcinoma

Superficial Basal Cell Carcinoma

MAL-PDT studies have demonstrated a clearance rate of 73–97 % at 3 months for sBCC (Basset-Séguin et al. 2008; Szeimies et al. 1996, 2008, Arits et al. 2013). In one randomized study, sBCC was treated with either a single baseline MAL-PDT application or cryotherapy (Basset-Séguin et al. 2008). In a second study, sBCC was treated with either two MAL-PDT applications 7 days apart or surgery (Szeimies et al. 1996, 2008, 2013). In both MAL-PDT protocols, two additional treatment cycles were applied as needed at 3 months. Both studies reported 1-year recurrence rates of 9 % and 5-year recurrence rate of 22 % following MAL-PDT. In addition, both studies reported equivalent clearance efficacy and superior cosmetic outcome following MAL-PDT compared to either cryotherapy or surgery. In a single-blind, randomized study comparing sBCC clearance following MAL-PDT to either topical fluorouracil or imiquimod, fluorouracil was observed to be non-inferior, while imiquimod was superior to MAL-PDT (Arits et al. 2013).

A review of 12 ALA-PDT studies published between 1990 and 1995 reported an average weighted clearance rate of 87 % for sBCC (Peng et al. 1997, 2001). ALA-PDT efficacy is comparable to cryotherapy and yields superior cosmesis (Wang et al. 2001). In a longitudinal study of

BCC treated with curettage and one or two sessions of dimethyl sulfoxide-supported ALA-PDT, 81 % of lesion sites were disease-free at 6 years (Christensen et al. 2009) and 75 % at 10 years (Christensen et al. 2012).

Lesion thickness and location predict therapeutic response to PDT, with thicker tumors and those in the H-zone less responsive (Morton et al. 1998; Vinciullo et al. 2005). Therefore, current guidelines recommend topical PDT for sBCC (Morton et al. 2013a).

Nodular Basal Cell Carcinoma

Studies yield mixed results regarding treatment of nBCC with PDT. One study demonstrated 91 % clearance at 3 months and 76 % clearance at 5 years following MAL-PDT (applied twice at 7 days interval with retreatment at 3 months as needed; Rhodes et al. 2004; 2007). A different study reported an overall response rate of 73 % for nBCC following MAL-PDT with prior minor tumor debulking, though clearance for facial lesions was higher at 89 % (Foley et al. 2009). Fantini et al. report a more modest response rate of 33 % for nBCC compared with 82 % for sBCC with no prior debulking of tumor mass. Specifically, nodular subtype and lesions located in the limbs were the least responsive. Compared with surgery, MAL-PDT yields comparable clearance at 3 and 12 months though a trend towards higher recurrence emerges at 24 months (Rhodes et al. 2004). However, MAL-PDT resulted in superior cosmetic outcomes at all time points. A recent study showed that fractional carbon dioxide laser pretreatment increases clinical effectiveness of MAL-PDT compared to curettage pretreatment (Lippert et al. 2013).

A phase III clinical trial found similar clearance efficacy following ALA-PDT (25 % recurrence at 12 months verified histopathologically) compared to cryosurgery (15 % recurrence), with no significant difference between the superficial and nodular subtypes (Wang et al. 2001). ALA-PDT produced superior cosmetic results. However, a smaller randomized pilot study comparing nBCC clearance and cosmesis following ALA-PDT with prior minimal curettage to surgery did not find any difference in either clearance or cosmesis (Berroeta et al. 2007). Fractionated ALA-PDT is comparable to surgery in clearing nBCC. However, failure rates during long-term follow-up vary between 20 and 31 % at 2–5 years depending on fractionated dosing protocol and debulking pretreatment (de Haas et al. 2007, 2008; Mosterd et al. 2008; Roozeboom et al. 2013).

Current guidelines recommend PDT for thin low-risk nBCC, especially in cases where surgery is contraindicated or a preference for superior cosmesis exists (Telfer et al. 2008). Patients treated with PDT should be monitored for recurrence for at least 1 year.

Nevoid Basal Cell Carcinoma Syndrome

Patients with NBCCS may benefit from PDT. In one cohort study, 33 patients were treated with either topical PDT for superficial lesions (<2 mm thick) or systemic PDT for lesions >2 mm as assessed by ultrasound with overall local control rates of 56 % at 12 months (Loncaster et al. 2009). In a case report of seven patients, including two children, treated with MAL-PDT, 60 % of lesions were cleared after one session and 78 % after three sessions (Girard et al. 2013). MAL-PDT treatment also resulted in excellent cosmetic outcome. In addition, MAL-PDT may improve patient satisfaction and lower the need for surgical procedures (Pauwels et al. 2011).

Other Cutaneous Malignancies

The following diseases have no standardized protocols given the lack of well-controlled high-power studies.

Cutaneous T-Cell Lymphoma

Topical ALA- and MAL-PDT have both been used in localized cutaneous T-cell lymphoma

(CTCL), and evidence is derived from case reports and series. The most promising data has been observed in thin plaque cutaneous B-cell lymphoma using PDT with ALA ($n=2$) and MAL ($n=1$) where patients achieved clinical and histological remission after one or two treatments with clearance maintained over 8–24 months (Mori et al. 2006). Other small studies have shown that multiple treatments may be necessary (1–11) to improve or clear patients with unilesional disease, plaque-stage CTCL, and extensive erosive facial mycosis fungoides (Zane et al. 2006; Edstrom et al. 2001; Debu et al. 2010). Topical hypericin in under occlusion for 24 h followed by administration of visible light has also been described as partially efficacious for CTCL (Rook et al. 2010).

Kaposi's Sarcoma

Case reports and case series of PDT have demonstrated PDT as an effective modality for AIDS-related Kaposi's sarcoma (Sk-AIDS). In 1995, Hebeda et al. described treatment with laser-based Photofrin-PDT (Ph-PDT) protocols in homosexual men with HIV ($n=8$). The response rates by patient for all treated lesions were 50–100 % with a median duration of 3 months. However, cosmetically, there was a high prevalence of scars and long-lasting hyperpigmentation. Based on this, the authors could not recommend Photofrin-PDT for Sk-AIDS (Hebeda et al. 1995). Bernstein et al. published a comprehensive study with 25 patients and concluded that Ph-PDT was effective as palliative treatment for Sk-AIDS; however, cutaneous phototoxicity reactions were seen in 27 % of the patients (Bernstein et al. 1999). In 2006, Tardivo et al. injected phenothiazinium compounds (methylene blue and toluidine blue) and used PDT with a noncoherent light source (RL50) to treat Sk-AIDS in a single patient. The patient was reported to have complete remission with an excellent cosmetic result although the patient required five PDT sessions to confirm histological clearance (Tardivo et al. 2006).

Paget's Disease

Case reports and small series of PDT in extramammary Paget's disease (EMPD) demonstrate that it may not be as effective in treating NMSC such as SCC and BCC. There may be some short-term improvement. ALA-PDT and MAL-PDT have been used with clearance rates of 50–100 %, but some cases have been complicated by recurrence less than 6 months after treatment (Shieh et al. 2002; Mikasa et al. 2005; Zawislak et al. 2004; Rapagliesi et al. 2006.).

Photodynamic Therapy of Other Skin Lesions

Several benign and inflammatory disorders have been treated with ALA-/MAL-PDT with remarkable preliminary clinical results. These include acne, cutaneous infections (i.e., atypical mycobacteria, leishmania), granuloma annulare, hidradenitis suppurativa, keloids, lichenoid dermatoses, lymphadenosis benigna cutis, necrobiosis lipoidica, psoriasis, rosacea, and several others (Morton et al. 2013b; Calzavara-Pinton et al. 2013a, b; Nie 2011; Takeda et al. 2005; Rose and Stables 2008). Most findings are based on anecdotal, observational, or small case series data. Protocols are still being refined, and larger studies are needed to confirm these findings. In-depth discussion of these lesions is outside of the scope of this chapter.

Photodynamic Therapy Combined with Other Modalities

Prevailing topical AK and NMSC therapies include destructive modalities, such as cryosurgery and electrodessication and curettage (ED&C), and topical regimens such as fluorouracil, diclofenac sodium, imiquimod, and PDT. Destruction by cryotherapy and ED&C is suitable and highly effective for treating a few lesions; however, these procedures may require local anesthesia and can result in scarring and pigmentary alterations. On the other hand, field

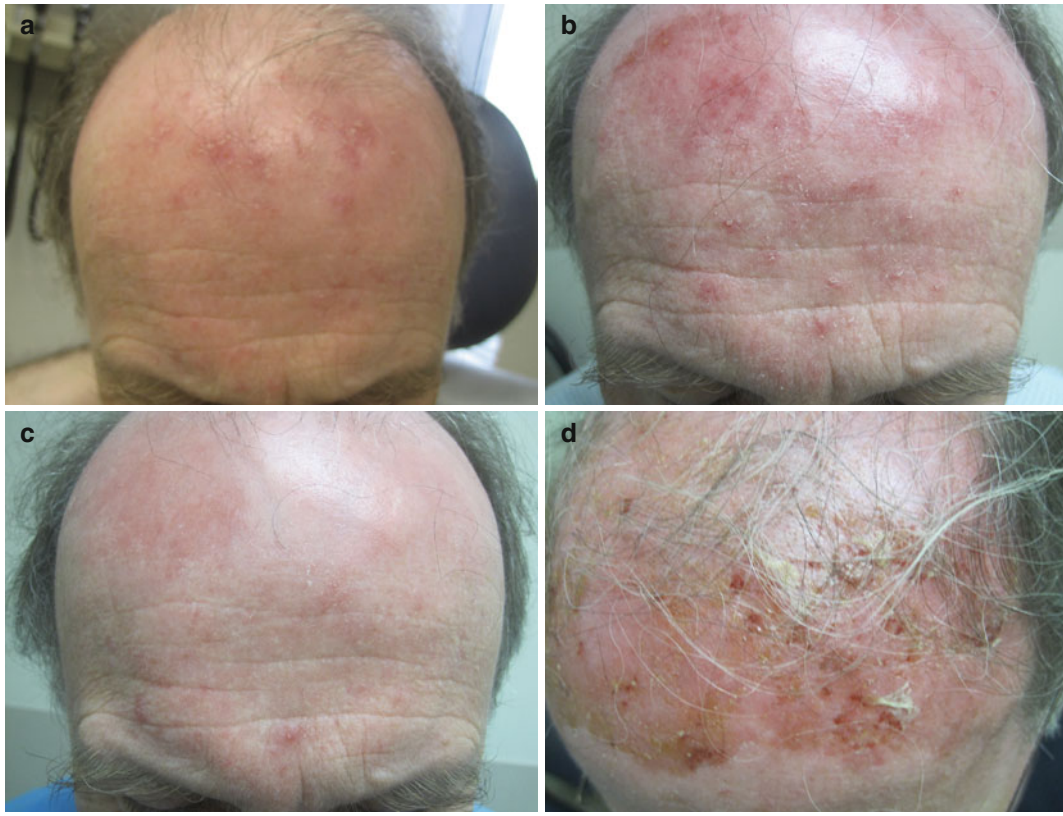

Fig. 126.3 ALA-PDT responses for actinic keratosis, post short 5 FU pretreatment: clockwise: (**a**) before treatment, (**b**) immediately after light exposure, (**c**) 3 days post light therapy with significant crusting, (**d**) 1 month following PDT

therapies including topical chemotherapy, nonsteroidal anti-inflammatory agents, immunomodulators, chemical peels, lasers, or photodynamic therapy (PDT) are suitable for treating multiple lesions. Singly, these treatment modalities have shown to be effective; however, each of these may require application over several weeks or multiple sessions. Additionally, immunomodulator response is variable from individual to individual, and a given response cannot be generalized.

Few sequential therapy studies with PDT have been derived from small pilot studies, case series, anecdotal evidence, or individual preference. Published combination therapies for AK include pretreatment with topical tazarotene gel, diclofenac gel, or 5-fluorouracil followed by ALA-PDT, ALA-PDT followed by topical imiquimod, and ablative fractional laser resurfacing-assisted MAL-PDT; detailed findings can be found in a review by Kaminska and Tsoukas (2013). Although data exploring combined field therapy with these modalities are limited, preliminary findings suggest that these may offer improved efficacy, tolerability, and long-term results compared with monotherapy (Fig. 126.3).

Organ Transplant Recipients

The management of AK and NMSC in solid organ transplant recipients (OTRs) presents many clinical challenges for physicians and bears special mention since this population is at a 65-fold increased risk for developing cutaneous SCC. This is the most common NMSC that develops after transplantation. These SCCs can be associated with significant morbidity, particularly in patients who develop multiple tumors. Risk factors that lead to an increased risk of NMSCs

include a past medical history of any previous cutaneous malignancy, a personal history of significant sun exposure, a fair skin complexion, and/or greater immunosuppressive medication levels. Field decancerization has enabled physicians to treat large affected areas quickly and effectively. PDT is often used in OTRs according to individual patient tolerability (Bangash and Colegio 2012).

In a recent study by Willey et al., high-risk OTRs ($n=12$) received cyclic ALA-PDT (every 4–8 weeks for 2 years) for the prevention of cutaneous SCCs. The study demonstrated a significant reduction of SCCs at the end of 24 months of treatment (95 % reduction) when compared to the baseline number of SCCs (the number of SCCs developed during the year before initiation of cyclic PDT). These data suggest that cyclic ALA-PDT could potentially prevent new SCCs in this high-risk patient population (Willey et al. 2010) and therefore decrease morbidity and mortality.

Cosmesis

The ultimate goal of PDT is for long-term treatment and prevention of large cutaneous areas of premalignant and malignant lesions. An additional benefit is excellent cosmetic results, superior to other modalities such as cryotherapy or surgery, which can leave scars and result in dyspigmentation. In a study using broad-area application of δ-ALA-PDT for treatment of AK and diffuse photodamage, improvement in Griffiths score, sallowness, and fine wrinkling accompanied reduction in AK (Touma et al. 2004).

PDT is also effective for skin photorejuvenation, with improvement in fine wrinkles, mottled hyperpigmentation roughness, and sallowness (Kohl et al. 2010; Alster and Surin-Lord 2006). Split-face studies demonstrated that adjunctive use of 5-ALA with intense pulsed light for photoaging (IPL) results in greater improvement in overall photodamage, mottled pigmentation, fine lines, crow's feet, tactile skin roughness, and telangiectasias compared with IPL alone (Dover et al. 2005; Gold et al. 2006). Split-face studies also demonstrated efficacy of MAL-PDT plus red light in improving fine lines, tactile roughness and skin tightness (Ruiz-Rodriguez et al. 2008), global photodamage, coarse lines, mottled pigmentation, sallowness, erythema, and sebaceous hyperplasia (Sanclemente et al. 2011). Combined fractional resurfacing and MAL-PDT has been reported to improve superficial wrinkles (Ruiz-Rodriguez et al. 2007). PDT combined with various pretreatment modalities (such as microneedling, microdermabrasion, fractional lasers) allows for synergist results and improved cosmesis on different anatomical sites (Szeimies et al. 1996, 2008, 2013).

Adverse Effects and Management

Adverse effects of PDT include induction of burning and stinging during light exposure. Clinically, crusting, peeling, erythema, edema, pigmentation, pustules, and pain may be noted. Of these, pain is the most severe of the adverse effects, sometimes resulting in treatment interruption and termination. Although uncomfortable, these side effects are not contraindicated and can be managed. Contraindications for ALA, MAL, and PDT are outlined in Table 126.2.

While the definitive pain mechanism of PDT is not yet fully understood, several modalities

Table 126.2 Contraindications for PDT

	Skin disease	NMSC	Hypersensitivity	Pregnancy class
ALA-PDT	Any photosensitive disorders such as porphyria	Morpheaform basal cell carcinoma[a]	Porphyrins, sensitivity to any component in product	C[b]
MAL-PDT	Same as above	Same as above	Porphyrins, arachis oil, peanut, soya to or any other component in product	Same as above

[a]Insufficient data to use PDT
[b]Off-label PDT for acne management has been practiced in later stages of pregnancy

may help prevent or decrease discomfort during therapy. Thermal spring water is thought to have anti-inflammatory activity in vitro. Cooling the skin with cold air may reduce metabolism, which decreases the effects of tissue damage. Infiltration anesthesia and nerve blocks without vasoconstrictor are useful in the management of pain in PDT. Lower irradiances are related to lower levels of pain. However, one therapy that has not proven efficacious is topical anesthetics in PDT. It is postulated that since both ALA and MAL have an acidic pH and the majority of the topical anesthetics have an alkaline pH, their combined use is incompatible (Chaves et al. 2012).

Future Perspectives

Investigators are currently studying ways to improve PDT outcomes. From combination therapies as mentioned above to refining the topical product (i.e., a patch ALA formulation that does not require pretreatment lesion preparation (Hauschild et al. 2009) or nanoemulsion ALA that increases ALA stability and skin penetration (Dirschka et al. 2012)) or optimizing the light protocol (i.e., a fractionated illumination scheme, in which two light fractions are delivered separated by a 2-h dark interval, following a single ALA application (de Haas et al. 2007, 2008)), PDT continues to evolve. Additionally, daylight PDT is practiced in Europe and can increase efficacy and compliance of the modality (Braathen 2012). As such, one can expect guidelines to adjust as the technique is perfected.

Conclusion

Aggressive nonsurgical treatment of precancerous lesions and NMSC may prevent the rate of conversion to more advanced tumors. Since PDT is an evidence-based treatment modality, it is appealing to both prospective patients and physicians alike. Its advantages include decreasing treatment costs and improving cosmetic outcomes. As more information becomes available on how to increase the absorption of the exogenous porphyrin prodrug (thereby amplifying PpIX production in lesional skin), enhance light penetration, and improve patient tolerability by decreasing pain, in the future, PDT may become the gold standard for field decancerization of AK and NMSC.

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Phototherapy

127

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Key Points

- Phototherapy is the use of ultraviolet radiation or visible light for therapeutic purposes. When artificial photosensitizers are used in combination with light, the appropriate term is *photochemotherapy*.
- Narrowband and broadband UVB, UVA as part of photochemotherapy (PUVA), UVA1, and targeted phototherapy (excimer lasers and nonlaser monochromatic excimer light sources) are in use today with success in dermatologic therapy.

General Principles

The different wavelengths of ultraviolet radiation penetrate the skin in different depth and interact with different molecules in the skin. As a consequence, each form of phototherapy has unique effectiveness for different diseases and unique side effects.

UVB radiation (290–320 nm) is absorbed in the epidermis and superficial dermis. Its absorption results in many different types of DNA damage but mainly pyrimidine dimers and 6,4 pyrimidine–pyrimidone photoproducts. UVB activates a series of signal transduction pathways and results in the generation of reactive oxygen species. These have DNA-damaging effects, activate other signal transduction pathways, and stimulate cytokine production.

UVA radiation (320–400 nm) reaches deeper than UVB in the mid- or lower dermis. The major biological effects of UVA radiation are due to the generation of reactive oxygen species, although direct DNA damage has also been shown after UVA irradiation. UVA-induced ROS are capable of harming DNA, lipids, proteins, and various cellular organelles.

Psoralens used in photochemotherapy intercalate with DNA, and following UVA exposure results in cross-linking of DNA strands in the double helix. This signals a DNA damage response, suppressing DNA synthesis and cell division, and is thought to contribute to the therapeutic response of psoriasis. Psoralens also react with RNA, proteins, and other cellular components and indirectly modify cellular components via ROS-mediated reactions.

In general, the therapeutic action of photo(chemo)therapy may fall into three major categories:

1. Effects on production of soluble mediators from skin cells
2. Modulation of the expression of cell-surface-associated molecules
3. Direct action on cells/apoptosis in pathogenetically relevant cells

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_127, © Springer-Verlag Berlin Heidelberg 2015

1. Soluble mediators induced by photo(chemo) therapy are thought to have anti-inflammatory, immunosuppressive, or both properties. The production of soluble, immunomodulatory mediators is well proven for UVB, for UVA, and for UVA1 radiation. In contrast, less is known about the effects of PUVA on the release of molecules from skin cells. Keratinocyte-derived cytokines of particular therapeutic relevance are IL-10 and prostaglandin E2, both of which have been shown to diminish the capacity of dendritic cells to present antigen to effector T cells and to suppress T-cell responses. Other immunosuppressive mediators that have been reported to be increased following UVB exposure include agonists of the platelet-activating factor receptor, alpha-MSH, cyclooxygenase-2, and calcitonin gene-related peptide.
2. UVB, UVA, and PUVA treatment can directly affect the expression and function of cell-surface receptors. Adhesion molecule intercellular adhesion molecule-1 (ICAM-1) is rarely expressed on the surface of normal human keratinocytes. However, it is greatly upregulated in inflamed skin (psoriasis, atopic dermatitis, T-cell lymphoma). This molecule serves as a counter-receptor for the lymphocyte function-associated antigen-1 (LFA-1), which is present on the surface of leukocytes. The ICAM-1-/LFA-1-mediated keratinocyte–lymphocyte adhesion is important for the generation and maintenance of different inflammatory and immune reactions in the skin. UVB and PUVA therapies are shown to decrease ICAM-1 expression. The mechanisms responsible for this effect are not known.
3. Induction of apoptosis. T cells have an increased susceptibility toward UV radiation-induced apoptosis compared to other cell populations such as monocytes or keratinocytes. This provides a partial explanation of the responsiveness of T-cell-dependent diseases to phototherapy and has been demonstrated for UVA1 phototherapy in the lymphocytic infiltrate in atopic dermatitis and for narrowband UVB in psoriasis. UVA1 radiation, but not PUVA, is capable of inducing apoptosis in skin-infiltrating mast cells of patients with urticaria pigmentosa and is associated with mast cell depletion from the skin and longer-lasting remission periods in patients with urticaria pigmentosa.

Effects on Melanocytes

Ultraviolet radiation is known to induce melanogenesis, which is at least in part a consequence of DNA damage and/or its repair. Gradual exposure to UV (artificial or not) and possibly the consequent tanning response may increase the tolerance of patients with certain photosensitivity disorders to ambient sun exposure. UV-induced tanning also decreases the efficacy of phototherapy unless the dose of ultraviolet radiation is gradually increased. For the same reason, darker phototypes (V–VI) are frequently poorer responders to phototherapy for certain diseases.

Narrowband UVB and PUVA are effective in repopulating vitiligo-affected skin with melanocytes. The mechanism underlying this observation may involve stimulation of hair follicle melanocyte proliferation and migration.

Effects on Collagen

One of the major consequences of UVA exposure of the skin is the activation of matrix metalloproteinase-1 (MMP-1), the major biologic activity of which is degradation of collagen. Collagen degradation is the aim of phototherapy use in sclerotic skin diseases.

Phototherapy in Daily Praxis

Prior to phototherapy initiation, patients should undergo detailed dermatological examination to assess the extent of skin lesions and any contraindications to treatment. Absolute contraindications are photoactivated disease photosensitivity, history of phototoxic drugs, history of skin cancer, prior exposure to ionizing radiation or arse-

nic, dysplastic nevus syndrome, and genetic defect in DNA repair mechanisms. On the other hand, the relative contraindications include the phototype I, age less than 10 years for UVB and 16 years for PUVA, the presence of actinic keratoses, and prior or concurrent administration of immunosuppressive drugs. Pregnancy and breastfeeding are contraindications for PUVA. Also, history of cataract, liver enzyme abnormalities, and renal failure should be taken into consideration prior to PUVA initiation.

Prior to PUVA initiation, blood tests including transaminase, creatinine, and antinuclear antibodies are desirable. During the treatment, it is necessary to cover the eyes with goggles, and for 12 h after taking psoralen, patients should protect their eyes from sunlight.

UVB

Ideally, minimal erythema dose (MED) of each patient should be calculated before treatment initiation in order to determine the optimal dose regimen (MED is defined as the minimum dose that causes erythematous reaction 24 h after exposure to radiation). The initial dose should be equal to 70 % of MED. If this dose is well tolerated, each session can be increased by 20 %. However it is noted that increasing the dose by 5 or 10 % per session may be equally effective. If the patient develops erythema, the next session should be canceled or delivered at a reduced dose (50 %). The sessions are conducted two to five times a week. In broadband UVB phototherapy, initial dose is equal to the MED and further increased by 50 %, 40 %, 30 %, etc. It is recommended that patients do not undergo more than 300–450 treatment sessions in their lives.

PUVA

The UVA doses depend on patients' phototype or on the minimum phototoxic dose (MPD), defined as the minimum dose of UVA radiation that causes the least erythema on skin surfaces exposed to increasing doses of UVA radiation after ingestion of psoralens. The test is read after 72 h. To achieve a good therapeutic result, multiple sessions with gradually increasing dose are required. When the desired effect is reached, the frequency of sessions is decreased, and the last dose of UVA is used as a maintenance dose in maintenance therapy if required.

To minimize the risk of carcinogenicity, patients should not exceed throughout their life the 150–200 PUVA sessions and the total dose of 1,200–1,500 J/cm^2. Thirty phototherapy sessions should not be exceeded per treatment cycle with an upper total radiation limit of 100–150 J/cm^2.

Psoralens may be administrated as a topical agent, a bath, or oral agents. The topical application of 8-MOP in the form of a cream, lotion, or ointment has several disadvantages. The uneven distribution of psoralen to the skin can cause severe phototoxic reactions and uneven pigmentation. Additionally, if there are numerous lesions, topical application is laborious and delicate while it does not prevent the appearance of new lesions in previously healthy skin. Thus, the use of topical PUVA with psoralens is indicated only in cases of limited disease or involvement of the palms and soles.

The use of psoralens to bath form offers uniform distribution on the skin surface, with very low levels of drug absorption and fast elimination of free psoralen to the skin. In this way gastrointestinal and ophthalmological side effects are not observed since there is no systemic photosensitization. The process involves immersing the entire body in a solution of 0,5–5 mg 8-MOP per liter of water. The radiation exposure is carried out immediately after the bath.

Systemic PUVA. The 8-MOP is administered orally (0,6–0,8 mg/kg body weight) 1–3 h prior to UVA exposure. The liquid form is absorbed faster than the microcrystalline form. For the 5-MOP, the usual dosage is 1,2–2,8 mg/kg.

Side Effects

Itching, burning sensation, nausea, and phototoxic erythema may result after PUVA treatments. Very rarely eruptions similar to the polymorphous light eruption, subungual hemorrhages, and facial

hirsutism may be seen but resolve after discontinuation of therapy. Long-term PUVA therapy can lead to solar elastosis, lentigines, actinic keratosis, and increased risk of developing skin cancer, especially SCC. The risk of melanoma also seems to be increased for individuals with at least 250 treatments and at least 15 years from the first PUVA treatment. Cutaneous carcinogenicity is a major concern with long-term high cumulative UVA doses. Both DNA damage and PUVA-induced immunosuppression are implicated in the PUVA-induced cutaneous carcinogenicity.

With respect to UVB and nonmelanoma skin cancer, most studies have shown that there is no or little risk beyond that associated with habitual sun exposure with either BB-UVB or NB-UVB phototherapy. Greater than 300 treatments BB-UVB is associated with a modest but significant increase in SCC and BCC.

Reported side effects of UVA1 phototherapy include intense tanning, erythema, pruritus, urticaria, tenderness, a burning sensation, polymorphous light eruption, eczema herpeticum, and bacterial superinfection. The long-term effects are still under investigation.

Diseases

The skin diseases that are amenable to phototherapy are summarized in Table 127.1.

Psoriasis

The narrowband UVB phototherapy is an essential treatment option for moderate to severe psoriasis. It has been shown that narrowband UVB radiation is clearly more effective than broad spectrum, as narrowband-treated patients have faster healing of skin lesions and longer periods of disease remission. On the other hand, the effectiveness of narrowband UVB seems to be comparable to oral PUVA and superior to bath PUVA. Thus, narrowband UVB is preferable than PUVA as it does not involve the use of psoralens, does not require eye protection after treatment, costs less, and can be used during pregnancy and childhood.

After achieving a good therapeutic result with photo(chemo)therapy, patients are often treated with maintenance sessions (twice a week for 1 month and then weekly for 1 month). Some authors, however, suggest maintenance therapy only in cases of known short relapses.

A combination of phototherapy with topical or systemic factors in order to achieve higher cure rates, longer disease-free intervals, and less risk of carcinogenesis is often used in psoriasis patients.

Local agents that can be used are anthralin, vitamin D analogues, retinoids, glucocorticoids, and emollients. The vitamin D analogues have anti-inflammatory action and also slow down cellular growth rate. The surface being treated should not exceed 30 % of the total body surface to avoid systemic side effects of the percutaneous absorption

Table 127.1 Phototherapy-amenable diseases and the type of phototherapy they are responsive to

	PUVA	UVB	NB-UVB	UVA	UVA1	Excimer
Psoriasis	+	+	+			+
Vitiligo	+		+			+
Atopic dermatitis	+		+		+	
T-cell lymphoma	+		+		+	
GVHD	+					
Pruritus		+	+			
Morphea						
Urticaria pigmentosa	+				+	
PLE	+		+			
Pityriasis lichenoides	+	+	+			

of the drug (such as hypercalcemia with accompanying nephrocalcinosis). The combination of vitamin D analogues with UVB phototherapy is more effective than phototherapy alone. Tazarotene is a topical retinoid effective in plaque psoriasis. Its use in combination with UVB phototherapy seems to improve the efficacy of treatment and to contribute to a rapid improvement. Topical corticosteroids may be useful in areas not reached by UV radiation, such as the head, the perineum, and the navel or on areas resistant to phototherapy. Furthermore, they can be used in particular inflammatory lesions, in order to achieve a rapid improvement.

Systemic factors that are administered in combination with phototherapy are retinoids, methotrexate, and rarely glucocorticoids. Retinoids increase the effectiveness of phototherapy acting synergistically and reduce the risk of carcinogenesis. Their administration starts 5–10 days before the initiation of photo(chemo)therapy and continued throughout the course of treatment. Methotrexate can reduce the required length of treatment with UV, the number of sessions, and the total dose of UV. Moreover, it may be effective in cases that do not show improvement only with PUVA or UVB phototherapy. However, methotrexate can act synergistically with UV to increase the risk of skin cancer and therefore should not be used for long periods. The use of oral corticosteroids is restricted only in special severe cases such as generalized pustular psoriasis. The combination of phototherapy with cyclosporin is not recommended since both substances increase the risk of developing skin cancer from UV radiation.

Excimer laser and nonlaser (MEL) light sources (308 nm) are also used for treatment of mild to moderate localized psoriasis. This localized phototherapy is indicated for patients with lesions localized in places difficult to access in other treatments (elbows, knees, palms, soles) or persistent psoriatic plaques that do not respond to other treatments. It cannot be used for large surfaces as the spot is small (2 cm^2). Advantages include using only the affected area and thus possibly reducing the cumulative dose of UV and the smallest number of sessions required.

Cutaneous T Lymphoma

The UV radiation causes apoptosis of T lymphocytes. Thus, phototherapy plays an important role in the treatment of diseases with involvement of T lymphocytes. UVA1, PUVA, and narrowband UVB may be used. The first appears to be as effective as the second but with fewer side effects, while the third is less effective and appropriate for the early stages of mycosis fungoides (IA, IB, IIA). Regimens with high and medium doses of UVA1 are effective in the treatment of stages IA and IB of mycosis fungoides. For the treatment of erythrodermic form (stages IB, IIB, III), high doses are required. PUVA dosage and frequency of sessions for cutaneous T-cell lymphoma are similar to psoriasis. The initial treatment sessions are followed from a 2-month maintenance therapy (two sessions per week for a month and one session per week for the next month). Subsequently, the patient is monitored once a month and then every 2 months. Treatments can be repeated. PUVA is an excellent treatment option for early-stage disease and achieves long disease-free periods. In more advanced stages, PUVA appears to improve quality of life and prolong survival when combined with other factors such as retinoids, bexarotene, and interferon-A2A.

Vitiligo

PUVA was the most common treatment for vitiligo in the past. However, studies have shown that the narrowband UVB phototherapy achieves repigmentation of vitiligo lesions to many patients, even in those with phototypes IV and V, as well as children. If no improvement is seen within 6 months, the narrowband UVB phototherapy should be discontinued. It should be noted that as in trials with PUVA, some body parts like the fingers and the tips of the hands and feet had poor response. Targeted phototherapy devices (excimer laser or lamp) with irradiation peak at 308 nm are particularly suitable for treating localized disease.

Atopic Dermatitis

The UVA1 phototherapy is effective as monotherapy in atopic dermatitis, particularly in acute, severe forms of the disease. UVA1 phototherapy appears superior to the combined UVA/UVB radiation. Moreover, it is significantly more effective than topical corticosteroids in comparison made the tenth day of treatment. The effectiveness of the treatment is dose dependent. Regarding the chronic form of the disease, UVA1 low-dose radiation may be used; however the narrowband UVB and the combined UVA/UVB give better results. The broadband and narrowband UVB phototherapy, combined UVA/UVB, and UVA broad spectrum seem to be effective in mild and moderate forms of atopic dermatitis used in combination with topical corticosteroids. The narrowband UVB phototherapy appears to have similar efficacy with PUVA. PUVA often requires greater number of sessions for complete healing of atopic dermatitis compared with other skin diseases. There is a high rate of early relapse indicating the importance of maintenance therapy. The combination of PUVA with local corticosteroids appears to be more effective than PUVA alone in maintaining remission.

Urticaria Pigmentosa

UVA1 phototherapy ameliorates urticaria pigmentosa, reducing urticarial lesions and pruritus. Urinary histamine levels also decrease in response to UVA1. PUVA leads to improvement of skin sessions, and possibly improvement of systemic symptoms. Recurrences respond to phototherapy as well as the original lesions. Since treatment of cutaneous mastocytosis has been unrewarding with other modalities, phototherapy, although not curative, is a good choice when patients' quality of life is impaired.

Polymorphous Light Eruption

For polymorphous light eruption, PUVA and narrowband UVB are effective in preventing the appearance of the disease. Sessions are held three to four times a week for 3–4 weeks, at the beginning of spring. The effect appears to last 2–3 months after loss of tanning. In order to maintain the therapeutic effect of phototherapy, patients should be regularly exposed for short periods in the sun.

Pruritus

Both the narrowband and the broadband UVB phototherapies appear to be effective in various types of pruritus, especially in cases related to diabetes, liver disorders, and idiopathic.

Lichenoid Pityriasis and Lymphomatoid Papulosis

Both UVB phototherapy and PUVA seem to be effective for the treatment of lichenoid pityriasis and lymphomatoid papulosis. PUVA is most probably superior to UVB and its use is recommended in chronic forms of the disease, resistant to UVB.

Localized Scleroderma (Morphea)

UVA1 for localized scleroderma significantly reduces the thickness of skin lesions and increases the elasticity of sclerotic plaques. The efficiency is dose dependent. PUVA is also effective. Both treatments may be applied to sclerotic lesions of chronic graft-versus-host disease. Narrowband UVB is also effective for superficial widespread lesions.

Chronic GVHD (Graft-Versus-Host Disease, GVHD)

Both chronic and acute forms of the disease seem to respond positively to PUVA. An improvement of lichenoid rash even in patients who have not improved with immunosuppressive therapy is expected. Sclerotic lesions appear more resistant.

Gradual increase in dose should not exceed 0,5 J/cm^2 every second to fourth session. The sessions are conducted three to four times a week.

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Sclerotherapy

128

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Key Points

- *Sclerotherapy* consists of intravenous injection of sclerosing agents for the treatment of cosmetic leg veins.
- Clinical examination of patients is fundamental before beginning sclerotherapy in order to determine the feasibility of this treatment as a primary mode.
- By understanding venous pathology and aetiology and by choosing the proper sclerosant and right technique for the vein being treated, a successful outcome will be achieved.
- Sclerotherapy agents can be divided in three classes: hyperosmotic agents, detergents and chemical irritants.
- In order to minimize side effects and reduce their incidence, it is necessary for physicians to understand the potential causes, to advice the patients and to be able to treat.

General Principles

Sclerotherapy consists of intravenous injection of sclerosing agents for the treatment of cosmetic leg veins. Several studies have reported that sclerotherapy has been successfully used for the treatment of minor branch vein varicosities not associated with saphenous incompetence.

Varicose veins are enlarged, tortuous veins that have lost their elasticity. They have a calibre greater than normal (more than 2 mm in diameter) and are placed in the deep derma and in the subcutaneous tissue. It is possible to distinguish primary and secondary varicose veins. The latter originate from a thrombotic occlusion of one or more deep veins and are often associated with abnormal valvular function.

The superficial veins of the legs are the most frequently involved. Telangiectases are small (diameter less than 2 mm), with visible blood vessels placed in the dermis that are permanently

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_128, © Springer-Verlag Berlin Heidelberg 2015

dilated. Women suffer more from vein problems: it has been estimated that more than half of European and American women are affected by telangiectases.

Varicose Veins and Telangiectases

The aetiology is multifactorial: various factors could be responsible for their pathogenesis such as hormones, pregnancy, obesity, frequent constipation, prolonged standing and individual problems, i.e. sex, hereditary, etc. For example, in pregnancy venous relaxations due to increased hormone levels, expansion of blood volume and increased venous pressure especially in the limb where the iliac vein is compressed by the enlarged uterus are causes of varicosity.

Thrombophlebitis leads to formation of varicose veins by destroying venous valves. Studies have suggested that an increase of venous pressure can induce leucocyte accumulation and subsequent free radical production and inflammatory response. Pathogenesis of telangiectases is related to many different pathological processes affecting the blood vessel endothelium and its supporting structures. Some situations are often connected with telangiectases such as the presence of varicose veins, hormonal factors and physical factors.

Clinical Features and Course

Superficial venous insufficiency is a common problem in young and working people.

Clinical examination of patients is fundamental before beginning sclerotherapy in order to determine the feasibility of this treatment as a primary mode.

Varicose veins are visible as dilated, tortuous, superficial veins, often thick walled. Most patients with varicose veins and chronic venous insufficiency have specific symptoms and signs as chronic pain, oedema, inflammation and/or ulceration.

However, in most patients, telangiectases may be the only abnormality noted on clinical examination, and they are not associated with symptoms. They appear on the skin as red, small, linear, stellate or punctate markings, usually treated for aesthetic purpose.

Diagnosis

Diagnosis of superficial venous insufficiency is usually based on clinical observation.

The need for laboratory data should be assessed on an individual basis. They are necessary usually in patients with hypercoagulability or severe venous symptoms.

The most commonly used tests to investigate the blood flow in the superficial and deep venous system are duplex scanning and venous Doppler study. Phlebography, photoplethysmography and light reflection rheography are other investigations usually reserved for those patients with venous symptoms and/or large vessel incompetence or large numbers of spider telangiectases indicating venous hypertension.

Instrumental examinations became useful in order to find a correct therapeutic strategy and to follow up the treatment.

General Principles of Treatment

The recommended approach to the sclerotherapy should be the following:

- If the patient reports symptoms as leg pain, itching and heaviness, vascular testing is indicated.
- Vascular testing is also indicated if the patient does not refer symptoms but has at least two of the following signs: oedema, vessel diameter greater than 4 mm, corona of lower extremities, changes of pigmentation, dermatitis, ulcer and fibrosis.

The treatment of varicose and telangiectatic leg veins can be approached in a logical and systematic way. Venous regions or entire abnormal superficial venous networks related to incompetent perforators should be injected in a single session, instead of randomly injecting as many veins as possible in a given period of time. Each patient

requires differing amounts of time for this systematic approach.

It is important not to limit treatment to telangiectatic veins but to consider the complete system.

Sclerosing Solutions

In the literature several studies dealing with the use of different sclerosing solutions for the treatment of both functional and cosmetic vein disorders are present. Each solution has a unique safety and efficacy profile. The type, concentration and quantity of solution selected are determined by the type and/or site of varicose vein injected.

There are three classes of sclerosant agents based on their mechanism of action: hyperosmotic agents, detergents and chemical irritants.

The purpose of sclerotherapy is not merely to achieve thrombosis of the vessel, which per se may be amenable to recanalization, but definitive transformation into a non-recanalizable fibrous cord.

The other depends on the endothelial cell surface alterations with direct damage of the endothelial cells resulting in inflammation and thrombus formation. They have the ability to denature biological molecules irreversibly within the vein wall.

Hyperosmotic agents as hypertonic saline (23.4 % sodium chloride) with or without lidocaine and heparin are dehydrating sclerosing agents commonly used. Hypertonic saline causes dehydration of endothelial cells by osmotic action with resultant injury, inflammation and thrombus formation. At the recommended dose of 10 mL per treatment session, it is effective and extensively used in Europe for the treatment of minor varicosity and telangiectases. The Food and Drug Administration (FDA) of the USA has approved it only as an abortifacient rather than a sclerotherapy agent. It may cause moderate pain on injection with occasional muscle cramps and risk of ulceration at the site of extravasation. One of the major advantages of this agent, when used pure, is the absence of adverse allergic reactions.

Sclerodex (10 % sodium chloride, 25 % dextrose and 1 % phenylethyl alcohol) is a dehydrating agent that is very effective and often used in Europe for the treatment of minor varicosity and telangiectases. The low concentration of chloride, associated with anionic dextrose, decreases injection pain and muscle cramps.

Sodium morrhuate derived from cod liver oil and sodium tetradecyl sulphate (STS) are other sclerosing solutions also approved by the FDA. They belong to the detergent class and cause vascular injury through the alteration of the surface tension around the endothelial cells. The first is rarely used because of its side effects (among which are anaphylactic reactions). The sodium tetradecyl sulphate (STS) is often used for varicose veins under ultrasound guidance. Furthermore it can be used in a dilute form for the treatment of telangiectases. The use of STS in a sclerosing foam (Tessari method) mixing 1 part liquid STD and 5/6 parts air was recently indicated to give good results.

A recent study of Subbarao et al. (2013) evaluated the safety and efficacy of STS sclerotherapy in the treatment of varicose veins and its dermatological complications.

The sclerosant was diluted to required concentrations using 0.9 % normal saline. Commonly used concentrations were 0.3–0.5 % of STS depending on the size of the veins. 0.75 % STS was used to inject the perforators.

In the study, 50 patients were included. At the end of the treatment, pain improved in 29 patients out of 38 cases (76 %), dilated veins reduced in 45 (90 %) out of 50 cases, oedema reduced in 7 of 15 patients (46 %), ulceration reduced in 10 (66 %), pigmentation responded poorly with 8 cases showing response out of 42 cases and eczema showed a good response in 33 (82.5 %).

Polidocanol (hydroxy-polyethoxy-dodecane) (POL) (0.25 %) is a surface tension-acting agent, with the same mechanism of action of sodium morrhuate and STD.

Lastly, chemical irritants, as chromated glycerine (72 % glycerine mixed with 1 % lidocaine and 1:100,000 epinephrine combined 2:1), which injure cells by causing a corrosive secondary to

the metal component, are indicated for the treatment of fine leg telangiectases (up to 1 mm of diameter) (Zaulyanov-Scanlan 2009).

Interestingly, an Italian–American study proposed a new therapeutic approach consisting in the use of polymerized hyaluronic acid (HA) mesotherapic injections following sclerotherapy in the areas of the skin affected by telangiectasia in patients without major vein insufficiency (Iannitti et al. 2012).

This pilot study suggests that the prolonged persistence of cross-linked HA, across the microvascular venous areas, is able to induce a stronger stromal tissue, thus preventing relapse.

The optimal sclerosant concentration may vary with the diameter of the veins being treated. In fact if the concentration is too weak, it can cause an insufficient damage to the endothelium followed by a thrombus that eventually may recanalize. If the concentration is too strong, side effects, as ulceration and hyperpigmentation, can occur.

In case of pregnancy, sclerotherapy should never be used. These agents are at least locally toxic, and no studies have been done to prove their safety in pregnant women.

Technique

With the patient standing, the veins must be carefully marked out and the needles inserted into the varicosities.

The sclerosing solution is injected into the vessel with a 30-gauge or smaller needle to maintain the needle parallel to the skin surface. The vessel is carefully cannulated under magnification. Then a small amount of sclerosing solution is injected until the vessel and interconnecting vessels are filling. In order to assess whether the vessel has been cannulated, it is recommended to inject a small amount of air before the sclerosing solution. The site of injection depends on individual experience. Normally, two or three points are selected on a very long anterolateral thigh vein, whereas one injection will suffice for short tributaries. The sclerosant quantity per injection should be no more than 0.1–1.0 mL.

Concentrations utilized range from 0.2 to 3 %, depending on the vein size and on the volume injected: when a higher concentration is injected, a smaller volume would be used.

Zummo (1991) tried to standardize quantities and concentrations of different sclerosing agents depending on the type of vein malformations to treat, suggesting that therapy must be adapted for each patient. The Tessari and Tessari/double-syringe system methods are recommended for the generation of foam sclerosant. Air is the most accepted gas component for the generation of foam sclerosant for all indications. A mixture of carbon dioxide and oxygen may also be used. The preferred ratio of liquid sclerosant and gas for the generation of a foam sclerosant is 1:4. The recommended maximum foam volume per leg and session (given in a single injection or in several injections) is 10 mL. The viscosity of the foam should be directly proportional to the calibre of the varicose veins.

Empty Vein Technique

The empty vein technique is used in the sclerotherapy of varicose veins. Firstly patient should be placed supine. Then the leg should be kept up until the complete emptying of the veins. A major advantage of this technique is the minimal dilution of the sclerosant agent.

Post-sclerotherapy Compression

In general telangiectases less than 1 mm in diameter may require no compression. However some veins may be more effectively treated with compressive dressing.

This may be accomplished by multiple techniques including bandaging and stockings. Bandage dressing could be elastic or not. The nonelastic are more commonly utilized. Compression bandages are recommended for patients with oedema. Graduated compression stockings are available in different models wherein the choice depends on the physical attributes of the injected leg as well as the type of varicosity

treated. The most important part of the stocking is below the knee, where the standing venous pressure is the highest. Although effective for symptom control, stockings may not be practical in elderly persons, for whom the application can be difficult; in obese patients, in whom fitting can be problematic; and in patients with skin damage.

Graduated stockings are usually left on the leg during the entire time of treatment or removed when the patient is lying down.

Immediate and sustained compression has considerable advantages: decrease of the volume of intraluminal thrombus and minimization of the duration required for complete resorption of the vein. In fact when a vein has undergone mural disruption, it still has enough intact long intraluminal space to be distended by blood which rapidly becomes coagulated.

The duration of compression depends on the size of the vein as well as its intraluminal venous pressure. Normally, the time of compression ranges from 2 to 8 weeks after treatment. However compression enhances the results of sclerotherapy that are directly correlated with duration of compression. Further it leads to a reduction of post-sclerotherapy hyperpigmentation.

The degree of compression applied can vary from 30 to 50 mmHg and is evaluated on the basis of hydrostatic pressure within the vein: the greater the hydrostatic pressure, the greater must be the externally applied compression. Although the evidence is limited, patients with uncomplicated varicose veins are prescribed stockings that compress at 20–30 mmHg to help with pain and oedema control. Patients with venous stasis ulcers need 30- to 40-mmHg stockings.

Complications

Managements of side effect can be challenging. Complications of sclerotherapy are partly drug specific and include allergic reaction. Some of them are acute, as pain and cramping, and resolve also quickly. Other common and cosmetically significant side effects of sclerosing agents, as hyperpigmentation, telangiectatic matting and cutaneous necrosis, are more chronic.

Hyperpigmentation is caused by haemosiderin extrusion, from an ectatic blood vessel treated by sclerotherapy. It is not caused by melanocytic deposition and it thus does not respond to topical bleaching agents.

It appears related to solution strength, vessel fragility, site of vessel treated, injection pressure and the type of solution used. The role of elevated serum ferritin level in post-sclerotherapy pigmentation is a matter of debate. Scott and Seiger (1997) consider the ferritin levels irrelevant. Further studies are needed to better understand it.

The general incidence of hyperpigmentation ranges from 10 to 30 %. Although it may persist for months, its presence rarely deters patient from continuing treatment. Spontaneous resolution occurs in 70 % at 6 months and 99 % within 1 year.

Telangiectatic matting is a recognized complication occurring in 15–20 % of patients treated. It represents a revascularization in the treated area, with vessels much smaller than the original sclerosed vessel. The exact mechanism of the phenomenon remains unknown. However it seems to play an important role in reactivation of inflammation and/or a neo-angiogenic mechanism. Telangiectatic matting is usually not permanent and resolves spontaneously within 3–12 months.

Both hyperpigmentation and telangiectatic matting may benefit from the treatment with intense pulsed light (IPL) (Zaulyanov-Scanlan 2009).

It is possible that under ideal circumstances or in the absence of error operator, cutaneous necrosis may occur with the injection of any sclerosing agent. It has been hypothesized that this phenomenon could be due to the presence of arteriovenous shunts under telangiectases. To prevent skin ulceration, it is suggested to administer to a single site a maximum of 0.2 mL of sclerosant.

When sclerosant extravasation occurs, dilution is needed immediately. However with careful technique and appropriate treatment of extravasation, necrosis can almost be avoided.

Thrombi may be seen within 1 week of injection, especially in larger (1–4 mm) treated vessels. They may produce pain that can be relieved by incising the vessels and expressing the thrombus.

Small ulcers develop in approximately 1 in 70,000 patients but are usually seen only when

skin is already damaged. The only systemic reactions that have been seen are allergic, such as urticaria, but also anaphylactic reactions. Sodium morrhuate and Sotradecol have significant allergenic potential, while polidocanol has only a 0.01 % reported rate of allergic reaction, and with Sclerodex and hypertonic saline, no allergic reactions have been seen yet.

In order to minimize side effects and reduce their incidence, it is necessary for physicians to understand the potential causes of complications following sclerotherapy:

- To advise patients prior to beginning the treatment on the common risk involved in sclerotherapy and on the relative incidence
- To understand the concept of minimal sclerosant concentration and how it can help to choose sclerosing solution concentrations to minimize risks

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Skin Resurfacing with Carbon Dioxide Laser

129

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Key Points

- Skin aging manifested by rhytides, laxity, and photoaging has been treated by laser skin resurfacing using a large variety of modalities, with carbon dioxide (CO_2) laser proving to be the gold standard for the past few decades.
- Standard ablative CO_2 laser resurfacing, while still the most highly effective, is associated with a greater side effect profile and risk of complications. For these reasons, fractional ablative CO_2 laser resurfacing has emerged as a highly effective, yet far safer, top tier treatment for rhytides and photoaging of the aging skin.
- In this chapter, we will address background information on standard and fractional CO_2 laser resurfacing; proper patient selection; pre-, peri-, and postoperative instructions; treatment, prevention, and management of complications; and clinical efficacy.

General Principles

A beautiful face is considered to possess smooth and flawless skin, an even complexion, and firm facial features. Beauty is strongly associated with healthy and youthful skin. Nevertheless, over the course of a lifetime, the body's outer shell changes significantly; genetics, aging, sun exposure, and lifestyle factors including nutrition, alcohol consumption, and smoking habits, as well as skin diseases and lesions, may contribute to visible skin changes. Consequently, wrinkles, brown spots, blotchy skin coloring, skin laxity, and scars become visible. However, since the desire for eternal youth and beauty is high and still increasing worldwide, the market for cosmetic and aesthetic treatment modalities is booming also.

In the past three decades, numerous techniques have been developed including chemodenervation with botulinum toxins or skin augmentation using injectable soft tissue fillers. Whereas these methods treat certain areas of the skin specifically, including wrinkles or volume

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_129, © Springer-Verlag Berlin Heidelberg 2015

loss, they do not achieve a uniform improvement to the entire facial skin surface. In contrast, skin resurfacing procedures globally improve the overall appearance of the entire face.

Skin resurfacing employs a variety of techniques, ranging from laser-, light-, to other energy-based treatments, but may be considered to also encompass chemical peels or dermabrasion. Common to all these techniques is that they use either thermal, mechanical, or chemical methods to induce a controlled dermal injury on the skin surface, prompting it to heal itself by creating new skin cells. The skin-rejuvenating effect therefore depends on the method used. Among the various skin resurfacing options, carbon dioxide (CO_2) lasers have long been established as the gold standard. CO_2 lasers are one of the highest-power lasers available on the market and have evolved since their inception in the 1990s into ultra-pulsed and fractional varieties.

Mechanism of Light: Tissue Effect

Skin resurfacing with CO_2 lasers, as well as other laser- and light-based modalities, is effective in skin rejuvenation and induces skin remodeling with subsequent new collagen fiber formation. It is also theorized that collagen shrinkage and wound-healing-induced fibroplasia are mainly responsible for the cosmetic improvement of the skin.

The biological effect of laser light can therefore be achieved by heating the skin tissue. While heating, light energy is absorbed within the chromophore and converted into thermal energy. This process of deep tissue heating results in a provoked dermal injury. Thereby, the total depth of dermal injury is the sum of the ablated skin area plus the depth of the RTD. Depending on the energy density, the pulse duration, and the heat conduction within the target, various effects, such as coagulation, vaporization, or shrinkage, can occur.

The photothermal effect results further in water vaporization and denaturation of collagen fibers followed by a wound-healing process. Recently, it has been shown with real-time temperature feedback experiments that denaturation temperature of collagen ranges between 65 and 70 °C but is also dependent on the time of laser light exposure; in general, for every 5 °C decrease in temperature, a tenfold increase in time is needed to achieve the same degree of denaturation (Alexiades-Armenakas et al. 2013). However, once collagen fibers have been denatured by laser-generated heat, collagen rapidly contracts as fibers shrink to one-third of their length resulting in immediate skin tightening.

Thermal injury of deep dermal collagen induces a vigorous healing process leading to dermal remodeling. Wound healing is initiated characterized by extremely high levels of collagenases, which degrade the fragmented collagenous matrix. This process is followed by proliferative phase including angiogenesis, collagen deposition, granulation tissue formation, and a rapid reconstruction of the epidermis. A prolonged period of dermal neocollagenesis of up to at least 6 months follows.

Laser Skin Resurfacing with CO_2 Laser

In 1964 Kumar Patel invented the carbon dioxide laser (CO_2), one of the earliest gas lasers developed. The CO_2 laser emits a 10,600 nm wavelength and operates in the infrared spectrum which is highly absorbed by intra- and extracellular tissue water allowing the vaporization of living tissue at the focal point. The CO_2 lasers of the 1960–1970s emitted a continuous and uninterrupted wave light which made these lasers highly usable for virtually bloodless photo-excision and coagulation of superficial skin lesions, such as warts, actinic cheilitis, or keloids.

The use of CO_2 laser technology for cosmetic and aesthetic indications was then introduced in the 1980s, when continuous-wave CO_2 lasers were first used to resurface photodamaged skin in a procedure named “thermabrasion.” However, early continuous-wave CO_2 laser technology was very effective in rejuvenating aged skin; the

continuous emitted and uninterrupted beam of light also led to an imprecise ablation and dermal heating of the skin tissue consequently increasing the risk for unwanted side effects, such as severe thermal damage and scarring.

The theory of selective photothermolysis, proposed by Rox Anderson and John Parrish in 1983, revolutionized the use of lasers in dermatology. The theory refers to the precise heating of chromophores, such as melanin, water, or oxyhemoglobin, using a specific wavelength of laser light with the intention of absorbing light into the specific target area and destroying structures within the skin, without affecting the surrounding tissues. However, in order to successfully conduct selective photothermolysis, the parameter wavelength, pulse duration, and fluence need to be tailored to the specific properties of the target chromophore and the clinical indication to obtain optimal outcomes with minimal effects on surrounding tissue (Bogdan Allemann and Kaufman 2011).

Based on the concept of selective photothermolysis, two CO_2 laser approaches were developed at the end of the 1980s/beginning of the 1990s utilized for the purpose of a safer and precisely controlled skin resurfacing, the high-energy pulsed CO_2 laser that delivers energy in individual pulses and the second type, the scanned CO_2 laser, that achieves well-controlled tissue ablation by rapidly scanning the focal spot of a focused CW CO_2 laser over the skin using an opto-mechanical flash scanner.

Fully Ablative CO_2 Laser

The CO_2 laser emits a monochromatic 10,600 nm wavelength, which is strongly absorbed by water, resulting in full ablation of the epidermis and part of the dermis. The penetration depth for CO_2 waves is dependent upon the water content in the dermal tissue. The beam diameter plays a role; with pulse duration of less than 1 ms and an energy fluence of 5 J/cm^2, approximately 90 % of carbon dioxide laser energy is absorbed in the initial 20–30 μm of skin, and residual thermal damage (RTD) can be confined to a layer of about 100–150 μm of tissue (Alexiades-Armenakas et al. 2008). At these settings, the skin temperature reaches approximately 120–200°°C and produces a thermal necrosis that is sufficient to seal small dermal blood vessels and lymphatics but yet narrow enough to reduce the prevalence of scarring. Smaller beams of 100–300 μm in diameter achieve high fluences and more rapid tissue vaporization, whereas larger beam sizes of greater than 2 mm induce non-vaporization heating and increase the risk of deep thermal damage.

Fully ablative CO_2 laser skin resurfacing treats mild, moderate, and severe signs of photoaging of the skin. Clinical rating by investigators shows a significant improvement of photoaged skin up to 86 %. Wrinkle reduction assessed with optical profilometry and microscopy confirms these results and found significant reduction in mean wrinkle depth of 91 %. In accordance to evaluate long-term results, Manuskiatti et al. and Ward and Baker examined and interviewed up to 104 subjects. With an average follow-up period of 24 months (range 12–44 months), the researchers observed high patient satisfaction ratings and significant persistence of wrinkle score improvement. Long-term histologic features confirm the long-lasting nature of the clinical improvement and demonstrated continuing, progressive improvement in solar elastosis deep in the dermis.

While fully ablative CO_2 is very effective in treating all signs of photoaging, it is also known for a significant risk of severe side effects such as permanent dyschromia, infections, hypertrophic scarring, as well as downtime and pain. About 100 % of patients further experience edema, burning, crusting, and erythema lasting up to 12 months after treatment.

The knowledge about these possible adverse events combined with further innovations in laser-based treatment technologies significantly changed skin resurfacing procedures in recent years. Fully ablative CO_2 laser skin resurfacing has lost its importance in the treatment of skin aging in the past decade and is currently used mainly in the removal of benign skin lesions and carcinomas, nevi, rhinophyma, keloids, or scars.

Fractional Photothermolysis Using CO_2 Lasers

In 2004, Manstein and colleagues introduced a dramatic improvement in laser resurfacing, called fractional photothermolysis (FP). Unlike conventional lasers, FP treats only a fraction of the skin, leaving up to a maximum of 95 % of the skin uninvolved. This is achieved by inducing small three-dimensional microscopic thermal zones (MTZ) of epidermal and dermal tissue by thermal damage or ablation. Depending on wavelength and pulse energy, the micro-columns can penetrate the skin to varying depths of up to 1,300 μm with a diameter usually smaller than 400 μm. The chosen parameters of energy per MTZ and the density of MTZs per square centimeter further influence the treatment coverage of the skin which can be anywhere from 3 to 40 %.

In 2007 Hantash et al. first described the use of fractional CO_2 on human skin in vivo and explained histological changes due to fractionated thermal damage. Immediately after FP treatment, MTZs appear as distinct columns of thermal coagulation surrounded by undamaged tissue permitting a rapid repair of the affected skin. Epidermal coagulation then activates epidermal stem cells that transiently increase proliferation for a rapid replacement of the damaged epidermal tissue which is completed about 3 days post treatment. Approximately 1 week after FP, collagen type 3 synthesis begins promoting dermal remodeling until MTZs are completely replaced after approximately 3 months.

Similar to fully ablative CO_2 laser skin resurfacing, fractional ablative CO_2 lasers also target the chromophore water, allowing selective thermal damage to various water-rich targets such as epidermal keratinocytes, collagen, and blood vessels throughout the skin (Geiges 2011). The first fractional CO_2 laser entered the market in 2007, promising a more rapid repair of the affected skin resulting in an optimized ratio of efficacy, downtime, and side effects.

Procedure

Patient Selection

As with any cosmetic treatment, successful outcome relies on proper patient selection. The ideal candidate for CO_2 laser skin resurfacing should be healthy and with lightly pigmented skin (Fitzpatrick's skin types I–III). However, since the wavelength of CO_2 laser is not absorbed by melanin, it has been used to treat darker skin types with effective and safe results. However, the possibility for postinflammatory hyperpigmentation should be discussed with the patient and may be averted by the use of lower treatment settings. In managing patient expectations, the reported studies demonstrate that the most superficial wrinkles and photodamage are usually eliminated with fully ablative and greatly improved with fractional CO_2 laser resurfacing, while the more severe aging signs are improved. It is imperative to modulate the patient's expectations and to convey a full understanding of the potential risks, complications, and side effects of the procedure and the requirement for postoperative care.

Contraindications to any version of CO_2 laser resurfacing include: active bacterial or viral infections, the use of isotretinoin within the last 12 months, pregnancy and breastfeeding, as well as ablative or invasive procedures in the treatment area within the prior 3 months (Alexiades-Armenakas et al. 2008; Manstein et al. 2004). Additional contraindications include patients with a history of hypertrophic or keloidal scarring, increased photosensitivity, and disturbed wound-healing process (e.g., patients with diabetes mellitus) or an immunosuppression.

Preoperative Care

All patients should be premedicated with oral antiviral medications (e.g., famciclovir) for *Herpes simplex* prophylaxis starting 1 day

prior to the procedure and for 5 days post treatment. Additionally, the author (MAA) recommends also prescribing antibacterial antibiotics (first- or second-generation cephalosporin such as cephalexin) starting 1 day prior and continuing for 5 days post treatment. One report suggests that prophylactic facial cleansing with chlorhexidine twice daily for 3 days preoperatively may further decrease the incidence of postoperative infection; however, such infections are exceedingly rare in the author's (MAA) experience. Patients should be advised to stop taking anticoagulants at least 2 weeks prior to treatment.

General Principles of Treatment

Prior to CO_2 laser skin resurfacing, the skin area is cleaned with a mild cleanser before baseline clinical photographs are taken. Topical anesthetic (lidocaine/prilocaine) is applied for a duration of 1 h. Following removal of the topical anesthetic, the treatment area should be cleansed with 70 % alcohol. In addition to topical anesthesia, forced cold air provided by a Zimmer Cooler (LaserMed, Monroe, CT) or similar device is recommended for perioperative pain control (Manstein et al. 2004). Immediately post treatment, cold compresses are applied.

Numerous fractional CO_2 devices are available on the market, each with recommended parameters. With increasing power or energy, the ablative depth increases (see (Manstein et al. 2004)). The spacing of the micro-columns should be placed conservatively to avoid the rare instances of hypopigmented scarring that may occur. In addition, the pulse duration will impact the degree of collateral thermal damage. It is prudent to be very familiar with the recommended energy settings recommended for each grade of skin aging severity (see reference (Alexiades-Armenakas 2006)), with the understanding that the time needed for postoperative recovery will increase with increasing parameter intensity.

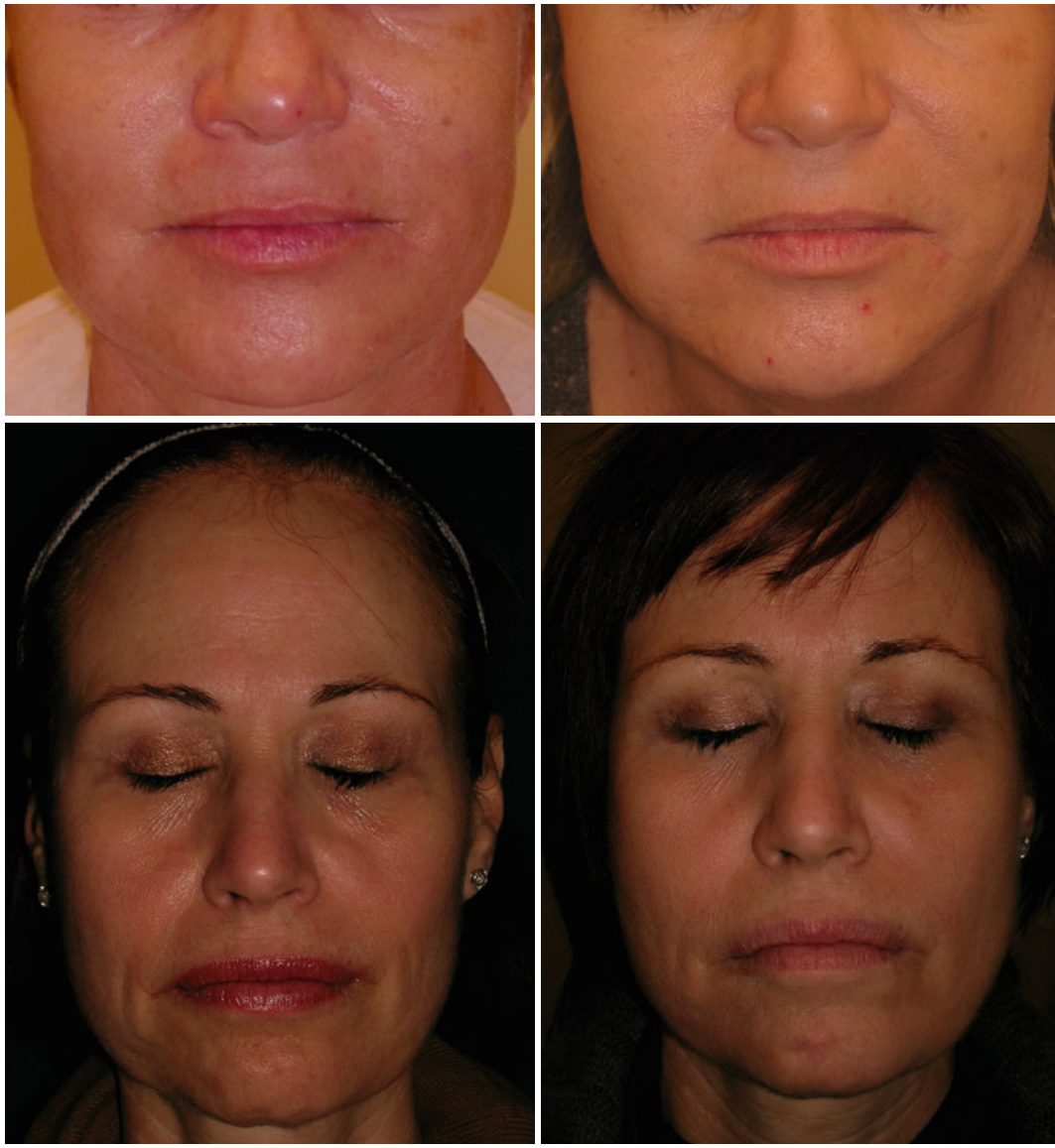
Postoperative Care

Postoperative care is of the utmost importance and significantly lowers the risk infections and scarring and will promote rapid healing. The standard therapy advises patients to use a topical wound healing, in most cases petrolatum ointment, for up to five times a day for at least 5–7 days after treatment to promote the skin barrier function. Reepithelialization is usually completed after 3–6 days, after which patients may apply makeup or sunscreen. Patients are advised to avoid significant sun exposure for at least 30 days post-procedure to avoid pigmentary changes. Although it is generally accepted that the use of SPF can significantly reduce the risk for postinflammatory dyschromia, the conventional treatment concept does not recommend patients to apply sunscreen from day 1 due to the potential risk for allergic irritations. However, a recently published meta-analysis indicates a relatively lower risk for SPF-related reactions, and yet Wanitphakdeedecha et al. recommend using SPF at day 1. They were able to show that the use of a sunscreen starting on the first day after ablative fractional skin resurfacing can decrease the incidence of postinflammatory hyperpigmentation after laser treatment. However, the author (MAA) avoids sunscreen application until reepithelialization is complete (Figs. 129.1, 129.2, 129.3, and 129.4).

Besides conventional treatment options, recently published study indicates that the injection of platelet-rich plasma (PPR) immediately after treatment might be beneficial to improve the wound-healing process and to reduce the risk for transient adverse effects. However, the effectiveness has to be proven in large randomized controlled trials.

Clinical Efficacy

Numerous clinical studies have demonstrated CO_2 laser resurfacing to be effective in treating all signs of photoaged skin, such as fine lines and



Figs. 129.1, 129.2, 129.3, and 129.4 CO_2 laser skin resurfacing: pre and post treatment

coarse wrinkles, pigment changes, sallow complexion, as well as skin roughness. Preferred treatment area is the face, but also more sensitive areas such as neck and chest may be treated with lower settings with fractional CO_2 laser resurfacing with excellent outcomes. Hands with photoaging may be treated as well with moderate improvement.

Investigator scoring of a 32-patient study by the author using a quantitative grading system demonstrated a greater than 50 % improvement after fractional CO_2 treatment on the face in the vast majority of subjects at 6-month follow-up. Those with the categories of photoaging of dyschromia and solar elastosis and rhytides demonstrated the greatest improvement.

Alexiades-Armenakas and colleagues subsequently conducted a multicenter trial of fractional CO_2 laser resurfacing for the treatment of rhytides, photoaging, and acne scars on the face. Evaluations

were conducted using a quantitative comprehensive grading scale (Table 129.1). The clinical findings demonstrated a 0.42- to 1.63-grade improvement on a 4-point grading scale, which correlated in direct proportion with power, pitch, and dwell time. Recovery time ranged between 3 and 10 days, also proportionate to laser parameter intensity. No adverse events were observed. In that study, striae albae were also treated with variable results (Tables 129.1 and 129.2).

A study from Kohls et al. confirms these results and further indicates that the best results regarding wrinkle size and depth were found for the cheeks (−58.3 %, $p = .018$, and −51.3 %, $p = .018$) and the periorbital area (−35.1 %, $p = .000$, and −31.1 %, $p = .001$). The homogeneity of melanin distribution in the skin was improved by 21.4 % on the cheeks ($p = .012$) and by 24.0 % in the periorbital area ($p = .000$), as well as the mottled pigmentation (51–75 %) (Kohl et al. 2014).

Long-term efficacy was assessed by Ortiz et al. (2010) who evaluated 10 subjects at 1 and 2 years after fractional CO_2 treatment of acne scarring and photodamage in the face. Investigators graded maintenance of improvement on a quartile scale based on clinical photography and found that subjects maintained 74 % of their overall improvement at their long-term visits compared to 3-month follow-up visits. However, while clinical improvement was maintained long term, the results were not as remarkable as those seen at 3-month visits.

Overall, patient satisfaction is generally high. At 3 months post treatment, subjects reported 67–80 % improvement in skin texture, facial wrinkles, and laxity, as well as in skin pigmentation. In a study of Clementoni et al., 40 patients (75.47 %) would recommend fractional CO_2 treatment to others because they had obtained an overall improvement greater than 75 %.

Stebbins and Hanke treated the skin of the dorsal hand of ten patients, each receiving three treatments to only one hand at 4–6-week intervals with fractional CO_2. At 1-month follow-up after final treatment, investigators rated mean improvement of 26–50 % for wrinkles, 51–75 % for pigment, and 26–50 % for texture. Participants rated mean improvement after final treatment as 26–50 % for wrinkles, 51–75 % for pigment, and 51–75 % for texture. Similar efficacy was assessed by Tierney and Hanke for the treatment of age-related changes on the neck. For skin texture, the mean score improved 62.9 %, skin laxity 57.0 %, and rhytides 51.4 %. For overall cosmetic outcome, the mean score improved 59.3 % (55.1 %, 63.5 %) at 2 months post treatment.

Side Effects

Frequent short-term side effects evolving with FP treatments are pain, facial edema, dry skin, flaking, pruritus, bronzing, and increased sensitivity. The procedure is usually reported as painful, however tolerable. Mild to severe transient erythema immediately after treatment is reported in 100 % of the patients treated. Unlike transient erythema, which usually resolve in 3–4 days, prolonged erythema is defined as post-treatment redness that persists longer than 1 month with ablative treatment. The occurrence of side effects highly correlates with higher density and treatment settings.

The rate of herpes simplex virus (HSV) infection, the most common type of infection after fractional laser skin resurfacing, has been reported in 0.3–2 % of cases. However, antiviral prophylaxis 1 day prior to treatment and continued for 5–7 days post treatment lowers the risk. The chance for bacterial infections, primarily *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is generally low (about 0.1 % after FP). However, increased pain, focal intense erythema, increased exudate, and erosions with crusting should alert the physician to the possibility of bacterial superinfection that usually presents 1–3 days after treatment (Stebbins and Hanke 2011; Metelitsa and Alster 2010). Especially in the first postoperative week, the risk for viral, bacterial, and fungal infections is generally high. In this critical phase the proper identification and treatment is essential to avoid further complications, including delayed wound healing, scarring, coinfection with other pathogens, and systemic dissemination.

Table 129.1 Quantitative comprehensive grading scale of rhytides, laxity, and photoaging (Alexiades-Armenakas et al. 2008)

Categories of skin aging and photodamage								
Grading scale	Descriptive Parameter	Rhytides	Laxity	Elastosis	Dyschromia	Erythema–Telangiectasia (E-T)	Keratoses	Texture
0	None	None	None	None	None	None	None	None
1	Mild	Wrinkles in motion, few, superficial	Localized to nasolabial (nl) folds	Early, minimal yellow hue	Few (1–3), discrete, small (<5 mm) lentigines	Pink E or few T, localized to single site	Few	Subtle irregularity
1.5	Mild	Wrinkles in motion, multiple, superficial	Localized, nl and early melolabial (ml) folds	Yellow hue or early, localized periorbital (po) elastotic beads (eb)	Several (3–6), discrete, small lentigines	Pink E or several T localized 2 sites	Several	Mild irregularity in few areas
2	Moderate	Wrinkles at rest, few, localized, superficial	Localized, nl/ml folds, early jowls, early submental/submandibular (sm)	Yellow hue, localized po eb	Multiple (7–10), small lentigines	Red E or multiple T localized to 2 sites	Multiple, small	Rough in few, localized sites
2.5	Moderate	Wrinkles at rest, multiple, localized, superficial	Localized, prominent nl/ml folds, jowls and sm	Yellow hue, po and malar eb	Multiple, small and few large lentigines	Red E or multiple T, localized to 3 sites	Multiple, large	Rough in several, localized areas
3	Advanced	Wrinkles at rest, multiple, forehead, periorbital and perioral sites, superficial	Prominent nl/ml folds, jowls and sm, early neck strands	Yellow hue, eb involving po, malar and other sites	Many (10–20) small and large lentigines	Violaceous E or many T, multiple sites	Many	Rough in multiple, localized sites
3.5	Advanced	Wrinkles at rest, multiple, generalized, superficial; few, deep	Deep nl/ml folds, prominent jowls and sm, prominent neck strands	Deep yellow hue, extensive eb with little uninvolved skin	Numerous (>20) or multiple large with little uninvolved skin	Violaceous E, numerous T little uninvolved skin	Little uninvolved skin	Mostly rough, little uninvolved skin
4	Severe	Wrinkles throughout, numerous, extensively distributed, deep	Marked nl/ml folds, jowls and sm, neck redundancy and strands	Deep yellow hue, eb throughout, comedones	Numerous, extensive, no uninvolved skin	Deep, violaceous E, numerous T throughout	No uninvolved skin	Rough throughout

This 4-point grading scale has been extensively tested and employed for evaluating laser- and energy-based cosmetic treatments

Table 129.2 Fractional CO_2 laser systems and parameters for treatment of skin aging

Fractional CO_2 systems overview							
	Solta Fraxel repair	Lumenis ActiveFX	Lumenis DeepFX	DEKA SmartXide DOT	Lasering MIXTO	Alma Pixel CO_2	Ellipse Juvia
Delivery	IOTS paintbrush	Scanned stamping	Scanned stamping	Scanned stamping	Scanned stamping	Stamping	Stamping
λ (nm)	10,600	10,600	10,600	10,600	10,600	10,600	10,600
Spot size (μ)	135	1,250	125	350	300	120–250 or 350	500
Density (%)	5–70	55–100	5–25	5–40	20	20	–
Energy	5–70 mJ/MTZ	80–100 mJ/MTZ	5–30 mJ/MTZ	1–60 mJ/dot	5–20 mJ/dot	74 or 122 mJ/pixel	5–15 mJ/MTZ
Depth (μ)	<1,600	80–100	<450	<350	500	150–250 to 400	<300
Pulse duration (ms)	0.15–3	0.5–5	0.5–5	0.2–2	0.2–2	50–300	5–7
Pulse delivery	UltraPulse	UltraPulse	UltraPulse	SuperPulse	Pulsed	Pulsed	SuperPulse
Consumables	Tip and cartridge	NA	Tip and lens	NA	NA	NA	Handpiece
Microdot delivery	Sequential	Random	Random	Random	–	Random	–
Scan areas	Square	Round	Round	Adjustable shape, size, ratio	Square	Round or square	–

The use of occlusive moisturizers and dressings can increase the risk for acneiform eruptions; the risk for acne is about 2–10 %, while the development of milia occurs in about 19 % of the treated patients. The avoidance of petrolatum-based healing ointments or a change to noncomedogenic equivalents can help to prevent acneiform eruptions. In moderate to severe breakout, short courses of oral tetracycline-based antibiotics are the treatment of choice.

Delayed purpura which may develop more than 3 days after skin resurfacing has been reported in some cases. Previous reports assume that the avoidance of nonsteroidal anti-inflammatory drugs and anticoagulants after treatment may decrease the risk for delayed purpura.

Pigmentary changes, hyper- and hypopigmentation, are much less frequent with fractional CO_2 than with fully ablative CO_2 but are still observed in 1–32 % of patients, depending on the system used, parameters applied, and skin phototypes treated. To minimize the risk, patients should avoid sun exposure for at least 2 weeks post-procedure and are advised to use sunscreen on a regular basis for at least 30 days after treatment. Special attention should be given when treating darker skin types due to their higher risk for developing any dyschromia (Clementoni et al. 2007). In general the use of higher fluencies, lower density settings, and longer treatment intervals can help to decrease this potential risk. In most cases postinflammatory hyperpigmentation resolves spontaneously without treatment; however, topical lightening agents, mild peeling agents, and protection can accelerate the resolution. Hypopigmentation, although rather uncommon, often has a delayed onset (6–12 months postoperatively) and frequently occurs in darker skin. In the author's (MAA) experience, patients have presented who have been treated repeatedly with fractional laser resurfacing and developed subtle hypopigmented patches and textural changes. It is therefore advised to space treatment intervals to allow for complete wound healing prior to repeating the treatment.

Scarring is a potential side effect after fractional CO_2 which may be due to overly aggressive treatments in those sensitive areas (including excessive energy, density, or both), lack of technical finesse, associated infection, or idiopathic (Manstein et al. 2004; Metelitsa and Alster 2010). However, the incidence for scarring increases with the area treated. Therefore, special care should be taken, when fractional CO_2 is used in areas other than the face, such as the neck and chest, or in location with very thin skin, such as the eyelids.

Conclusions

A half-century after the CO_2 laser was developed, the device remains a top tier form of therapy for rhytides and photoaging of the skin. The technological progress of the past decade in the form of fractionated delivery has helped to transform this laser procedure to an effective and safe approach for skin rejuvenation. When first used for resurfacing in the early 1990s, pulsed CO_2 lasers were revolutionary; never before it had been possible to apply such high energy to human skin to achieve both physiological and aesthetic changes. For a long period of time, the fully ablative CO_2 laser, although associated with serious side effects, was the gold standard and the treatment of choice for many physicians to rejuvenate aged skin. With the introduction of the fractional photothermolysis, it was possible to significantly lower recovery time and the risk for serious side effects while maintaining an acceptable clinical outcome.

In addition to the 10,600 nm CO_2 laser, the Er:YAG 2,940 nm and YSGG 2,790 nm lasers have also been used to perform fractional ablative resurfacing. While these newer technologies exist, the fractional CO_2 laser has maintained its preeminence as the first choice for ablative resurfacing. The efficacy of clinical outcomes from the fully ablative and fractional CO_2 laser has been well demonstrated owing to its high absorption spectrum for water in the living tissue, penetration depth, and collateral thermal injury which serve to induce neocollagenesis and skin rejuvenation.

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Surgery

130

Myrto Trakatelli and Elena Rossi

Key Points

- The first principle of skin surgery is that appropriate margins should always be respected according to the type of the tumor excised.
- A preoperative evaluation of the patient is necessary to make the right choice about the type of reconstruction and to prevent complications such as bleeding or infections.
- One of the key steps in planning the elliptical excision is determining the proper placement and orientation.
- The ideal closure provides the best esthetic and functional results while avoiding potential complications.
- Alternatives for closure of a defect include primary closure, second-intention healing, skin grafting, or local tissue transfer with flaps.

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General Principles

Before any surgical decision, for any skin lesion we must respect the fundamental oncologic principle: "*Tumor removal first*, *reconstruction second*." This is particularly relevant when the lesion is malignant. The best-designed flap reconstruction is a failure if performed without complete tumor clearance. One should respect the margins both lateral and deep and in case of doubt perform two-stage surgery or Mohs surgery to be able to guarantee complete extraction of the lesion.

Several factors must be evaluated before determining a method of reconstruction:

1. Patient considerations include patient needs, general medical condition, and psychosocial factors.
2. Defect considerations include the size, depth, and location of the defect. The location of the defect influences structure, function, and the availability of adjacent tissue reservoirs.
3. The surgeon's experience and personal preferences play a role.

The ideal closure provides the best esthetic and functional result while avoiding potential complications, accommodating the patient's needs, and incorporating the patient's ability to participate in postoperative care. Alternatives for closure of a given surgical defect include primary closure, second-intention healing, skin grafting, or local tissue transfer with flaps.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_130, © Springer-Verlag Berlin Heidelberg 2015

Defect Closure

Closure is the process of joining the edges of a wound. It can be done through the use of different materials. The suture with the needle and the thread is the most used one, but also sterile skin-closure strips, cyanoacrylate glue, and staples are available. The choice of the material and the type of stitches depend on several factors such as anatomical site, dimension, and tension of the wound. Atraumatic sutures are defined as needle-suture combinations, where the needle is firmly attached to the suture in order to reduce tissue trauma.

Material for Closure

Needle

Today it can be assumed that, at least with respect to European manufacturers, stainless steel needles are generally used for surgical suture materials. There are different needle shapes (fishhook-shaped, three eighth circle, five eighth circle, straight, one half circle, semi-curved, spoon-shaped, one fourth circle, etc.), types (round-bodied or reverse cutting), points, radius, and lengths. In dermatology we mostly use the reverse cutting ones.

Suture Material

The "thread" can be of various dimensions from 3 to 12-0 (the number itself means an increasing order, whereas if the number is followed by 0, it means a descending order so thinner suture). The most used sizes in dermatologic surgery are from 3-0 to 5-0. It is best to use fine sutures on the face while on areas where cosmetic concerns are less important, sutures 3-0 or 4-0 are best, because the larger size makes the technique easier and the thicker sutures are stronger.

The suture material can be classified in natural (silk and catgut) and synthetic (such as polyamide, polyesters and polymers derived from polyglycolic acid).

According to the material absorbability in human tissue, suture material can be classified as absorbable or nonabsorbable. Absorption can occur enzymatically, or hydrolytically, as with the absorbable synthetic polymers: the latter is less reactive because the polymeric chain of the material is hydrolyzed by water that breaks it. The nonabsorbable material is permanent and if not removed will last in the tissue.

According to the structure, the material can be either monofilament or multifilament (composed of many fine individual threads either twisted or braided together). The single filament is less traumatic for the tissue but less resistant and more difficult to handle when compared to a braided thread. Monofilaments are less involved in infections. An increased adherence of bacteria to braided sutures has been demonstrated: this is correlated with higher infection rates (Katz et al. 1981).

Suture Technique

Sutures can be divided in buried (strong, tough, and effective) or superficial (less visible as possible: the opposite edges should be juxtaposed without differences of level), interrupted, or continuous.

The most used suture in dermatologic surgery is the *simple interrupted suture* (Figs. 130.1, 130.2, and 130.3). It consists of a series of single

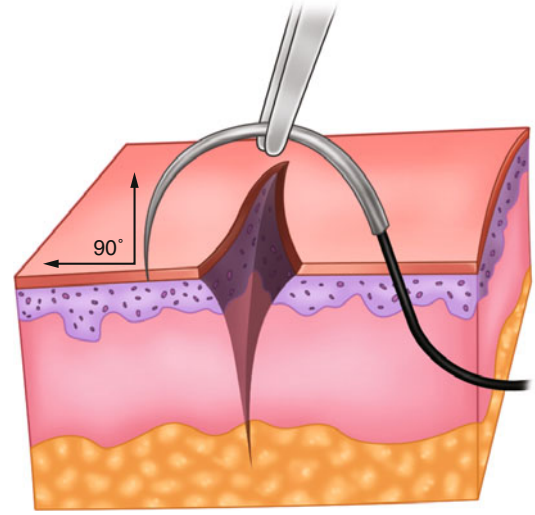

Fig. 130.1 Simple interrupted suture

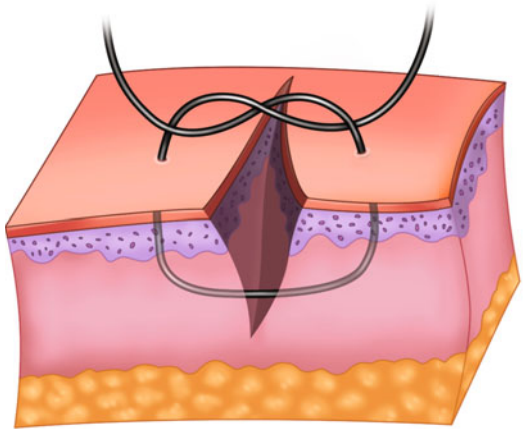

Fig. 130.2 Simple interrupted suture

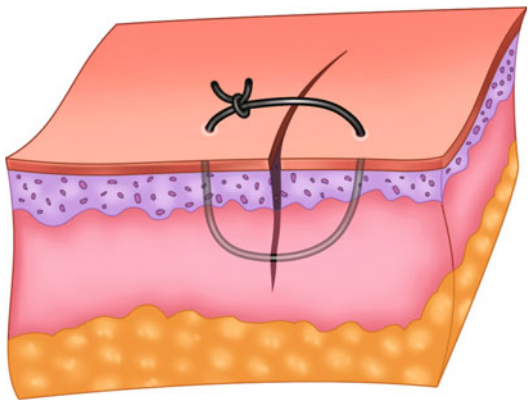

Fig. 130.3 Simple interrupted suture

stitches individually placed and tied. To perform an optimal stitch, the needle must be correctly positioned within the holder, with the first third of the needle within the jaws so that the curve of the needle can be used to advance. The same amount of tissue has to be taken in each margin, at the same depth of the wound. The orientation of the needle to the skin should be perpendicular (Fig. 130.1), 3–5 mm from the wound edge, in order to take enough tissue and properly evert the wound edge. The tip of the needle is retrieved using tissue forceps; the thread is pulled through leaving 2–3 cm at its tail, to guarantee the possibility to knot it (usually with the needle holder, but also hand tying can be performed). The closure is ensured by a squared knot: the long end

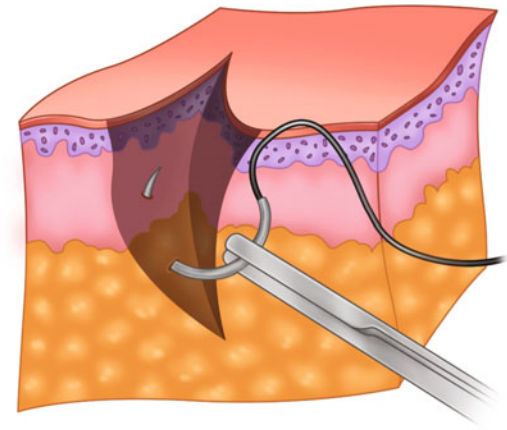

Fig. 130.4 Buried intradermal suture

of the suture is wrapped around the tip of the closed needle holder twice and anticlockwise before grasping the short end of the suture with the needle holder; then, it is pulled gently tight. The second loop is locking clockwise and it determines the tension of the stitch. That has to be sufficient to ensure the juxtaposition of the margins but not too tight so that it causes tissue bunching or an ischemic area. The third loop is single and anticlockwise: it is placed to secure the knot. When using monofilament material, more knots can be placed in order to prevent the slipping. All the knots should lie on the same side of the wound, and not on the wound itself. If the knots are too tight, this could lead to tissue ischemia, whereas if they aren't properly locked, there could be wound dehiscence. The distance between the single stitches should be about 1 cm in the body while in the face it should be about 0.5 cm.

When the injury is deeper and wider, it is useful to perform the *buried intradermal suture* (Figs. 130.4, 130.5, and 130.6). It lines up the dermis in order to help the skin closure and it spreads the tension of the wound in the deep dermis. The suture is done with absorbable material; the beginning is at the subcutaneous level, the needle comes out below the epidermis (going from deep to more superficial tissues). The needle then enters the same dermal level on the opposite side of the wound and exits in the same subcutaneous level as it was initially entered into on the first side of the wound. The knot is tied

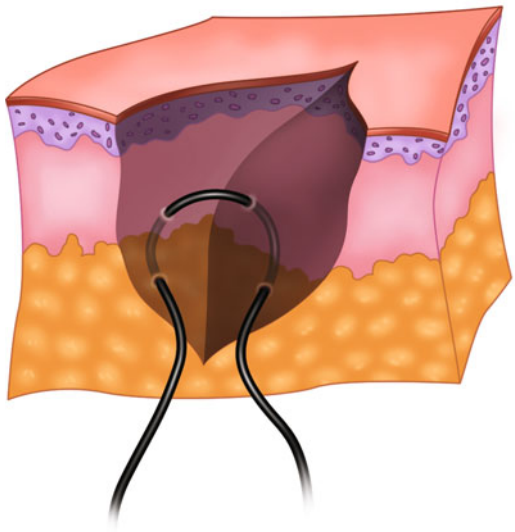

Fig. 130.5 Buried intradermal suture

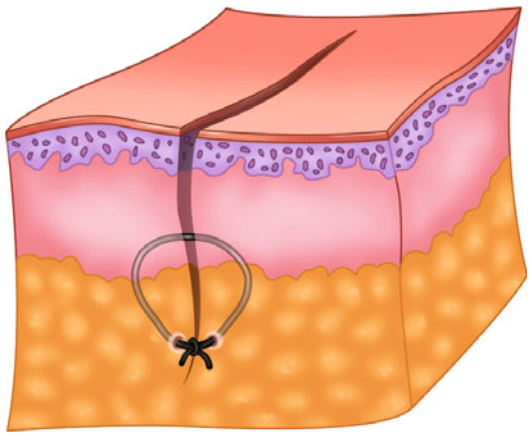

Fig. 130.6 Buried intradermal suture

deep at the subcutaneous level. The knot can be correctly buried in the wound only if the two ends of the thread are put at the same side of the stitch and not over the stitch.

When there is asymmetry of the anatomic layers, irregularity of the edges, dead spaces to be closed, it is difficult to evert the edges, or hemostatic effect is needed, *mattress suture* can be performed. It is especially helpful when the excision leads to the formation of dead space (i.e., when excising cysts, lipomas, etc.)

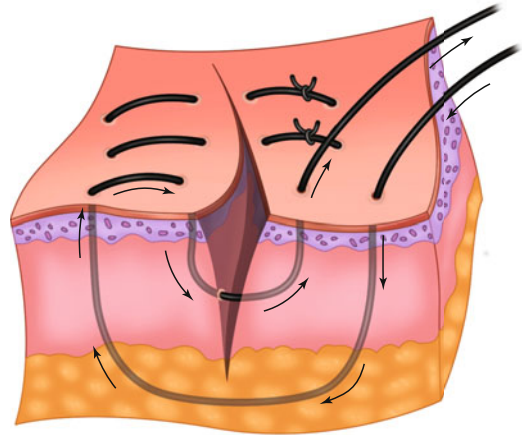

Fig. 130.7 Blair-Donati suture

This suture can result in tissue ischemia or bad cosmetic result: so it should be used only when necessary and simple interrupted sutures should be positioned between mattress sutures to improve the final result.

The *vertical mattress suture* (Zitelli and Moy 1989) is a two-row suture: the first stitch is placed wide and deep, and then a smaller and superficial reverse stitch is placed above the first one, in the same vertical plane, perpendicular to the wound. A square knot is then tied. It has the shape of a vertical U.

The *Blair-Donati suture* (far-far, close-close, and deep-deep-superficial-superficial) is a particular vertical mattress suture: after the first stitch, the second, reverse one is very superficial and close to the edge (Figs. 130.7 and 130.8). The first part of the stitch ensures the juxtaposition of the deeper layers and closes the wound. The second part of the stitch allows a correct position of the dermis and the epidermis thus providing a better cosmetic result.

Another variation is the *Allgöwer suture* that is a half-buried vertical mattress suture: on one side of the wound, the thread does not come out from the skin but is passed under the epidermis (Fig. 130.9). It minimizes the scar and can be properly placed at the border of the scalp to hide the scar between the hair.

The *horizontal mattress suture* is performed by the placement of the first stitch and then the second one in parallel in the same layer

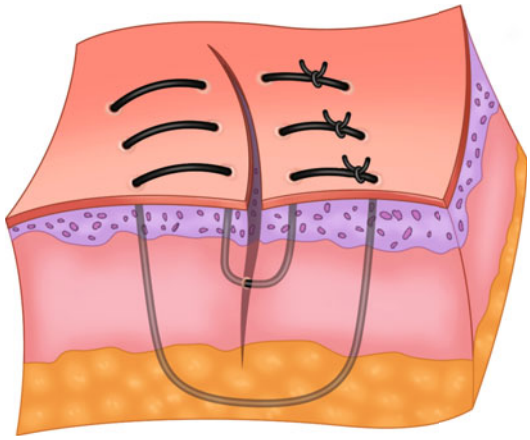

Fig. 130.8 Blair-Donati suture

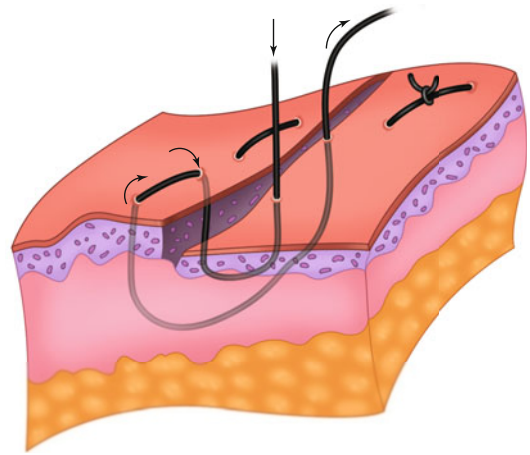

Fig. 130.10 Horizontal mattress suture

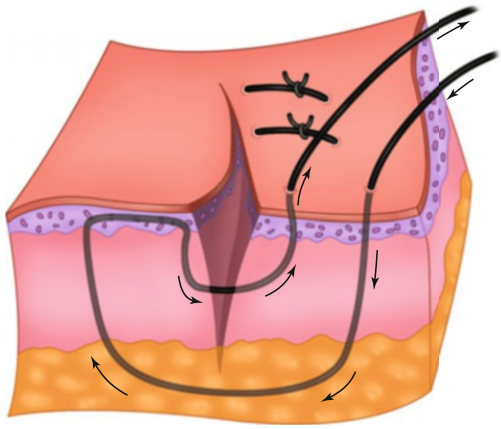

Fig. 130.9 Allgöwer suture

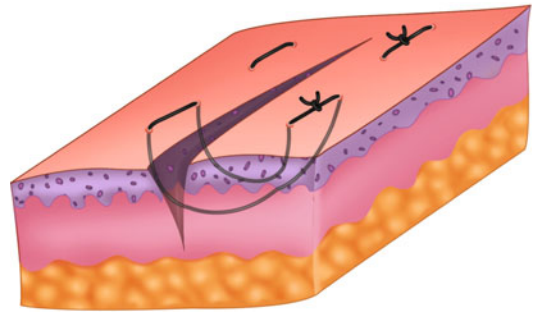

Fig. 130.11 Horizontal mattress suture

(Figs. 130.10 and 130.11). It has the shape of a horizontal U.

The *angle* (*or corner*) *stitch* (Figs. 130.12 and 130.13) is a particular horizontal mattress suture used to close wounds that are angled or Y-shaped without compromising blood supply to the wound tip. It begins on the side of the wound on which the flap is to be attached. The needle is introduced into the skin 3 mm away from the defect, and then it passes through the dermis of the wound edge to the dermis of the flap tip. The needle is passed horizontally staying in the same dermal plane in the flap tip, exits the flap tip, and reenters the other side of skin to which the flap is to be attached. The needle is directed perpendicularly and exits the skin; then, the knot is tied. It is important that no part of the suture must overlie the tip as this may reduce its viability.

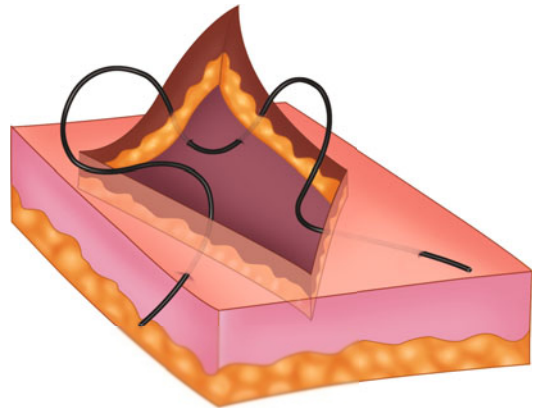

Fig. 130.12 Angle (or corner) stitch

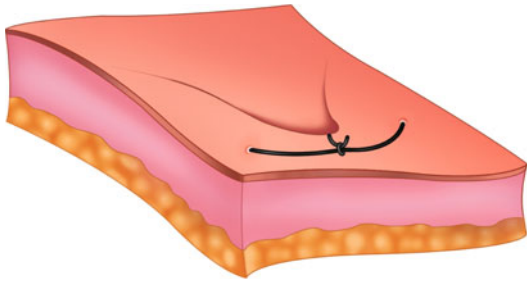

Fig. 130.13 Angle (or corner) stitch

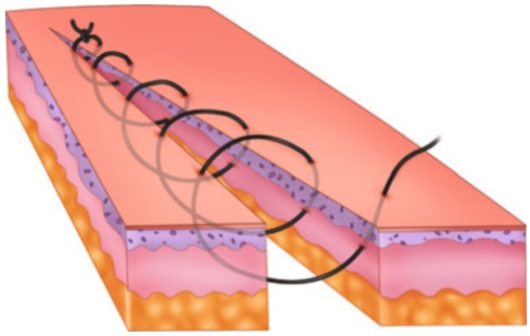

Fig. 130.14 Running or continuous suture

The *running or continuous suture* (Fig. 130.14) starts with a single stitch at the beginning of the wound; then, once the knot is tied, the thread is not cut but is used to make a series of loops through the skin running the length of the wound. The suture is pulled until the edges oppose but not too tight. The end is tied to the final loop. This suture is useful for long wounds and flaps on the face. It can be performed very quickly and leads to good cosmetic result. It is better to use this suture only when associated with buried intradermal suture in order to avoid tension on the edges of the wound as it is less resistant than the single interrupted suture. A variation is the locked running suture: every time the needle emerges from the skin, it is hooked under the previous loop. It induces greater suture marks but can be useful to obtain hemostasis especially in the scalp.

The *running subcuticular suture* (Cordova et al. 2013) (Fig. 130.15) creates a very fine scar but needs no tension of the wound; it must be always associated with a buried suture. The epidermis is pierced only at the beginning and end of the suture line, and then the suture is not visible. The needle enters in the skin at about 1 cm from the end of the wound; the needle is driven through the dermis parallel to the skin taking small bites alternately on one side of the wound and then the other. It exits the skin surface approximately 1 cm from the wound end and is pulled gently to approximate the wound sides. At both ends, the thread can be tied or taped to the skin.

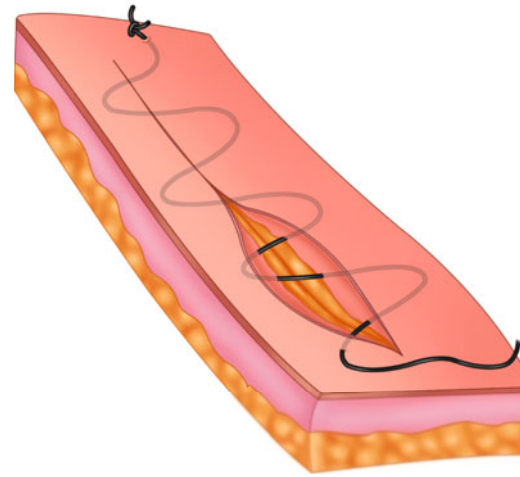

Fig. 130.15 Running subcuticular suture

Table 130.1 Average time for stitches removal depending on the area

Area	Removal time (days)
Face	5–7
Eyelid	4–5
Ear	14–21
Scalp	7–10
Arms and legs	10–14
Trunk and limbs	8–12
Palms and soles	14–21

Suture Removal

Depending on the area, the stitches can be removed at varying times (Table 130.1). Common periods of time for removal are listed above. These are general indications: the surgeon will evaluate the wound itself and the general condition of the

patient that sometimes could delay the process of healing. Moreover, sutures may be taken out all at one visit, or sometimes, they may be taken out over a period of days if the wound requires it.

Other Wound-Closing Methods

Metal clips (Biancari and Tiozzo 2010) (staples) made of stainless steel or titanium can be used for the approximation of the skin. The application is fast and good wound eversion can be reached, the risk of infection is decreased. Special tools for removal are needed. These are often used on the scalp and on the back.

Surgical adhesives (Coulthard et al. 2010) are better used to close lacerations in emergency departments, above all in children. These can't be used if the wound has tension and they will not evert the wound edges. The cosmetic result is often less favorable than with traditional suture (Patel and Price 2011).

Sterile skin-closure strips can be used alone or associated with suture (Duscher et al. 2013). When placed without suturing, they can be used only when there is no tension. They do not evert the edges (so a depressed scar is possible). It is better to associate them with the running subcuticular suture or place them after the removal of the stitches.

Primary Closure: The Fusiform Excision

The primary closure refers to the direct side to side apposition of a skin defect: the skin edges of the wound are sutured together to close the defect.

An excisional biopsy is commonly done in a fusiform or elliptical shape. The proper planning of this procedure will help the surgeon to avoid or to minimize the formation of puckering of the skin at each end of the wound called tissue cones or dog-ears.

The dog-ear formation depends on several factors (Weisberg et al. 2000):

- Tissue dynamics: the skin is an elastic structure and its elastic properties vary according to several factors (age, location, scarring from prior surgery, etc.). The excessive tension on a wound might cause a depression of the central portion that will lead to the formation of "pseudo-dog-ears" at the end of the wound (Rohrer et al. 2009).
- Geometry of the wound: shape, correct length-to-width ratio, apical angles.
- Surface contour: wounds on convex surfaces are prone to develop dog-ears at the distal margins (mandible, chin)
- Surgical technique: the correct blade angle, the shape of the specimen.

First of all it is important to make a preoperative evaluation of the patient: drug allergies, systemic medications (Kearon and Hirsh 1997) (MAO, aspirin, warfarin, etc.), presence of any electronic devices (i.e., pacemaker or defibrillator), mitral valve prolapse, endocarditis, prosthetics, lifestyle (i.e., smoke, alcohol), and other pathologies (Otley 2006). This allows the correct pre-, intra- and postoperative care for every situation to maintain the patient's safety, to make the right choice about what type of reconstruction will be used, and to prevent any complications such as bleeding or infections.

One of the key steps in planning the elliptical excision is determining *the proper placement* and *orientation*. It is better to orientate the long axis of the ellipse following the long axis of the lesion. More specifically the incision should be placed following relaxed skin tension lines and in the face, bearing in mind the concept of *cosmetic units*.

It is an incontroversible fact that there is a naturally occurring tension (and thus extensibility) within the skin, which varies at different sites. Relaxed skin tension lines are fictitious lines "drawn" on the skin that correspond to the lines created by underlying muscle activity and are often visible in older patients; these lines are parallel to dermal collagen bundles and lie perpendicular to the long axis of the underlying muscles. An ellipse placed parallel to these lines leads to a fine linear scar as the maximum traction is exerted in the direction of these lines; if it is placed perpendicular to these lines a widened scar may result, as the distraction forces are maximal at the widest part of the wound. So the right orientation

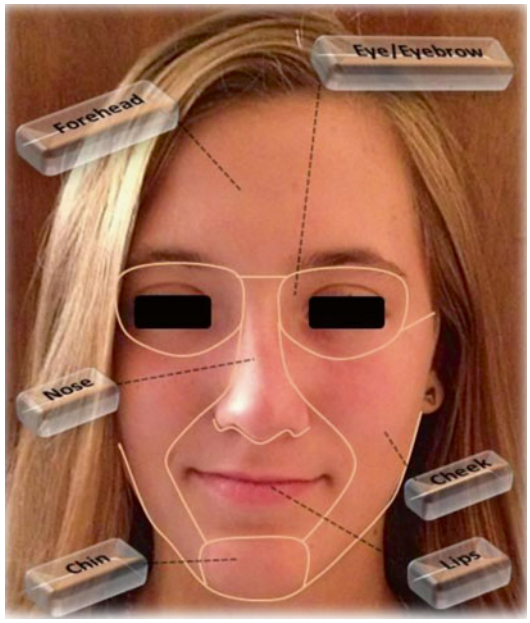

Fig. 130.16 The main cosmetic units of the face

of the ellipse should never be in an angle of more than 20° from these lines (Bush et al. 2007).

The face consists of six major esthetic units (Fig. 130.16): forehead, eye/eyebrow, nose, lips, chin, and cheek. The borders of the esthetic units are important in facial surgery and are natural lines separating distinct anatomic units. Every cosmetic unit can be divided in other smaller units. When possible, the placement of a scar along the border of a unit will give optimal esthetic results. This concept is very important for surgery performed on the face and plays an important role when planning flaps.

An important point that must always be considered when planning the orientation of an excision is that the vectors of tension of the planned closure will not pull on a freely mobile skin structure such as the eyelid, the eyebrow, and the lip. Also, proper orientation of a fusiform excision on the extremities will avoid contracture of an underlying joint.

Once the correct orientation of the wound (Fig. 130.17a) is determined, the ellipse is drawn on the skin. This procedure is done with the patient in the upright position and before the administration of anesthesia as a horizontal position and a large amount of anesthesia can interfere with the placement and orientation of relaxed skin tension lines. It is better to first mark a circle around the lesion itself, and then define with a second marking the recommended oncologic margins according to the diagnosis.

A lot of different excision shapes have been described in the past years; the best and simplest approach is the fusiform shape. To minimize the formation of dog-ears, the length should be three times the width, but the ratio of length to width may vary from 3:1 to 4:1 (Fig. 130.17b). The length of the short axis of the ellipse is predetermined by the size of the lesion being removed. For instance, an 8-mm malignant tumor to be excised with 5-mm margins will have a short axis of 18 mm, and the long axis will be approximately 38 mm in length. It is important to recognize that even a proportionate and properly designed ellipse may produce a closure with small standing cones or "dog-ears," at each pole that must be removed. Each tip of the wound should create a 30-degree angle. If the length-to-width ratio is reduced, the ellipse is not symmetrical, or its angles are greater than 30°, then the possibility of tissue cones formation is increased (Goldberg et al. 2004). If an anatomical landmark must be avoided, the ellipse may be asymmetric and the tissue cone will result more in the opposite tip to the landmark.

After the preoperative evaluation is done, the surgeon has to explain carefully to the patient everything about the surgical act. It is important to enlighten him about the geometry of the excision (even using some images) so as to clarify why the incision line will be certainly longer than the lesion being removed. Informed consent should then be obtained.

Once the preparation and the draping of the surgical site are performed, anesthesia is done. The choice of the right scalpel blade is important. There are disposable scalpels or stainless steel handles designed for smooth, reliable loading of surgical blades; different sizes are available, but for cutaneous surgery, the most used ones are numbers 15, 11, and 22/23 that have all different shape, dimension, and sharpness. The number 15 blade has a small curved cutting edge with an unsharpened back edge and is the most frequently

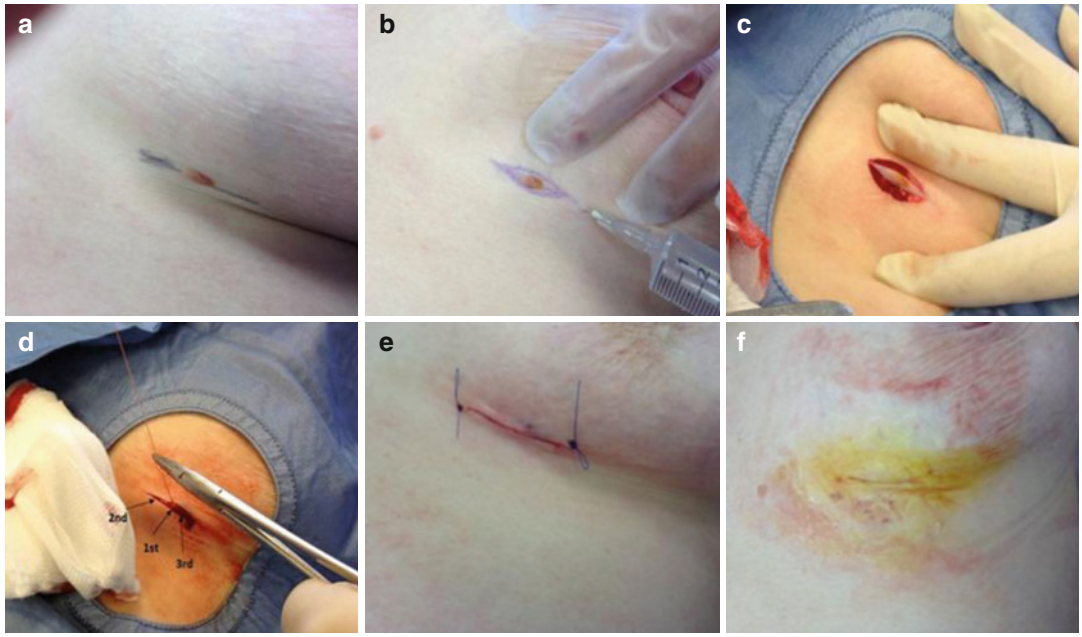

Fig. 130.17 (**a**) The ellipse is planned respecting relaxed skin tension lines that can be marked on the skin. (**b**) Then the ellipse is drawn respecting the ratio of length to width from 3:1 to 4:1 and both the tips of the wound are at a 30-degree angle; anesthesia is performed. (**c**) The incision is continued along the designed lines with constant pressure and minimizing the passes of the scalpel. (**d**) Once the lesion has been excised, hemostasis and undermining are done, the key point is placed, buried suture is the first to be placed proceeding with the rule of the halves. (**e**) If there is low wound tension, a running subcuticular suture can be done. (**f**) After 1 week the suture can be removed. Steri-strip are applied for one more week. Note the presence of contact dermatitis caused by adhesive

used one, mainly for facial defects. The number 11 is an elongated triangular blade sharpened along the hypotenuse edge and with a strong pointed tip: it is ideal for excising very small lesions. The number 23 is a leaf-shaped blade sharpened along its leading edge, similar to 15 but larger: it is required for making long incisions through thick skin (i.e., on the back).

The correct position of the blade on the skin is usually perpendicular. Only in hair-bearing regions, it is better to angle the incision lines so that they are parallel to the hair follicles.

The incision is initiated from the one tip of the drawn fusiform excision, with the scalpel held perpendicular to the skin. After the entry of the blade in the skin, the scalpel is then gently tilted to a 45° angle for incising the remaining margin until the other tip is reached. At that point the blade is then returned again to the perpendicular position. The same procedure is done on the opposing side (Kaufmann and Landes 1994). To avoid unnecessary injuries, it is desirable that the tips of the ellipse meet at a fine point, without unnecessary extension of the incision beyond that point. The incision has to be continuous along the designed lines so that there are less nicked edges. The amount of pressure or force used when incising the skin is learned only by experience, but the force depends on the thickness of the dermis and it is very important to try to be the most constant possible. Minimizing the number of passes of the scalpel through the dermis (Fig. 130.17c) avoids «stair casing» wound margins that would hamper the correct juxtaposition of the margins (Leshin).

The ellipse is excised through full-thickness skin to the appropriate depth with either a scalpel or scissors. The specimen should be of uniform thickness and wedge shaped. A common mistake is to leave more fat and dermal tissue at the tip and tail of the ellipse than at the center. This "boat-shaped" specimen will lead to redundancies and elevation of the end of the ellipse.

More importantly, the tissue left in the defect may cause protrusions at the two tips creating pseudo-dog-ears.

The process of undermining adjacent tissue, once the specimen is excised, avoids unnecessary vascular compromises, facilitates the eversion of the margins and the closure, and enhances the cosmetic outcome after scar contraction because it minimizes the tension. It can be done both with scissors or blade (but more often with scissors), and while executing this procedure, the wound margins are gently handled with forceps or hook. Undermining if needed should be carried out using blunt-tipped scissor as superficially as possible to avoid unnecessary damage to blood vessels and nerves. The depth varies with the anatomic area: on the scalp it is best carried out below the galea to avoid transection of hair follicles. The forehead is best undermined in the deep subcutaneous tissue to avoid damage of the sensory innervation of the scalp. To avoid injury of the superficial motor nerves, undermining on the temple, cheeks, and chin should be carried out in the superficial subcutaneous tissue. On the trunk, undermining can be carried out at any level above the muscle fascia. At sites of minimal subcutaneous tissue such as the hands and the feet, undermining should be done just below the dermis.

Before proceeding to suture the wound, hemostasis (stopping of the bleeding) must be done: achieving hemostasis is an essential component of all surgery. The goal of hemostasis in surgery is to control bleeding while avoiding unnecessary tissue destruction. Hemostasis can be reached by chemical agents that produce superficial hemostasis or by electrocoagulation (monopolar or bipolar) for deeper hemostasis. Hemostasis may also be done by physical methods that involve pressure, sutures, or gelatin sponges.

Depending on the dimension and the depth of the wound, the suture can be on only one layer or on more layers. Usually a double-layered suture is performed: the deeper one is placed in the dermis and allows spreading the tension of the wound, then the surface one is more superficial and is done only to ensure the juxtaposition of the edges.

To avoid the formation of dog-ears, it is important, as a general principle, to follow the rule of the halves while suturing. The "key point," that is, the one that carries the most tension, is usually positioned at the widest part of the ellipse (i.e., in the middle): this is the first stitch to be placed (Fig. 130.17d). Then the surgeon proceeds toward each tip of the wound placing every stitch in the middle of the remaining defect. This helps the spreading of the eventual exceeding tissue to both the extremities of the wound.

If one of the ends of the excision is better suited to be the location of any tissue cone formation, suturing from the opposite end first will push the tissue cone to the desired end.

Sometimes, the surgeon can decide first to excise the lesion, then to manage independently each tissue cone resulting after the placement of the key point. This allows many different orientations of the scar.

To perform a linear repair, the surgeon hooks the tissue cones (Fig. 130.18a) and makes the first incision along the line of the initial excision (Fig. 130.18b). The hook placed in the end of the wound defines the geometry of tissue protrusion in the shape of a standing cone. Then the base of the triangle is incised and undermined. The triangle-shaped tissue is then moved toward the other side of the previous incision (Fig. 130.18c) and then removed on the same line of the initial excision (Fig. 130.18d). This procedure is a simple way to remove puckering tissue, resulting in a lengthened linear scar (Petres et al. 1996).

At each tip of the ellipse, the first cut performed to remove the puckering tissue is the one giving the direction of our final scar: there are very different shapes such as linear repair, hockey-stitch repair, curved repair, L-shaped repair, and T-repair (Fig. 130.19).

Dealing with tissue cone repair is fundamental in every type of dermatologic surgery, from the primary closure to flaps and more complex reconstructions. Every surgical planning has to consider and to manage the puckering tissue.

Ellipse Variations

According to the location, the orientation, and the anatomy of the region, there are some variations of the classic ellipse that can improve cosmetic and functional results. The most used variations are:

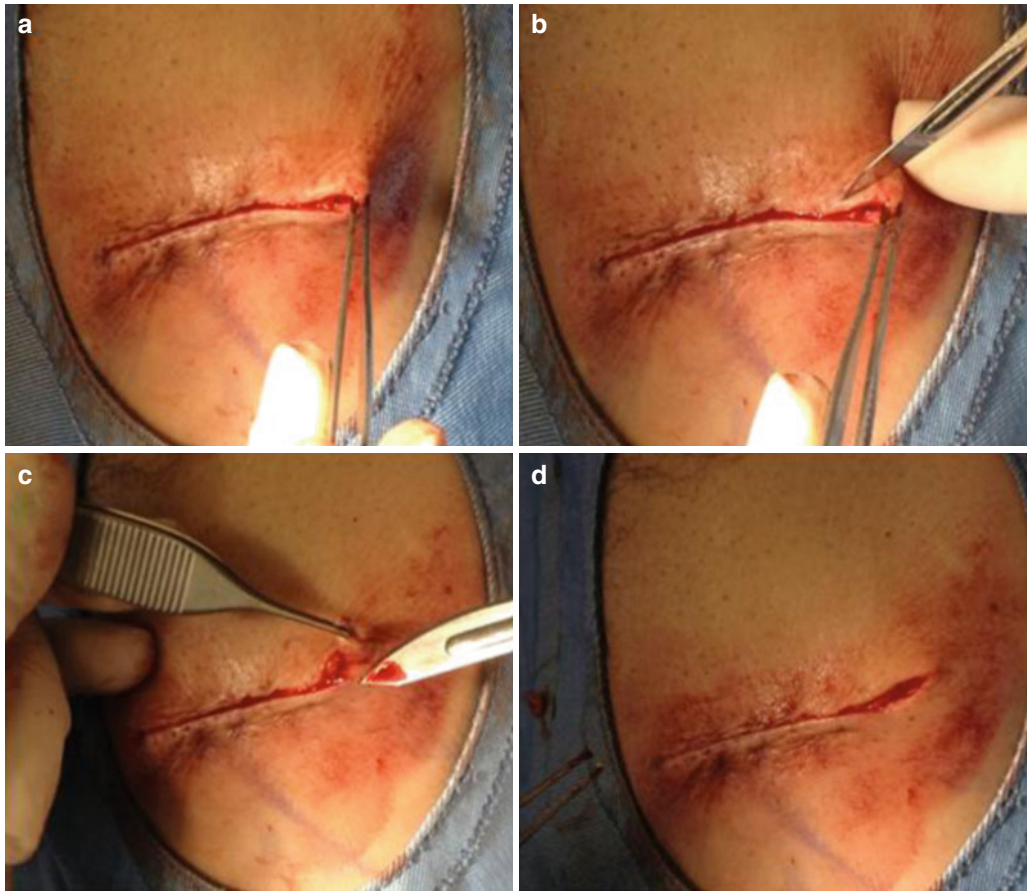

Fig. 130.18 Linear repair of tissue cone

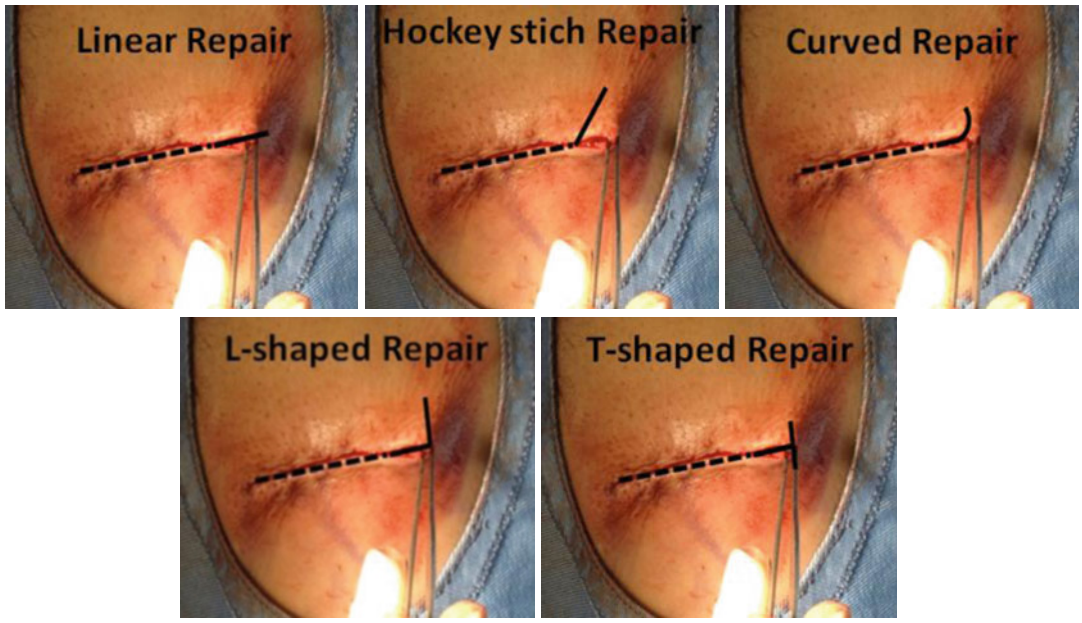

Fig. 130.19 Modification of tissue cone repair

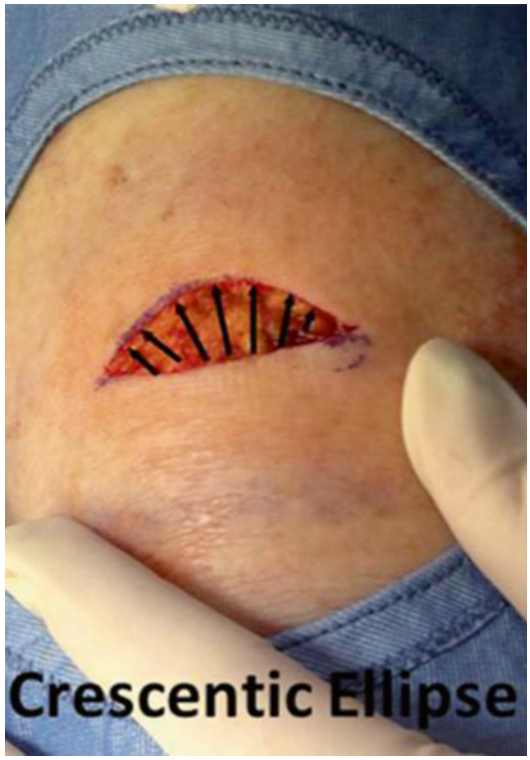

Fig. 130.20 Crescentic ellipse

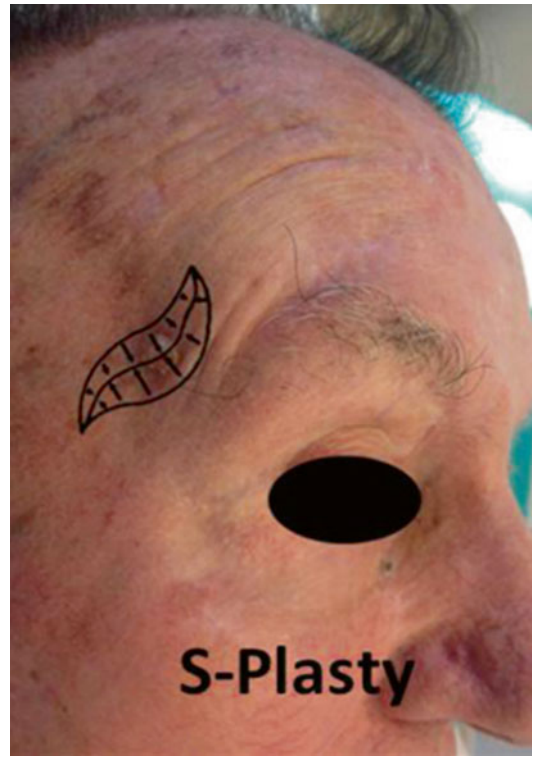

Fig. 130.21 Lazy S-shape

- Crescentic ellipse
- S-plasty
- M-plasty
- Relaxing incision
- Serial excision
- Wedge excision repair.

The *crescentic ellipse* (Fig. 130.20) is a curved ellipse: in some areas such as the mid cheek, the nipple, or the melolabial fold, it is preferred to obtain a curved scar. The sides of the ellipse are not of the same length. This difference is spread in the whole wound while suturing: the vector of the stitches is not perpendicular, but every stitch takes a little more tissue in the longer side. The difference between the two sides must not be too large (Goldberg and Alam 2004) to prevent dog-ear correction.

On convex areas or if the skin elasticity is low, the shape of the ellipse can resemble a *lazy S-shape* (Fig. 130.21). This varies the distribution of the vectors of tension of the wound: in the classic fusiform excision, they are oriented perpendicularly to the wound, when performing a lazy S-plasty, these vectors are diagonally oriented. This improves the central scar depression. When this alternative plastic reconstruction method is chosen, the suture is reduced in length by approximately one third and assumes a curved profile, which is better esthetically. This technique is simpler than a flap and shorter (and more esthetic) than a simple elliptical excision (Boggio et al. 2003).

The *M-plasty* can be used to shorten the scar, to avoid crossing an esthetic boundary, or to accommodate the anatomy of a special area (i.e., lateral canthus). It is a tissue-sparing dog-ear repair. The classic fusiform excision can be drawn while planning an M-plasty, but the end of the excision is incised inward, toward the center of the ellipse, creating an M in one or both the sides of the wound (Fig. 130.22). The angles of the limbs of the M-plasty should not be greater than 30° to avoid the formation of a standing cone deformity.

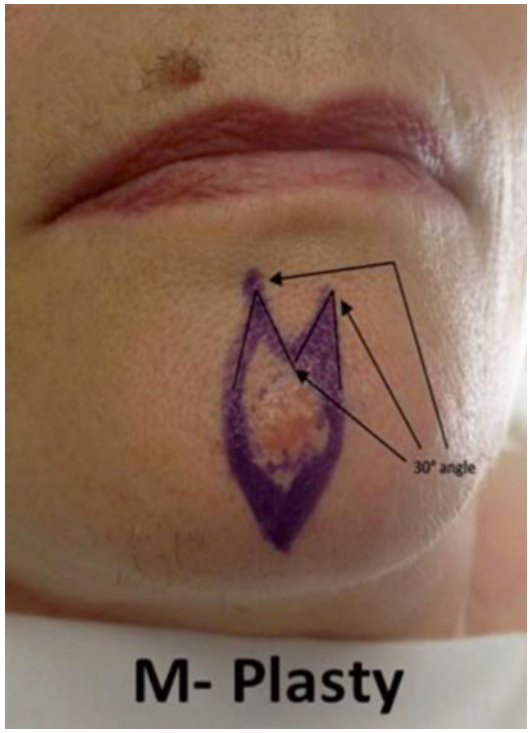

Fig. 130.22 M-plasty

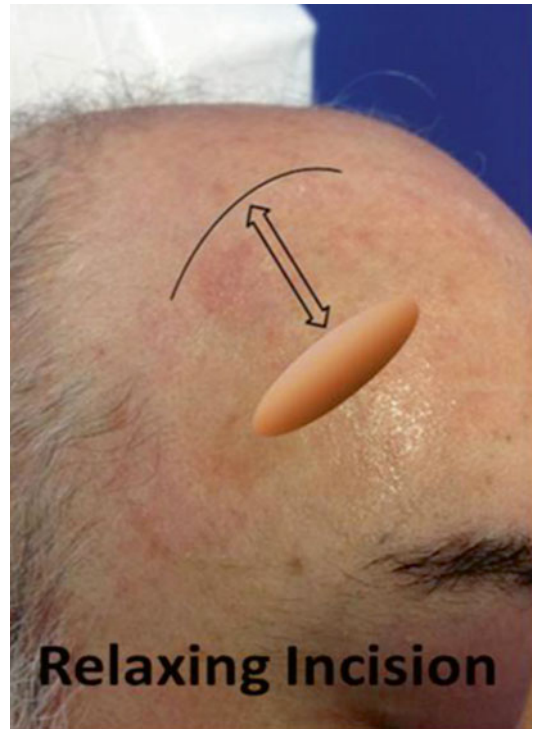

Fig. 130.23 Relaxing incision

The *relaxing incision* is an incision made to allow movement of skin for closure of a wound of a parallel incision: it allows primarily closure of wounds that would need more complex surgery. It can be used for wounds placed on the forehead: a full-thickness incision (including galea) is made near the defect, hiding the second incision behind the hairline (Fig. 130.23). This allows the spreading of a defect of two different sites of closure, allowing primary closure of both regions.

For benign lesions (i.e., congenital naevi), the complete removal of the whole lesion in one-time surgery could mean a very large ellipse or a complex reconstruction with a large resulting scar. *The serial excision* allows for a better cosmetic result even if more surgical time is needed. The elasticity of the skin, after the first partial excision with primary closure, allows subsequent re-excision at least few months later with a smaller resulting scar (Fig. 130.24).

Wedge excision is a surgical procedure to remove a full-thickness triangle-shaped slice of tissue (Fig. 130.25). It is applied on the free margins of the skin. Ideally, the inner corner of the wedge is 30° to minimize the formation of a dog-ear. Small defects on free margins such as the eyelid (one fourth), helix (one third), and of the lip (one third lower, one fourth upper) can be repaired with a wedge excision.

Wound Dressing and Follow-Up

Covering a wound with a dressing mimics the barrier role of epithelium and prevents further damage. Furthermore, the application of compression provides hemostasis and limits edema. A primary dressing is placed directly on the wound and may provide absorption of fluids and prevent desiccation, infection, and adhesion of a secondary dressing. A secondary dressing is one that is placed on the primary dressing for further protection, absorption, compression, and occlusion. To protect the stitches, steri-strip

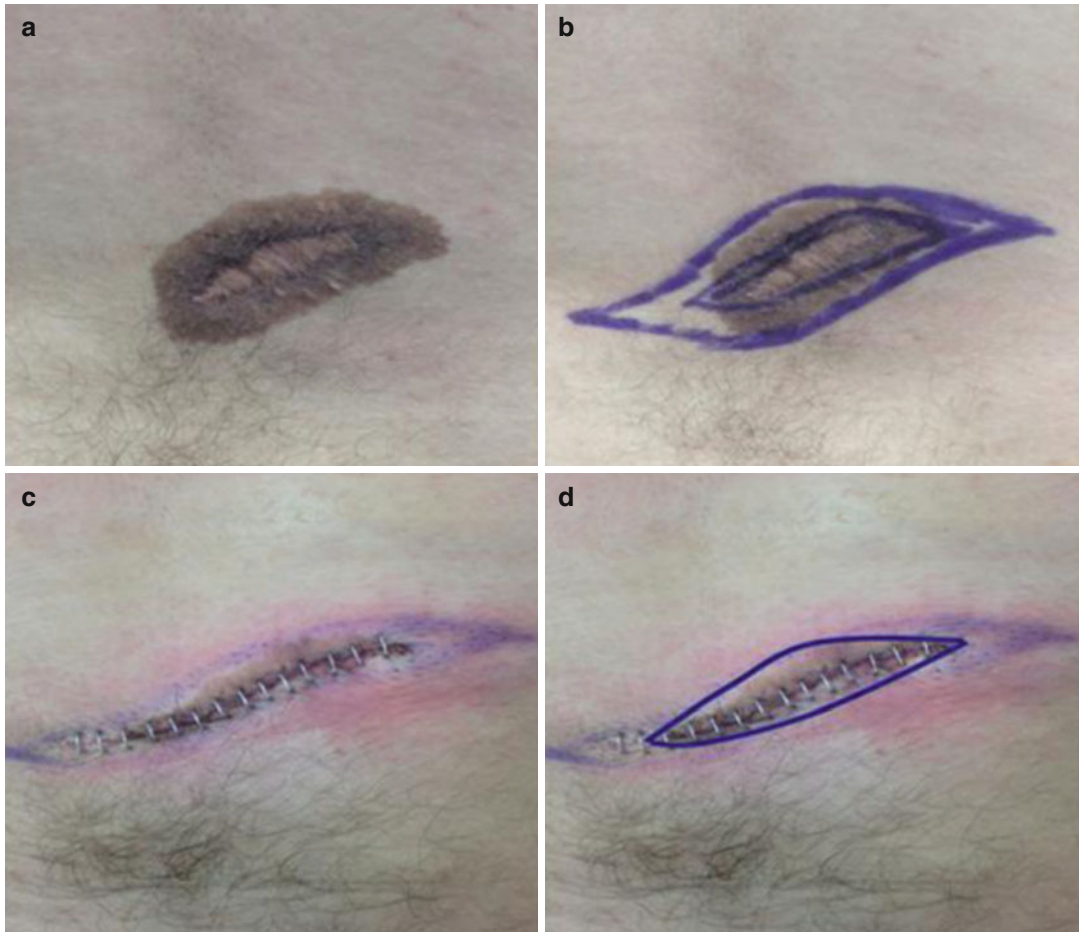

Fig. 130.24 (**a**) On the central area of the congenital nevus, there is a visible scar of the previous first excision. (**b**) Difference between the lengths of the scar if the lesion was totally excised, or if we plan another re-excision. (**c**) Final scar of partial excision. (**d**) Part of the lesion remaining to be excised: the scar won't be longer than the existing one

Fig. 130.25 Wedge excision

can be applied on the dry wound after thorough cleaning and topical antiseptic application. The wound is covered when it is still sterile in the operative field, so if there isn't any complication, it can remain closed for some days. Oral antibiotics therapy is usually not necessary: it should be reserved for clinically suspected and swab-proven infections rather than being prescribed empirically (Cherian et al. 2013). The surgeon has to inform carefully the patient and the caregiver about the changing of the dressing and explain the possible risks to facilitate early recognition and reporting of potential adverse events (Fonder et al. 2008). The patient should have a follow-up visit. Topical application of antiseptic (povidone-iodine solution or chlorhexidine) is useful to prevent infection (Milstone et al. 2008): after the removal of the first dressing, it should be changed once a day until the stitches are removed. Sterile skin-closure strips after the removal of the stitches can help to prevent wound dehiscence.

Postoperative Complications

Most surgical wounds will heal without causing any problems. The prevention of surgical complications depends on correct preoperative evaluation, proper surgical technique, postoperative care, and follow-up care. Even if all precautions have been taken, some complications might occur (Table 130.2). The important role of the surgeon is to assume responsibility and manage correctly any situation. The early identification will allow a correct approach to the complication, adjusting any possible worsening.

Infection: It is uncommon but is usually heralded by pain on days 4–8. It is managed by prescription of topical and systemic antibiotics and wound care.

Seroma: It is the deposit of serous fluid under the wound. It can occur after the excision of large lesions such as lipomas or cysts or in areas of wide undermining. The body is simply reacting to the presence of a dead space. When occurring,

Table 130.2 Postoperative complications

Complication	Prevention	Treatment
Infection	Sterile surgery Management of dressing	Topic and systemic antibiotics Wound care
Seroma	Accurate buried multilayer suture Compression	Aspirate with a needle Puncture with a lancet
Bruising, bleeding or hematoma	Systemic therapies adjustment Hemostasis Pressure dressing	Drainage Remove of hematoma Ligation or cauterization of the vessel
Tissue necrosis	Undermine at correct depth/avoid wound tension	Keep wound moist but not wet Remove necrotic tissue Perform debridement
Contact dermatitis	Accurate anamnesis	Topical steroid Avoid exposure to the allergen Patch test
Nerve injury and alteration of specific anatomical sites	Surgical anatomy knowledge	Surgical correction if possible
Hypertrophic scarring and keloid formation	Accurate evaluation before surgery Follow-up	Medication Topical or intralesional steroid Laser treatment Needling
Dehiscence	Sutures into multiple tissue layers Undermining to allow minimal tension Don't remove sutures too early	Scar revision

this could resolve spontaneously in some days or some drainage could be necessary to alleviate pain and tension on the wound.

Tissue necrosis can occur if the undermining is too superficial or if there is too much tension on the wound. If the skin is left too thin, it may not have enough blood supply from deeper tissues and some tissue could start to suffer or to necrose. If the tension is more than moderate, the lack of vascularization could occur in the central area of the wound: this is due to the fact that the blood flow in a random flap decreases in an inverse manner with increased tension.

Bruising, *Bleeding, or Hematoma*: Patients on anticoagulants (Bordeaux et al. 2011) or aspirin may be associated with increased intraoperative bleeding in dermatologic surgery (Shimizu et al. 2008). To prevent it, an accurate hemostasis must be achieved, and if needed, compression should be applied after surgery to stop the bleeding.

Nerve Injury and Alteration of Specific Anatomical Sites: Mainly the cervicofacial region requires a good knowledge of the surgical anatomy of the area with special attention to known danger zones. A nerve transection may result in sensory (trigeminal nerve and its branch) or motor (cranial nerve VII and its branch or the spinal nerve in the neck) deficits. When performing surgery in special areas such as the eyelid or lip, the preoperative planning must respect the correct position of the free skin margin. Ectropion, lagophthalmos, or eclabium are all conditions that could result from inappropriate surgery: they often require another surgical intervention to restore functionality and if possible the cosmesis.

Contact Dermatitis: This inflammation is caused by irritation or delayed-type hypersensitivity to any topical agent that is part of the dressing (ointments, bandages, topical antibiotics, or adhesives). This clinically appears with erythema, sometimes associated with vesicles, and it is often shaped like the part of the dressing responsible.

Hypertrophic Scar and Keloid: Scarring is an inevitable part of wound healing. In most people, if the wound is closed properly, the scars are small and barely visible. The size of the scar varies by location on the body and the individual person. Some people are genetically predisposed to formation of large hypertrophic scars particularly for surgery on the chest and back. The hypertrophic scars do not grow beyond the boundaries of the original wound and arise within a month of surgery; they can spontaneously regress. Keloids may arise from 3 month to years after surgery, they do not regress spontaneously, and they frequently recur. The primary risk factor for keloids is darkly pigmented skin (Murray 1994), but a familial predisposition is recognized.

Dehiscence: For reasons such as high tension or poor surgical closure, the wound edges can come apart. The term for that is wound dehiscence. In order to avoid this wound complication, sutures should be placed into multiple tissue layers to hold the wound together under minimal skin tension: to achieve this result, the correct undermining of adjacent tissue and a proper knotting technique are important. Wound dehiscence can also be caused by increased stress to the wound area as a result of trauma, strenuous exercise, and heavy lifting: this has to be explained to the patient.

Pigmentary or surface alterations of the wound or suture granulomas can occur sometimes.

Other Reconstructive Options

As mentioned already every single wound has to be individually considered: the surgeon should make the right choice by evaluating different options (Table 130.3) and carefully explaining the benefits and the risks of any different surgical approach. Primary approximation, flaps, grafts, and secondary healing all have an appropriate indication. The decision depends on several factors: the nature of the lesion to be excised, the functional and esthetic result desired, the patient's status and wishes, as well as the surgeon's experience.

A *flap* consists of skin and subcutaneous tissue only partially removed from one part of the body so that it retains its own blood supply during transfer to another site. There are many classifications of flaps, but the most used ones

Table 130.3 Options for closure of cutaneous surgical defects

SURGICAL OPTIONS			
PRIMARY CLOSURE	SECOND INTENTION	FLAP	GRAFT

are the ones based on blood supply and on tissue movement. According to vascularization, flaps can be divided in arterial (or axial) flaps and random flaps. Most of the flaps used in dermatologic surgery are random, that means they are vascularized by the perforating subdermal plexus. The axial flap takes its blood supply from a specific artery. The classification based on the tissue movement distinguishes advancement, rotation, and transposition flaps.

A *skin graft* is constituted by epidermis and varying amounts of dermis. It is excised from a donor site and placed on a recipient site (bed). The graft has no vascularization: the new blood vessels will arise from the recipient site. Grafts are classified in terms of thickness or depth: a split-thickness graft (further classified as thin or thick) takes the whole epidermis and a portion of the dermis, whereas a full-thickness graft contains the entire epidermis and dermis.

During the process of *secondary intention healing*, the wound is left open: it heals by contraction, granulation, and epithelialization. The healing duration will depend on the amount of tissue that must be replaced. The resulting scar may be quite extensive but an adequate alternative especially on concave areas of the head and neck. The esthetic and functional result even if it is not perfect could represent a good compromise that can spare the patient more complex procedures such as flaps or skin grafts reconstruction. The final scar is less noticeable in older patients with skin laxity and in lighter-skinned patients.

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Part III

Drugs

Antibacterial Agents

131

Maria Souli and Helen Giamarellou

Key Points

- *Staphylococcus aureus* and streptococci are the most common pathogens in SSTIs.
- The global emergence of community-acquired methicillin-resistant *S. aureus* (MRSA) is responsible for a change in the current treatment algorithm of SSTIs. Risk factors for this pathogen should always be pursued before prescribing empirical treatment for SSTIs.
- The current evidence on the limitations of the glycopeptides for the treatment of severe MRSA infections and the introduction of some newer antimicrobials in the market necessitate an update in the treatment of SSTIs.

General Principles

The contemporary dermatologist quite often confronts bacterial skin and/or soft tissue infections (SSTIs). Therefore, he should be familiar with antibacterial agents, particularly with newer antibiotics and their role in modern chemotherapy. Classification of cutaneous infections according to morphological and clinical criteria is helpful in providing initial clues regarding the most likely responsible pathogens, which will lead to the appropriate antimicrobial chemotherapy.

Furthermore, in the past decade there has been a global increase in the burden of staphylococcal SSTIs due to the increase in dissemination of specific clones of methicillin-resistant *Staphylococcus aureus* (MRSA), which are genetically and epidemiologically distinct from hospital-acquired clones, designated community-acquired MRSA, CA-MRSA. These clones carry smaller staphylococcal chromosomal cassette *mec* (SCC*mec*) elements, mostly type IV or V, frequently carry genes for virulence determinants such as Panton-Valentine leucocidin (PVL), and they are susceptible to many non-β-lactam classes of antimicrobial agents including many oral agents (clindamycin, minocycline, trimethoprim/sulfamethoxazole, fusidic acid, etc.). Also, they typically affect groups lacking risk factors for exposure to health-care system. The modern dermatologist should be able to recognize and to adequately treat this pathogen.

Finally, and despite the scope of the present manual, it was considered appropriate to also include some clinical data on the common streptococcal and staphylococcal skin infections, which will help the dermatologist to choose rationally from among the available antimicrobial agents. Emphasis will be placed on the newer

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_131, © Springer-Verlag Berlin Heidelberg 2015

antibacterial agents, while for the older ones the discussion will be confined mainly to their indications in current dermatological therapy.

Common Bacterial Infections in Dermatology

The commonest bacterial skin and soft tissue infections in the immunocompetent host are those in which staphylococci and streptococci are implicated. However, in immunocompromised patients, several *Enterobacteriaceae*, *Pseudomonas aeruginosa* and a variety of fungi (yeast and moulds) are implicated. The common SSTIs are represented by the following entities.

Folliculitis

This consists of small erythematous papules topped by a central pustule located within hair follicles; *S. aureus* is the main cause, but *P. aeruginosa* has been implicated in 'swimming pool' folliculitis attributed to inadequate chlorination. Folliculitis may extend to the deeper structures creating a furuncle which is a deeper inflammatory nodule occurring in areas of the skin subjected to friction and perspiration like the neck, axillae, buttocks and face.

A more extensive process is a 'carbuncle', which extends into the subcutaneous fat whenever the involved skin is inelastic and thick. In the latter case, multiple abscesses develop draining along hair follicles. Diabetes mellitus is considered a predisposing factor. *S. aureus* is the unique aetiological agent. Invasion of the blood stream by staphylococci may result in endocarditis, osteomyelitis or other serious infections, while location at the upper lip and nose may spread staphylococci via the facial and angular veins to the cavernous sinus.

Impetigo

This is a superficial, infection of the skin appearing initially as vesicular and rapidly as thick, golden-yellow-crusted lesions in the exposed areas of the skin. In 90 % of the cases, group A streptococci are involved and rarely group B (in the newborn) as well as group C and G. In 10 % of the cases, a bullous form of impetigo is observed due to *S. aureus*.

Erysipelas and Cellulitis

This refers to superficial skin infection with distinctive lymphatic involvement. In 70–80 % of cases, the lower extremities are affected and only in 5–20 % the face. In almost all cases, group A streptococci and uncommonly group C and G are implicated. However, in the neonate, group B is also involved. Patients with diabetes mellitus, venous stasis, nephritic syndrome or lymphatic obstruction (as after radical mastectomy) are vulnerable to erysipelas. Portals of entry for streptococci are skin ulcers, abrasions, postoperative wounds, eczematous or psoriatic lesions and even skin fungal infections. Erysipelas is painful with a red 'peau d'orange' picture and a characteristic raised border which is sharply demarcated from the surrounding normal skin. As a rule, streptococci cannot be cultured from the skin lesions. The infections can be complicated with cellulitis, subcutaneous abscesses and even necrotizing fasciitis. However, cellulitis can appear as an acute infection extending from the beginning into deep subcutaneous tissues. Cellulitis may be caused by numerous organisms, indigenous to the skin or to particular environmental niches.

Cellulitis associated with furuncles, carbuncles or abscesses is usually caused by *S. aureus*. In contrast, cellulitis that is diffuse or unassociated with a defined portal is most commonly caused by streptococcal species. Important clinical clues to other causes include physical activities, trauma, water contact, and animal, insect or human bites.

Staphylococcal Scalded Skin Syndrome

This represents a severe *S. aureus* infection characterized by widespread large flaccid clear bullae, which promptly rupture resulting in

exfoliation that exposes large areas of bright red skin. It starts with fever, skin tenderness and a scarlatiniform rash. The early stage should be differentiated from 'toxic shock syndrome', which is characterized by hypotension or shock, functional abnormalities of at least three organ systems and desquamation of the skin lesions. *S. aureus* strains, with the capacity to produce exotoxins, are the main cause; however, group A streptococci are also implicated.

Necrotizing Infections

Necrotizing fasciitis (NF) may be monomicrobial and caused by *S. pyogenes*, *Vibrio vulnificus* or *Aeromonas hydrophila*. Recently, necrotizing fasciitis was described as a complication of MRSA infection. Polymicrobial NF may occur following surgery or in patients with peripheral vascular disease, diabetes mellitus, decubitus ulcers and spontaneous mucosal tears of the gastrointestinal or gastrourinary tract (i.e. Fournier gangrene). As with clostridial myonecrosis, gas in the deep tissues is frequently found in these mixed infections.

Gas gangrene is a rapidly progressive infection caused by *Clostridium perfringens*, *Clostridium septicum*, *Clostridium histolyticum* or *Clostridium novyi*. Severe penetrating trauma or crush injuries associated with interruption of the blood supply are the usual predisposing factors. *C. perfringens* and *C. novyi* infections have recently been described among heroin abusers following intracutaneous injection of heroin. *C. septicum* may cause spontaneous gas gangrene in patients with colonic lesions (such as those due to diverticular disease), adenocarcinoma or neutropenia.

Necrotizing fasciitis and gas gangrene may cause necrosis of skin, subcutaneous tissue and muscle. Disproportionate pain as compared to initial clinical findings should always prompt to this diagnosis. Cutaneous findings of purple bullae, sloughing of skin, marked oedema, crepitus, foul odour and systemic toxicity mandate prompt surgical intervention because necrotizing skin infections represent a medical-surgical emergency and they are life threatening.

Hidradenitis Suppurativa

This is a chronic suppurative subcutaneous process that results from occlusion of follicles, secondary inflammation and sometimes infection of the pilosebaceous and apocrine glands of the genital, perianal and axillary regions. Recent investigations suggest that the interleukin-12-interleukin-23 pathway and tumour necrosis factor α (TNF-α) are involved in the pathogenesis of hidradenitis suppurativa, supporting the suggestion that it is an immune or inflammatory disorder. Red nodules that become fluctuant and drain are the initial lesions, which result in chronic draining sinuses and cicatricial scars. Secondary infections involve staphylococci, streptococci, Enterobacteriaceae, *Pseudomonas* spp. and anaerobes. Therefore, a therapeutic decision should not be empirical but based on 'pus' culture results. For severe and refractory disease, TNF-α inhibitors, oral retinoids, immunosuppressants and other therapies are used.

Antibacterial Agents

Penicillin G

Today this is still the drug of choice for streptococcal infections as well as for anthrax and *Erysipelothrix* infection (soft tissue and/or systemic infection after exposure to domestic or marine animals and seafood). Depending on the severity of the infection, it is given either orally as penicillin V, in case of impetigo (1.5 million IU every 6 h) with an empty stomach (at least for an hour) or parenterally as i.v. penicillin G (3–4 million IU every 4–6 h, over 30 min). Oral penicillin (1.5 million IU every 12 h with empty stomach) or i.m. benzathenic penicillin G (2.4 million IU every 20 days) given for a period of 12–18 months is effective as prophylaxis for recurrent cellulitis (for patients with a history of two or more episodes).

The major side effects of penicillins in general are hypersensitivity reactions, which range in severity from rash to anaphylactic shock and death. While allergic rash reactions occur

in 4–7/1,000 penicillin treatment courses, immediate anaphylactic reactions occur mostly with penicillin G from 0 to 1 h post administration and are expressed as urticaria, angiooedema, laryngeal oedema, bronchospasm and shock. They occur in 4/100,000 penicillin treatment courses with fatalities reported once in every 32,000–100,000 treatment courses. Late allergic reactions observed after 72 h of β-lactam administration are manifested by morbilliform rash, Stevens-Johnson syndrome, exfoliative dermatitis, drug fever, serum sickness, neutropenia, thrombocytopenia, haemolytic anaemia, interstitial nephritis, vasculitis, pruritus and contact dermatitis.

The detection of anaphylactic reactions to penicillin requires skin testing using minor antigenic determinants, a test not available in several countries. However, a negative result when testing with the major antigenic determinants, available commercially as the Pre-pen test, does not exclude the possibility of an anaphylactoid reaction, while skin testing with diluted penicillin G is very dangerous in individuals prone to express an anaphylactoid reaction. Therefore, whenever the appropriate tests are not available, a careful history of any potential for previous allergic reactions should be noted. In cases of an immediate reaction, adrenaline solution (1:1,000) should be given i.m. and repeated every 15 min until recovery, followed by corticosteroids.

Antistaphylococcal Penicillins

Oxacillin, dicloxacillin, cloxacillin, flucloxacillin and nafcillin, either orally at a dose of 1 g every 8 h for mild infections or parentally at a dose of 3 g every 6–8 h for serious infections, are still the drugs of choice for staphylococcal infections. However, it should be seriously considered that 20–50 % of *S. aureus* strains are now resistant to them (methicillin-resistant *S. aureus*, MRSA). Interestingly such infections, although mostly hospital acquired, are also encountered in the community (community-acquired MRSA, CA-MRSA). Therefore susceptibility tests, at least in serious infections, are required. It should be pointed out that MRSA strains are obligatorily resistant to any type of β-lactam antibiotic including the inhibitor combinations, the cephalosporins and the carbapenems.

The remaining group of penicillins, i.e. aminopenicillins (ampicillin and amoxicillin), carboxypenicillins (carbenicillin and ticarcillin), ureidopenicillins (mezlocillin, azlocillin, piperacillin) as well as the β-lactam group of monobactams (aztreonam) and carbapenems, will not be included since they are out of the scope of this handbook.

β-Lactamase Inhibitors

These compounds, which are by themselves weak antibiotics, are potent inhibitors of many plasmid-mediated, and also of some chromosomal, β-lactamases, produced by *S. aureus* and several Enterobacteriaceae. Three derivatives are in clinical use, clavulanic acid, sulbactam and tazobactam. These restore the antibacterial activity of amoxicillin and ticarcillin (when combined with clavulanic acid), ampicillin (combined with sulbactam), piperacillin and cefoperazone (combined with tazobactam) against Gram-positive cocci, including staphylococci (but not MRSA strains) and several common Gram-negative species. Ticarcillin and piperacillin combinations are also active against *P. aeruginosa*.

Clavulanic acid and sulbactam bind primarily to plasmid-encoded β-lactamases, while tazobactam binds also to chromosomally encoded enzymes, produced mainly by *Klebsiella* and *Bacteroides* species.

The pharmacokinetics of clavulanic acid and sulbactam in humans are similar to those of amoxicillin and ampicillin. They are both available in oral and parenteral formulations with a weight ratio of inhibitor to the relevant β-lactam of 1:5 and 1:2, respectively. When clavulanic acid is combined with ticarcillin, the ratio is 1:25, and for tazobactam-piperacillin is 1:8. With the exception of clavulanic acid, the excretion of which is influenced in renal failure (and therefore amoxicillin plus clavulanic acid should not be administered in patients with renal insufficiency)

the dose of the remaining combinations should be reduced proportionally to the decrease of the relevant β-lactam dose. Tissue kinetics of the inhibitors are compatible with those of the combined β-lactam.

Clavulanic acid plus amoxicillin is given in adults orally at a dose of 1 g every 12 h, while i.v at a dose of 1.2 g every 6 h. An oral extended release (XR) formulation is available, which is administered at a dose of 1.25 g every 12 h. Sulbactam plus ampicillin is given orally at a dose of 3.75 g every 8 h and i.v. at a dose of 3 g every 6–8 h. Clavulanic acid plus ticarcillin is given only i.v. at a dose of 3.2 g every 4 h or 5.2 g every 6 h, while tazobactam plus piperacillin is given at a dose of 3.375 g every 6 h or 4.5 g every 6 h (depending on the available formulation).

As with any β-lactam antibiotic, allergic reactions are the main threat, and they are mainly attributed to the combined β-lactam and very seldom to the inhibitor itself. Diarrhoea with the oral compounds exceeds in some series 10 % of the treated cases.

Because of their very wide spectrum of activity, which disturbs gastrointestinal tract flora and destroys colonization resistance, the inhibitors should not be given for the common streptococcal or staphylococcal infections, taking also into consideration that MRSA strains are by definition resistant. On the contrary, when SSTIs are likely to be polymicrobial such as surgical site infections of the abdominal wall, or in proximity to the genital tract or rectum, diabetic foot infections and human or animal bites, β-lactam/β-lactamase inhibitor combinations should be among the preferred treatment options.

Table 131.1 Classification of cephalosporins with half-lives and daily dosage schedules

Generic name	Half-life (h)	Daily dosage regimen and route of administration
First generation		
Cefazolin	1.8	1 g every 8 h i.v. or i.m.
Cephradine	0.7	0.5 g every 6 h orally or 1–2 g every 4–6 h i.v.
Cephalexin	0.9	0.5–1 g every 6 h orally
Cefadroxil	1.2	0.5–1 g every 12 h orally
Second generation		
Cefamandole	0.8	2 g every 4–6 h i.v.
Cefoxitin	0.8	2 g every 4–6 h i.v,
Cefuroxime	1.3	1.5 g every 6–8 h i.v.
Cefotetan	3.5	2–3 g every 12 h i.v.
Ceforanide	3.0	1–2 g every 12 h i.v.
Cefuroxime axetil	1.3	0.25–0.5 g every 12 h orally
Cefaclor	0.8	0.5–1 g every 8 h orally
Cefprozil	1.2	0.5–1 g every 8 h orally
Loracarbef	1.1	0.4 g every 12 h orally
Third generation		
Cefotaxime	1.0	2 g every 6–8 h i.v
Ceftriaxone	8.0	2 g every 12–24 h i.v.
Ceftazidime	1.8	2 g every 8 h i.v.
Ceftizoxime	1.7	2 g every 8–12 h i.v.
Cefoperazone	2.0	2 g every 8–12. h i.v
Cefixime	3.7	0.4 g every 24 h orally
Cefpodoxime proxetil	2.2	0.4 g every 12 h orally
Cefetamet	2.2	0.5 g every 12 h orally
Cefditoren pivoxil	1.6	0.4 g every 12 h orally
Ceftibuten	2.5	0.2 g every 12 h orally
Fourth generation		
Cefepime	2.1	1–2 g every 8–12 h i.v.
Cefpirome	1.0	1–2 g every 8–12 h i.v.
Anti-MRSA		
Ceftaroline fosamil	2.6	0.6 g every 12 h i.v.
Ceftobiprole	3.0	0.5 g every 8–12 h i.v.

Cephalosporins

Based on their in vitro activity and their stability to β-lactamases, cephalosporins are divided into four generations (Table 131.1). They represent broad-spectrum antibiotics, the first and second generation being more potent against the Gram-positive cocci, the third and fourth against the nosocomial Gram negatives, including the various Enterobacteriaceae and *P. aeruginosa*. Also, the fourth generation has greater coverage against Gram-positive organisms than the third-generation agents.

Cephalothin, cephradine, cefazolin, ceforanide and cefamandole possess the highest activity against staphylococci; cefoxitin and cefotetan are the only ones active against *Bacteroides fragilis*, but acquired resistance is increasing. Ceftazidime is the most potent against *P. aeruginosa*. The

latter compound, however, is practically not active against streptococci and staphylococci. None of the first-, second-, third- or fourth-generation agents are active against methicillin-resistant staphylococci.

The pharmacokinetic properties of the parenteral compounds differ in that the half-life ($t_{½}$) can range from 30 min to 8 h, mandating the frequency of administration (Table 131.1). Based on the much lower minimal inhibitory concentrations (MICs) for Gram-negative bacteria as well as the addition of different side chains at position 3 of their nucleus, which modifies their kinetic properties, third- and fourth-generation cephalosporins in comparison with earlier compounds have kinetics which are particularly advantageous when treating infections in the cerebrospinal fluid or the prostatic and bone tissues.

Adverse effects associated with the cephalosporins are similar to those from other β-lactams and concern mainly allergic reactions. However, anaphylaxis/angiooedema reactions are rare relative to the frequency of 0.04 % associated with penicillin. Allergic cross-reactions with the penicillins are expected at a range of <7 %. Haematological adverse effects and coagulation abnormalities (hypoprothrombinaemia) have been reported mainly with moxalactam (which has been removed from the market), while gastrointestinal reactions such as antibiotic-associated diarrhoea including pseudomembranous colitis occur at a frequency of 1–7 %.

Like the β-lactam/β-lactamase inhibitor combinations, cephalosporins should not be given for common SSTIs since their extremely broad spectrum of activity disturbs the normal flora, facilitating colonization with enterococci and fungi. Additionally, cephalosporin use favours selection of resistant clones, especially Gram-negative species producing extended-spectrum β-lactamases (ESBLs) in normal floras. Furthermore, these agents do not provide coverage against MRSA, so if this pathogen is a concern, empiric coverage with another active agent is recommended pending culture results. The appropriate dosage regimens for adults are shown in Table 131.1.

Ceftaroline

Ceftaroline fosamil is the prodrug of the active metabolite ceftaroline. Ceftaroline is a novel agent that belongs to the antimicrobial class of cephalosporins. Because of its unique spectrum of activity, which includes methicillin-resistant staphylococci, it has been described in the literature as a 'fifth-generation' cephalosporin.

Like other β-lactams, ceftaroline exerts its rapid bactericidal effect by binding to key penicillin-binding proteins (PBPs). It has a high affinity against MRSA PBP 2A and against penicillin-resistant *Streptococcus pneumoniae* PBPs.

Ceftaroline has a broad-spectrum activity against Gram-positive and Gram-negative organisms including *S. pneumoniae*, *S. aureus* (methicillin-resistant as well as vancomycin-intermediate and – resistant isolates), *Streptococcus pyogenes* and other Streptococci and Gram-negative species (*Haemophilus influenzae*, *Moraxella catarrhalis* and Enterobacteriaceae non-ESBL producers). The majority of MRSA isolates are inhibited by ceftaroline concentration ≤1 mg/L (MIC range, ≤0.12–2 mg/L). Similarly, ceftaroline MIC_{90s} for hetero-resistant vancomycin-intermediate *S. aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) strains are ≤2 mg/L (MIC range, ≤0.25–4 mg/L).

Ceftaroline fosamil is dosed at 600 mg i.v. every 12 h (infusion over 1 h) in adults. Dosage adjustment is necessary in patients with moderate to severe renal impairment. Ceftaroline is well tolerated. The most common adverse events reported in clinical trials were diarrhoea, nausea and headache. The most common adverse event leading to discontinuation of ceftaroline was hypersensitivity (0.3 % of patients).

In 2010, ceftaroline fosamil was approved by the FDA for the treatment of acute SSTIs and community-acquired pneumonia. In cases where coverage for MRSA is necessary but *Pseudomonas* and *Acinetobacter* are not among the possible pathogens, ceftaroline is an attractive option because of its favourable safety and

tolerability profile. The lack of activity against non-fermenters is another positive characteristic since the use of ceftaroline is not expected to increase the burden of selective pressure against these problematic nosocomial pathogens.

Aminoglycosides

They are represented by tobramycin, netilmicin, amikacin and isepamicin for systemic use, neomycin for topical application and gentamicin for both. It should be pointed out that all aminoglycosides are inactive against streptococci as well as against anaerobes, while despite their in vitro activity, they do not behave as bactericidal agents against staphylococci. However, after combination in vitro with antistaphylococcal penicillins and/or rifampicin, they exhibit a synergistic result. Therefore, the dermatologist at least for the common streptococcal or staphylococcal infections should not prescribe any aminoglycoside either systemically or locally, as solutions or as ointments. Aminoglycosides are by definition ototoxic and nephrotoxic agents. Local application facilitates development of resistance among the Gram negatives and particularly in *P. aeruginosa* strains (which serve as colonizers and future pathogens) since the exposed skin area favours transfer of resistance genes. It should also he considered that various non-antimicrobial ointment ingredients are capable of inducing allergic skin reactions aggravating inflammatory signs.

Tetracyclines

The tetracyclines currently in use for systemic administration are the short-acting compound, tetracycline ($t_{½}$, 8–9 h) and the long-acting derivatives, doxycycline and minocycline ($t_{½}$, 16–18 h).

Tetracycline should be administered on an empty stomach to increase absorption, while doxycycline and minocycline are absorbed almost completely, achieving high serum levels with relatively small doses. Despite their broad spectrum of activity covering both Gram-positive and several Gram-negative aerobic and anaerobic species, acquired resistance has emerged both among *S. pyogenes* and among *S. aureus* strains. In particular, minocycline is the most effective against *S. aureus*, including both MRSA and CA-MRSA strains.

The long-acting tetracyclines are lipophilic, and they are diffused in many tissues and fluids. However, they all cross the placenta. They concentrate in fetal bone and teeth causing hypoplasia of the enamel with subsequent permanent grey-brown to yellow discoloration of the teeth and depression of skeletal growth in premature infants. Therefore, tetracyclines should not be given during pregnancy, at the breastfeeding period or to children up to the age of 8 years when tooth enamel is being formed. Tetracyclines may cause photosensitivity reactions, gastrointestinal tract disturbances and hepatotoxicity. Vertigo is a side effect unique to minocycline, usually beginning on the second or third day of therapy, and it is more frequently observed in women than in men.

Food in general decreases the absorption of tetracyclines, while all form inactive complexes with divalent or trivalent cations. Therefore, tetracyclines should not be given simultaneously with calcium, magnesium and aluminium in antacids, milk or iron-containing compounds. Also, they should not be prescribed in pre-existing renal or hepatic insufficiency.

Tetracycline is given at a dose of 500 mg every 6 h. Minocycline is given at a loading oral dose of 200 mg followed by a daily dose of 100 mg every 12 h and doxycycline at a dose of 100 mg every 12 h. Doxycycline or minocycline has been proposed by the 2011 Infectious Diseases Society of America (IDSA) guidelines as one of the options for empirical treatment of SSTIs caused by CA-MRSA in outpatients. In case coverage for both β-haemolytic streptococci and CA-MRSA is desirable, a combination with a β-lactam is recommended.

Tigecycline

Tigecycline is the first member of a new class of broad-spectrum antibiotics, the glycylcyclines. It

is a derivative of minocycline, designed to avoid both *tetK* (tetracycline-specific efflux-mediated) resistance and *tetM* (target modification) class resistance to tetracyclines. It inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit but with a five times higher affinity than that for the tetracyclines. Tigecycline exhibits a bacteriostatic activity. Its antimicrobial spectrum includes staphylococci (both methicillin-susceptible and methicillin-resistant isolates), streptococci, enterococci (both vancomycin-susceptible and vancomycin-resistant isolates) and multidrug-resistant Enterobacteriaceae (with the exception of *Proteus*, *Providencia* and *Morganella* spp.), *Acinetobacter* spp. as well as anaerobes. It is not active against *P. aeruginosa*. Tigecycline is administered at a loading dose of 100 mg i.v. the first day, followed by 50 mg every 12 h from the second day on. No dose adjustment is required in renal impairment and in moderate hepatic impairment, while a 50 % reduction of the daily dose is required in case of severe hepatic impairment.

Tigecycline has been approved for the treatment of cSSTI by susceptible pathogens. Monotherapy with tigecycline could be a choice when a broad-spectrum antimicrobial coverage is indicated (for polymicrobial or mixed infections) provided that *P. aeruginosa* is not among the causative bacteria. Tigecycline has not been approved for the treatment of diabetic foot infection. Clinicians should add an antipseudomonal agent to empirical regimens in patients with risk factors for pseudomonal infections. A concern is that tigecycline has not been evaluated in randomized trials for the treatment of severely ill patients. Observational non-randomized studies have shown a clinical success rate of around 80 % in critically ill patients with cSSTI. The data from the pivotal trial with tigecycline versus vancomycin-aztreonam in cSSTI revealed a non-significant difference in mortality of 0.7 %. The bacteriostatic action of the drug and the limitations of its PK/PD characteristics, mainly a low achievable Cmax, create concerns about its use in the case of bacteraemic and septic patients.

Tigecycline is in general well tolerated. Frequently observed side effects are of gastrointestinal origin (nausea, vomiting) but the most serious ones consist of a decrease in fibrinogen and a reversible coagulopathy and thrombocytopenia.

Macrolides and Clindamycin

The macrolides (erythromycin, roxithromycin, azithromycin and clarithromycin) and the lincosamides (lincomycin and clindamycin) although chemically unrelated, they have similar properties. Among the macrolides, clarithromycin possesses the most potent in vitro action against group A streptococci and methicillin-susceptible staphylococci (MSSA) strains followed by erythromycin, while azithromycin is two- to fourfold less active than erythromycin. However, cross-resistance among macrolides and lincosamides is usually the rule. It is a matter of concern that resistance rates of *S. pyogenes* to erythromycin have been increasing. MRSA strains are almost always resistant to macrolides. Lincomycin or clindamycin resistance has been reported in 20–85 % of MRSA strains including 50 % of erythromycin-resistant strains. Clindamycin resistance among erythromycin-resistant strains could be inducible, and it may be overlooked if the laboratory does not perform a special test, called 'D test'. However, cross-resistance of *S. aureus* between lincomycin and clindamycin is complete. Clindamycin activity against streptococci is more potent than lincomycin but similar to that of erythromycin.

With the exception of azithromycin, which is better absorbed without food, all others can be taken with food. Half-lives are 1.4 h for erythromycin, 3–7 h for clarithromycin, >70 h for azithromycin and >2.5 h for the lincosamides. Therefore, erythromycin should be administered at doses of 500 mg every 8 h orally or i.v., clarithromycin at 500 mg every 12 h orally or i.v., azithromycin at 500 mg every 24 h orally or i.v., lincomycin at 600 mg every 8 h i.v. or i.m. and clindamycin at 600 mg every 8 h i.v. or orally. With the exception of CSF, all have good tissue penetration, and all are selectively concentrated in the neutrophils and the macrophages. A dose

adjustment is required for erythromycin and clarithromycin in patients with renal impairment.

Macrolides in general are safe drugs. Their main adverse reactions concern the gastrointestinal tract, more with erythromycin and much less with clarithromycin and azithromycin. However, with lincosamides, diarrhoea occurs in up to 20 % of patients, while 1.9–10 % of clindamycin-treated patients will suffer from the complication of pseudomembranous colitis caused by toxin-producing *Clostridium difficile*.

Macrolides and lincosamides can be used as alternatives to penicillin, particularly in β-lactam allergic patients when streptococci and MSSA are the potential pathogens. However, macrolides should not be used alone in the treatment of deep-seated staphylococcal infections because of the fear for the emergence of resistance during therapy. Clindamycin has been proposed by the 2011 IDSA guidelines as one of the options for empirical treatment of SSTIs caused by CA-MRSA. It can be used as monotherapy when coverage for both CA-MRSA and β-haemolytic streptococci is needed. An advantage of clindamycin is that it suppresses toxin production in toxin-producing strains of *S. aureus* or streptococci, which could be responsible for serious complications in the setting of SSTIs (necrotizing fasciitis, toxic shock syndrome, etc.).

Quinolones

The fluoroquinolones are represented by norfloxacin, ciprofloxacin, ofloxacin, moxifloxacin, levofloxacin and prulifloxacin. They represent fluorine- and piperazinyl-substituted derivatives of the original nalidixic acid structure, which is a 1, 8-naphthyridine. They are characterized by a broad spectrum of activity and good tolerability. Most are available for oral and parenteral use and possess similar bioavailability for both routes. Despite their broad spectrum of activity, the above-mentioned fluoroquinolones (with the exception of moxifloxacin) are not active against streptococci, anaerobes and MSSA, while their activity against MRSA is considered as borderline. Therefore, there is no absolute indication for their use in common dermatological infections. However, whenever *P. aeruginosa* is implicated, ciprofloxacin is an option because it is the only orally available antimicrobial agent with antipseudomonal activity. Furthermore, norfloxacin and prulifloxacin have no indication for SSTIs.

Ciprofloxacin is administered at a dose of 500–750 mg every 12 h p.o. or 600 mg every 12 h i.v. A formulation of extended release (XR) is also available, and it is given at a dose of 500 or 1,000 mg every 24 h. Ofloxacin is administered at a dose of 400 mg every 12 h p.o. or i.v. and levofloxacin at 500–750 mg every 24 h p.o or i.v. A dose adjustment is needed for ciprofloxacin and levofloxacin in patients with renal impairment.

The most important but rare adverse effects of the above-mentioned quinolones include QTc interval prolongation, central nervous system (CNS) excitatory symptoms, glucose dysregulation, hepatotoxicity, hypersensitivity, phototoxicity, peripheral neuropathy and tendonitis. Also, quinolones have been associated with *C. difficile-associated* diarrhoea.

Moxifloxacin is a novel 8-methoxyfluoroqulnolone with an improved spectrum of activity, which includes Gram-positive, Gram-negative, aerobic and anaerobic bacteria as well as intracellular pathogens. As with other quinolones, moxifloxacin acts by binding to and inhibiting bacterial topoisomerases (i.e. topoisomerases II and IV), exhibiting a bactericidal effect. It is very active against streptococci, pneumococci, irrespective of β-lactam or macrolide resistance and against MSSA. It has a more variable activity against MRSA strains. It is also active against Enterobacteriaceae, but not against *P. aeruginosa*. Its spectrum also includes several species of anaerobes: *Clostridia*, *Fusobacteria*, *Prevotella*, *Porphyromonas*, *Peptostreptococci*, *Propionibacterium* and *B. fragilis*. Moxifloxacin has also good in vitro activity against pathogens isolated from patients with animal or human bite infections and the causes of more exotic cSSTIs, such as *Bacillus anthracis*, *Yersinia pestis*, *Vibrio* spp. and *Francisella tularensis*.

It is administered orally at a dose of 400 mg once daily. It has a favourable pharmacokinetic profile with advantageous tissue penetration at

skin and soft tissue sites. It is metabolized by conjugation to inactive metabolites, and it is excreted by both renal and hepatic routes, reducing the potential for drug accumulation in patients with renal or liver impairment.

The most common, adverse events are gastrointestinal disturbances. In contrast to some other fluoroquinolones, it appears to have a low propensity for photosensitivity and CNS toxicity. As it is not metabolized by the cytochrome P450 pathway, it shows no interactions with methylxanthines, ranitidine, oral anticoagulants or contraceptives. Its bioavailability is reduced by the co-administration of antacids, sucralfate or iron preparations, but not by food.

It is licensed for the indication of respiratory tract infections, as well as for the treatment of mixed aerobic and anaerobic SSTIs from susceptible pathogens. The IDSA guidelines recommend fluoroquinolones for the treatment of infections that are likely to be polymicrobial, including surgical wound infections involving the abdominal wall, perineum and genital tract as well as animal and human bite infections.

Rifampin

Primarily used for tuberculosis, rifampin has also very promising bactericidal activity against staphylococci, including a high percentage of MRSA strains. However, it should never be administered as a single agent, because staphylococci will rapidly develop resistance in vivo even after the first dose. To protect, against this, rifampin should be combined with another agent possessing antistaphylococcal activity, like trimethoprim-sulfamethoxazole, a fluoroquinolone, a glycopeptide or daptomycin. It should not be given empirically but only in cases where MRSA strains have been isolated and their susceptibility to rifampin has been confirmed. As an extremely lipophilic substance, rifampin penetrates well into all body tissues and stains brightly red almost all body excretions.

It is given in adults as a daily dose of 600 mg plus 300 mg orally or i.v. with an empty stomach (at least 1 h before meals). Rifampin may cause hepatotoxicity, while it is one of the most potent inducers of intestinal and hepatic microsomal enzymes leading to decreased serum $t_{½}$ for several compounds, among which are digoxin, dicumarol anticoagulants, prednisone, ketoconazole and oral contraceptives, requiring dosage adjustments for the latter drugs or therapeutic drug monitoring or even drug discontinuation.

Fusidic Acid

This antibiotic, despite its advantageous properties, is not available in the USA. It is mainly active in vitro and in vivo against staphylococci, including a high percentage of MRSA strains. Fusidic acid possesses excellent tissue kinetics and has a $t_{½}$ of 14 h. With the exception of self-limited hepatotoxicity, fusidic acid is safe and well tolerated by the oral route. The i.v. formulation should be given by slow infusion (3–4 h) to avoid chemical irritation of veins and subsequent thrombophlebitis. It is administered at a dose of 500 mg every 8 h orally or i.v. Topical use of fusidic acid in the form of gauzes or ointments should be avoided since it is rapidly followed by emergence of resistance in staphylococci colonizing the skin.

Trimethoprim/Sulfamethoxazole

The combination acts synergistically against Enterobacteriaceae and staphylococci since trimethoprim potentates the sulfonamide activity by the sequential inhibition of folic acid synthesis. It is given at a dose of 980 mg every 8–12 h p.o or i.v., with a dose adjustment in case of renal impairment. The most important side effects are attributed to the sulfonamide component and include acute haemolysis related to glucose-6-phosphate dehydrogenase deficiency, haematologic toxicity (leukopenia, thrombocytopenia or pancytopenia), hypersensitivity reactions and erythema multiforme often expressed as Stevens-Johnson syndrome. The combination has bactericidal activity against staphylococci. It has proven to be in vitro active against 95–100 % of CA-MRSA strains, and although clinical studies for its efficacy in the treatment of staphylococcal

infections are limited, the 2011 IDSA guidelines recommend it as one of the options for empirical treatment of SSTIs caused by CA-MRSA in outpatients. The good tissue penetration, the availability of oral formulation and the low cost make trimethoprim/sulfamethoxazole an attractive alternative to newer more expensive drugs or drugs that require intravenous administration. Nevertheless, it should be avoided as monotherapy in cellulitis because it has poor activity versus *S. pyogenes*.

Glycopeptides

This group is represented by vancomycin and teicoplanin. They bind with high affinity to the D-Ala-D-Ala C-terminus of late peptidoglycan precursors and prevent reactions of cell-wall synthesis in Gram-positive bacteria. Glycopeptides are active against staphylococci, including methicillin-resistant strains, streptococci, enterococci, *Corynebacterium* spp. and *B. anthracis*. They are also active against Gram-positive anaerobes including *Clostridium* spp. However, some *S. haemolyticus* and *S. epidermidis* strains are resistant.

Vancomycin is administered i.v. at a dose of 15–20 mg/kg/dose every 8–12 h. Therapeutic drug monitoring is recommended, and trough levels should not be lower than 15 mg/L for a successful clinical outcome. Teicoplanin has an extremely prolonged $t_{½}$ (30–180 h); therefore, it is given both i.v and i.m. at a dose of 8–10 mg/kg twice daily for the first day and once daily afterwards.

For decades, vancomycin has been the standard therapy for patients with serious infections due to MRSA. In addition, vancomycin is the antibiotic most extensively studied in clinical trials involving patients with SSTIs, and it is recommended by the 2011 IDSA guidelines as one of the treatment options for patients with cSSTIs due to MRSA. However, its efficacy has come into question, with concerns over its slow bactericidal activity, the emergence of resistant or hetero-resistant strains and the MIC 'creep' among susceptible strains. The rate of treatment failure is high in infections caused by MRSA with MIC >1 mg/L. In this case and particularly for severe infections, antistaphylococcal agents other than the glycopeptides are recommended. Vancomycin kills staphylococci more slowly than do β-lactams in vitro and is clearly inferior to β-lactams for methicillin-sensitive *S. aureus* infections. Only in cases of serious allergy to β-lactams could the glycopeptides replace them for MSSA infections.

Rapid or bolus administration of vancomycin can cause flushing and hypotension, the so-called 'red-man' or 'red-neck' syndrome, which is not an allergic reaction. Therefore, vancomycin should always be given over a 30–60 min infusion. Vancomycin is also ototoxic and potentially nephrotoxic particularly when combined with aminoglycosides or diuretics, while drug fever is the most frequent side effect. Teicoplanin is well tolerated; it does not require slow infusion, but ototoxicity, nephrotoxicity (microscopic haematuria), thrombocytopenia and drug fever may be encountered. Allergic cross-reactions are not anticipated between the two agents.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that disrupts cell membrane function via calcium-dependent binding, resulting in rapid bactericidal activity in a concentration-dependent fashion. It is active against Gram-positive cocci and Gram-positive bacteria including MRSA as well as staphylococci with reduced susceptibility to the glycopeptides.

Daptomycin is administered intravenously at the dose of at least 6 mg/kg/dose once daily, which could be safely increased to 8–10 mg/kg/dose once daily in patients with serious infections such as bacteraemia or infective endocarditis. No dose adjustment is needed for patients with a mild renal insufficiency, whereas for patients with a CL_{CR} of <30 ml/min including patients in haemodialysis, administration of the same dose every 48 h is recommended.

It is approved for the treatment of *S. aureus* bacteraemia, right-sided infective endocarditis and cSSTI. It should not be used for the treatment of pneumonia, because its activity is inhibited by

pulmonary surfactant. Consequently, daptomycin is one of the preferred treatment options in patients with cSSTI caused by MRSA and a high risk or evidence for bacteraemia. Furthermore, the once-daily regimen and the advantageous safety profile make daptomycin an attractive option for outpatient treatment in cases where no appropriate oral regimen is available. The IDSA guidelines for the treatment of MRSA infections published in January 2011 recommended daptomycin as one of the first-line options (AI) for the empirical therapy of cSSTI and of bacteraemia with or without endocarditis of any site in hospitalized patients.

In phase III clinical trials for the efficacy of daptomycin for the treatment of cSSTIs, the percentage of patients with a successful outcome (clinical cure or improvement) only after 4–7 days was significantly higher in the daptomycin group than in the vancomycin group. In a prospective open-label study of patients treated for the same indication, those receiving daptomycin had a significantly shorter duration of i.v. antibiotic therapy and a shorter median length of antibiotic-related hospital stay than those treated with vancomycin.

The most serious side effects consist of creatinine phosphokinase (CPK) elevations with or without symptoms. Patients should be observed for development of muscle pain or weakness and have weekly CPK levels determined, with more frequent monitoring in those with renal insufficiency or who are receiving concomitant statin therapy. Nevertheless, this is rarely treatment limiting. Treatment discontinuation is required in case of symptomatic myopathy with an increase >5 times ULN or 1,000 units/L or in asymptomatic patients with a CPK ≥10 times ULN. Also, case reports of daptomycin-induced eosinophilic pneumonia have been described.

It should be noted that non-susceptible isolates have emerged during therapy in clinical trials, leading to treatment failure. Prior exposure to vancomycin and elevated vancomycin MICs have been associated with increases in daptomycin MICs, but analysis of data from the Cubicin® Outcomes Registry and Experience (CORE) retrospective observational study showed that daptomycin treatment for a variety of staphylococcal infections was associated with similar outcomes, regardless of the level of vancomycin MIC and multivariate logistic regression failed to identify vancomycin MIC as a predictor of daptomycin failure.

Mupirocin

Mupirocin is a locally applied agent, which is bactericidal against streptococci and staphylococci both MSSA and MRSA at concentrations achieved by topical administration (20,000 mg/mL with the 2 % formulation) after 24–36 h exposure. It was formerly called pseudomonic acid because the major metabolite responsible for most of its antibacterial activity is derived from the submerged fermentation by *Pseudomonas fluorescens*. Despite its name, it is not active against *Pseudomonas* spp. Its weak in vitro activity against normal skin flora, e.g. *Corynebacterium*, *Propionibacterium* and *Micrococcus* spp., is advantageous because it preserves the skin's natural defence against infection. Unfortunately, prolonged courses of mupirocin for chronic skin infections can lead to development of resistant staphylococci. Therefore, mupirocin should not be used for long-term therapy.

Mupirocin is used for localized impetigo and folliculitis with clinical and bacteriological cure rates of 85–100 % and 80–95 %, respectively, and it is recommended for this indication by the 2005 IDSA guidelines for the management of SSTIs. However, in cases of widespread impetigo, systemic therapy is preferable. It is also effective in the therapy of secondarily infected eczema, lacerations, burns and leg ulcers. Mupirocin can also eliminate nasal carriage of *S. aureus*. No substantial toxicity in humans has been reported.

Synercid

Synercid is a combination of two semisynthetic streptogramin molecules, quinupristin (a group B or type I streptogramin) and dalfopristin

(a group A or type II streptogramin) in a 30:70 ratio (w/w). The combination has synergistic antibacterial activity in vitro against a wide range of Gram-positive organisms, including methicillin- resistant and glycopeptide-intermediate strains of staphylococci (GISA), penicillin and macrolide-resistant strains of streptococci and multidrug-resistant and vancomycin-resistant strains *of E. faecium*, while it is intrinsically inactive against *E. faecalis*. It is also active against *S. pneumoniae*, *M. catarrhalis*, pathogenic *Neisseria* spp. and Gram-positive anaerobes such as *Clostridium* and *Peptostreptococcus* spp. Synercid exerts its activity through inhibition of protein synthesis. It is bactericidal against staphylococci and pneumococci and bacteriostatic against enterococci. The recommended dose is 7.5 mg/kg every 8 h or every 12 h for SSTIs, infused over 60 min. A dose reduction is required for patients with hepatic cirrhosis or severe renal insufficiency. The drug combination is a potent inhibitor of the cytochrome P450 enzymes, exhibiting clinically important interactions with many other drugs such as antihistamines, antiretroviral agents, antineoplastic agents, benzodiazepines, calcium channel blockers, cholesterol-lowering agents, gastrointestinal motility agents, immunosuppressive agents and steroids, as Synercid enhances their activity.

It is approved for the treatment of cSSTIs and as a salvage therapy for invasive *E. faecium* and MRSA infections in the setting of vancomycin treatment failure. The most common adverse effects are arthralgia, myalgia, gastrointestinal disturbances, rash, headache, generalized pain and pruritus and increased conjugated bilirubinaemia. Peripheral venous irritation is common and can be minimized by infusion via a central venous route.

Linezolid

Linezolid is the first member of the oxazolidinone class of synthetic antibacterial agents to be introduced into clinical practice. It has a unique mechanism of action: it inhibits protein synthesis by interfering with initiation complex formation. Cross-resistance with other inhibitors of protein synthesis (i.e. macrolides, streptogramins, aminoglycosides, fusidic acid, tetracyclines, chloramphenicol) has not been observed since the oxazolidinones act early in translation, inhibiting this process at a different stage.

Linezolid inhibits most Gram-positive organisms such as staphylococci, including methicillin-resistant, glycopeptide-intermediate (GISA) or glycopeptides-resistant (GRSA) strains; *Streptococcus* spp. including macrolide-resistant strains; *E. faecium* and *E. faecalis*, including vancomycin-resistant strains; pneumococci including penicillin-resistant strains; *Bacillus* spp.; *Corynebacterium* spp.; and *Erysipelothrix* spp. Anaerobes such as *Clostridium* spp., *Propionibacterium acnes*, *Bacteroides* spp. and *Fusobacterium* spp. are also susceptible to linezolid, whereas Enterobacteriaceae and *P. aeruginosa* are not. It has bacteriostatic activity against staphylococci and enterococci.

Linezolid is available for both oral and i.v. administrations at the same dose of 600 mg every 12 h. It is rapidly and completely absorbed after oral administration with a bioavailability of approximately 100 %, not influenced by the presence of food. It has an elimination $t½$ of 5–7 h and is excreted by both renal and non-renal routes. No dose adjustment is required for renal or liver impairment.

Linezolid is approved for adults and children for the treatment of SSTI and nosocomial pneumonia due to MRSA. It has been demonstrated to be superior to vancomycin for the treatment of cSSTI caused by MRSA on the basis of a phase IV clinical trial. For serious SSTI, such as necrotizing fasciitis or infections by CA-MRSA producing Panton-Valentine Leucocidin, linezolid may be particularly useful because of its ability to impair toxin production.

Long-term linezolid use (>14 days) is limited by haematologic toxicity (thrombocytopenia occurring more frequently than anaemia and neutropenia), peripheral and optic neuropathy (with vision loss) and lactic acidosis. Although myelosuppression and optic neuropathy are generally reversible, peripheral neuropathy is not always reversible. Linezolid is a weak, nonselective,

reversible inhibitor of monoamine oxidase and has been associated with serotonin syndrome in patients taking concurrent selective serotonin receptor inhibitors (SSRIs). For this reason, treatment with SSRIs should be discontinued during therapy with linezolid.

Linezolid offers the possibility of early switch to oral therapy and, consequently, early discharge, which may be of possible economic advantage, particularly in the field of cSSTI.

Telavancin

Telavancin is a lipoglycopeptide derivative of vancomycin. It has a dual mechanism of action; it is a potent inhibitor of peptidoglycan synthesis, with a tenfold greater activity than vancomycin but also triggers rapid concentration-dependent dissipation of cell membrane potential, which results in membrane pores and leakage of cytoplasmic adenosine triphosphate and potassium ions. This second mode of action is specific for bacterial membranes and appears to contribute to the more rapid bactericidal activity of telavancin, compared with vancomycin.

Telavancin is consistently active against *S. aureus*, including methicillin-resistant, vancomycin-intermediate, linezolid-resistant and daptomycin-non-susceptible strains, against coagulase-negative staphylococci, streptococci, vancomycin-susceptible enterococci as well as *Clostridium* spp.

The drug is usually administered intravenously at 10 mg/kg every 24 h. It is excreted by the kidneys, and thus, dosage adjustments are required in cases of renal failure. Clinical trials have demonstrated non-inferiority, compared with vancomycin, in the treatment of cSSTIs and pneumonia, but it is currently approved by the FDA for the treatment of cSSTIs only. The IDSA guidelines for the treatment of MRSA infections published in January 2011 recommended telavancin as one of the first-line options (AI) for the empirical therapy of cSSTI in hospitalized patients. Telavancin is associated with higher rates of nephrotoxicity, altered taste, nausea and vomiting but lesser rates of pruritus and infusion-related events, compared with vancomycin. Telavancin might be an alternative to vancomycin in cases of difficult-to-treat MRSA infections. The potent antistaphylococcal activity of telavancin should be weighed against the potential for nephrotoxicity.

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Antifungal Drugs

132

Roderick J. Hay

Key Points

- A wide number of antifungal drugs is currently used for the treatment of skin and mucosal diseases. They can be grouped into two large families and a number of smaller ones.
- Most of them are available as either topical or systemic treatments.
- The largest family of antifungals is the azole family, a group of synthetic antimicrobials that can be further subdivided into imidazoles and triazoles. There is another family of polyene antifungals that have a large macrolide ring structure. Other important antifungal agents include the allylamine and the morpholine groups as well as griseofulvin, flucytosine and ciclopirox. The echinocandins a most recently introduced group are largely used to treat systemic infections.
- The availability of these drugs for medical use varies between different countries.

General Principles, Classification and Structure

The antifungal drugs currently used for the treatment of skin and mucosal diseases can be grouped into two large families and a number of smaller ones. Most of the antifungal drugs are broad spectrum in their antifungal activity in vitro and inhibit a wide variety of different fungi that cause superficial fungal disease. Many are available as either topical or systemic treatments. In vitro some behave as cidal compounds; in other words, the concentration at which they inhibit growth, the minimum inhibitory concentration (MIC), is the same or very close to the concentration at which they destroy the fungi, the minimum cidal concentration (MCC). In theory, this property is an advantage, as it should mean that fungal cell death depends on drug concentration alone, although in real infections other factors such as local availability and in vivo structural adaptations play a key role in determining the outcome of treatment.

The largest family of antifungals is the azole family, a group of synthetic antimicrobials that can be further subdivided into two distinct subdivisions, the imidazoles and the triazoles. The chemical structure of both is based on an azole ring with different side chains that affect the solubility, antifungal activity and antimicrobial resistance properties of each compound. There is another family of polyene antifungals that have a large macrolide ring structure. In distinction to

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_132, © Springer-Verlag Berlin Heidelberg 2015

the azoles, the polyenes are derived from *Streptomyces* species, and although a large number of different polyene derivatives are known, there are few in clinical use.

Other important antifungal agents include the allylamine and the morpholine groups as well as griseofulvin, flucytosine and ciclopirox. The echinocandins a most recently introduced group are largely used to treat systemic infections. The availability of these drugs for medical use varies between different countries.

Azole Antifungals

Mechanism of Action

There are two distinct groups of compounds within the azole family, the imidazoles and the triazoles. The imidazoles are synthetic antifungal agents. They include miconazole, clotrimazole, econazole, isoconazole, ketoconazole, tioconazole and bifonazole. The triazole series contains two potent oral agents, fluconazole and itraconazole. Two other triazoles, voriconazole and posaconazole, are mainly used for the treatment or prevention of systemic fungal infections (Table 132.1).

Many azoles have been developed for topical use although some, particularly the triazoles, are effective in the treatment of widespread or deeply seated infection, for instance, ketoconazole (oral), itraconazole (oral and intravenous), fluconazole (oral and intravenous), posaconazole (oral) and voriconazole (oral and intravenous). The azoles are metabolised in the liver and affect fungal cell-membrane synthesis through inhibition of cytochrome P450-dependent 14β demethylation which is responsible for a key stage in the synthesis of ergosterol in the cell membrane. To some extent azoles all show some affinity for certain human cytochrome P450 isoenzymes, a property which may lead to drug interactions or competition with human metabolic processes. There is, however, considerable variation amongst the different drugs in this respect. Apart from fluconazole and voriconazole, most azoles penetrate cerebrospinal fluid and urine in low concentrations. The azoles have a broad spectrum of activity against many fungal pathogens, although fluconazole, miconazole and ketoconazole are not effective for *Aspergillus* infections. By contrast, itraconazole and voriconazole are active in vitro against a very wide variety of mould fungi including aspergilli as well as dematiaceous (pigmented) fungi. Fluconazole is less active against mould fungi, and there are instances of both primary (*C. krusei*, *C. glabrata*) and secondary (*C. albicans*) antimicrobial resistance to this compound. However, all the azoles can be used for treatment of the common superficial mycoses such as dermatophytosis, candidosis and *Malassezia* infections.

Table 132.1 Azole antifungals (only the more commonly used compounds have been shown)

Class	Oral	Topical
Imidazole	Ketoconazole	Clotrimazole, miconazole, econazole, sulconazole, bifonazole, ketoconazole, tioconazole
Triazole	Itraconazole	Terconazole
	Fluconazole	

Indications and Other Uses

Topical Azoles

Many of the imidazole antifungals are available as topical agents for the treatment of superficial mycoses such as dermatophytosis and pityriasis versicolor. Some Gram-positive bacterial infections such as erythrasma caused by *Corynebacterium minutissimum* as well as *S. aureus* may respond to many imidazoles but not triazoles. Although topical imidazole creams, ointments or powders are usually given twice daily, there is evidence that some, e.g. sulconazole, can be given once daily; it is possible that this is an appropriate regimen for many azoles, but unfortunately there is no clinical trial data to support a wider recommendation at present.

The duration of treatment using topical azoles is also variable. Most of the original clinical trials were based on a 4-week treatment duration, and

their efficacy is established on this basis. However, some topically applied compounds, such as ketoconazole, appear to be effective after shorter periods of treatment; again it is not clear whether these shorter treatment regimens would also be appropriate for other topical azoles.

Ketoconazole

Ketoconazole is an imidazole antifungal available as topical therapy or as an oral tablet (200 mg). It is active against most superficial fungi including dermatophytosis *Malassezia* infections and candidosis but not against Gram-positive bacteria, a property of most other topically active imidazole antifungals. Ketoconazole is used in doses of 200–400 mg daily. However, it is seldom prescribed, in long courses, due to a risk of symptomatic hepatic reactions in some patients. There is also a shampoo formulation of ketoconazole used for the treatment of seborrhoeic dermatitis of the scalp or the management of the carrier state in tinea capitis.

Drug resistance of yeast species to ketoconazole can occur (see below).

Itraconazole

Itraconazole is an orally active triazole. Its mode of action, as with all azoles, is through the inhibition of the formation of ergosterol in the fungal cell membrane via inhibition of the 14β-demethylase enzyme. Itraconazole is fungistatic in vitro but is active against a wide range of organisms including dermatophytes, moulds such as aspergilli and dimorphic fungi such as *Histoplasma* and *Penicillium marneffei*; it is also active against yeasts including *Candida albicans*. Most countries do not have a product licence for the use of itraconazole in children. Itraconazole comes in two main formulations: a capsule containing pelleted itraconazole and an oral solution containing itraconazole in cyclodextrin. A new formulation (SubaCap) with better absorption has been approved for use, but it is not currently marketed. The oral solution is designed for the treatment of severe oropharyngeal and oesophageal candidosis in severely immunocompromised patients.

Itraconazole is also effective in dermatophyte infections. The daily doses in adults are 200 mg daily for 1–2 weeks for tinea corporis but 200 mg twice daily given each day for 1 week every month for 2–3 months in onychomycosis. This approach to treatment is known as pulse(d) therapy (De Doncker et al. 1999). Doses of 200 mg twice daily for 1 week are appropriate for dry-type tinea pedis. For tinea capitis in children, itraconazole is generally given in 3–4 mg/kg daily doses. The regimens used vary between 3 and 5 mg/kg daily for 4–6 weeks which is effective in over 80 % of children with tinea capitis due to *T. tonsurans*. A pulsed regimen using 5 mg/kg for 1 week every 3 weeks has been evaluated in a small number of children. There is no ideal therapeutic formulation for children at present.

The use of itraconazole extends to superficial candidosis, particularly to proven cases of *Candida* onychomycosis and oropharyngeal candidosis. Like ketoconazole, it is mainly used at higher dosage in AIDS patients (e.g. 200 mg daily), but the oral solution formulation can be given at 100–200 mg daily in such patients. *Malassezia* infections including pityriasis versicolor and *Malassezia* folliculitis respond to itraconazole, which is also used in severe cases of seborrhoeic dermatitis.

Itraconazole is useful in some deep mycoses such as sporotrichosis, chromoblastomycosis and subcutaneous zygomycosis. It is used as primary or secondary treatment in histoplasmosis, paracoccidioidomycosis and blastomycosis and also coccidioidomycosis and infections due to *Penicillium marneffei*. In HIV/AIDS patients, suppressive therapy in histoplasmosis and *Penicillium* infections after initial treatment is used in many countries for several months until there is evidence of cure and/or restoration of CD4 counts to prevent recurrence of infection.

Drug resistance to itraconazole is not common, but some fungi develop multiple resistance to azoles (Vanden Bossche et al. 1998) (see below).

Fluconazole

Fluconazole is an orally active triazole antifungal. As with other triazoles, the main site of action is through the inhibition of the 14α-demethylase enzyme. There are both oral

and liquid formulations of fluconazole as well as an intravenous form for deep infections.

The drug is active against a range of fungi including yeasts such as *Candida albicans* and *Cryptococcus neoformans*, as well as some mould fungi including dermatophytes. It is less active in other mould infections such as aspergillosis and zygomycosis.

Fluconazole is effective in superficial candidosis, including oropharyngeal candidosis, and dermatophytosis in doses of 100–200 mg daily. In practice, it is often given as a 150 mg weekly treatment for 2–8 weeks in tinea corporis. In onychomycosis, it is given in weekly doses of 150–300 mg and the duration monitored by clinical and mycological recovery. Fluconazole is effective against a range of different dermatophytes including both *Trichophyton* and *Microsporum* species. It has been used in tinea capitis in doses ranging from 1.5 to 6 mg/kg daily up to 8 mg/kg weekly (Scher et al. 1998).

Fluconazole is very active against *Candida* species apart from *Candida krusei* and *Candida glabrata*. However, there is a risk of resistance developing if the drug is continued in the presence of persisting infection. Resistance to fluconazole is now seen mainly in chronic vaginal infections where *C. glabrata* has become more common and in some oropharyngeal *Candida albicans* infections in AIDS patients. There are at least four different mechanisms for drug resistance including increased efflux from the fungal cell, changes in the site of action of the drug, decreased binding at the active site and the existence of supplementary paths of ergosterol biosynthesis. Drug resistance to ketoconazole and to a lesser extent itraconazole may also occur. There is no evidence that resistance may also occur among dermatophytes. Fluconazole is used for oropharyngeal candidosis and can be given at the same dosage (50–200 mg daily) to all patients. It is active against vaginal candidosis where a single oral treatment of 150 mg is given.

Fluconazole is also widely used for systemic candidosis as either oral or intravenous therapy and in the primary or secondary treatment of cryptococcosis at higher doses, e.g. 400–600 mg daily.

Newer Azoles

Neither voriconazole nor posaconazole is much used in superficial infections as their main targets are internal or systemic mycoses. Posaconazole has been found to be effective in onychomycosis and both drugs in oropharyngeal candidosis. Their high cost is at present likely to limit their use for fungal diseases seen in dermatology. Other new azoles such as albaconazole and pramiconazole of potential value in onychomycosis have not been developed to marketing.

Side Effects, Contraindications and Drug Interactions

Most of the topical azoles can occasionally cause mild stinging and, exceptionally, allergic contact dermatitis. Oral azoles have a low frequency of adverse reactions such as nausea, dyspepsia and gastrointestinal discomfort or headache. The frequency of severe adverse events is low. However, these are important to note. Ketoconazole causes hepatitis in a small proportion of cases estimated to be approximately 1:7,000. The risk factors for this are not well understood, although patients with a previous history of liver disease may be at risk. For this reason, the drug is rarely used long term for, for instance, the management of fungal nail disease. Ketoconazole may also cause gynaecomastia in males and menstrual irregularities in women when used in doses over 400 mg daily, problems associated with interferences with androgen metabolism. With itraconazole and fluconazole, the incidence of symptomatic hepatitis is much lower; in the case of itraconazole, for instance, less than 1:100,000 cases. With fluconazole, it is more difficult to estimate the frequency of adverse reactions as the cohort of patients treated with this drug has been different and includes many with severe systemic disease; attributing hepatic dysfunction in such cases to a single cause is correspondingly difficult. Exceptionally rare adverse events include angioedema (itraconazole), thrombocytopenia (fluconazole) and toxic epidermal necrolysis (fluconazole). Voriconazole has been associated with hepatotoxicity, transient visual disturbances

Table 132.2 Main drug interactions and oral antifungals

Drug name	Interaction
Terbinafine	Terbinafine serum levels reduced by *rifampicin*
	Terbinafine increases levels of *nortriptyline*, *warfarin*
Itraconazole, *fluconazole*, *ketoconazole*	Azole serum levels may be reduced by *rifampicin*, *rifabutin*, *phenytoin*, *phenobarbitone*, *carbamazepine*
The breadth of the data provided depends on reports of clinical interactions. These vary between the different drugs and between patients	Azoles may increase levels of: *terfenadine*, *astemizole*, *digoxin*, *cyclosporin*, *tacrolimus*, *midazolam*, *triazolam*, *warfarin*, *loratadine and tolbutamide*. This varies between drugs and is more prominent with itraconazole
	Azoles may also reduce serum levels of some drugs such as *oestrogens*, *cisapride* (mainly itraconazole), *busulfan*
	Itraconazole interacts with statins such as *lovastatin* and *simvastatin* to cause rhabdomyolysis
Griseofulvin	Griseofulvin serum levels reduced by *phenytoin*, *phenobarbitone*
	Griseofulvin may reduce levels of *oestrogens* and *warfarin*

Many of these drug reactions depend on interactions between drugs and cytochrome P450 isoenzymes such as P3A4. Unfortunately, these are not necessarily either predictive of the likelihood of reaction nor can they always explain the mechanisms of drug interaction. Those listed here are the commonly reported or potentially dangerous reactions. Theoretically terbinafine can interact with P2D6, but only one report of a reaction with nortriptyline is associated with this mechanism

and photosensitivity. It is also known to cause rapid onset non-melanoma skin cancers in patients on chronic treatment, e.g. after bone marrow grafting.

There is an important list of drug interactions with the azoles that should be remembered. As a general principle, itraconazole is more likely to be associated with drug interactions, but those that may cause serious consequences, e.g. terfenadine, astemizole and digoxin, are seen with all azoles. In addition, statins, e.g. somatostatin, appear to interact with itraconazole to cause rhabdomyolysis.

Table 132.3 Drug combinations that are contraindicated with the azoles – ketoconazole, itraconazole and fluconazole

Terfenadine, *astemizole*, *azolam compounds*, *cisapride* (*particular caution with digoxin*)
In addition, statins such as lovastatin should not be given with itraconazole

These interactions and those of other oral antifungals are summarised in Table 132.2. Contraindications of the use of azoles are shown in Table 132.3.

Polyene Antifungals

Mechanism of Action

The polyenes antifungals have been known for longer than the azoles. They are macrolide substances derived originally from *Streptomyces* species. Although comprising a large family, only three polyenes, amphotericin B, nystatin and natamycin, are in current use for treatment. More recent experimental additions to this group were partricin and mepartricin, but neither has been developed further. Amphotericin B, which is derived from *S. nodosus*, is the only polyene widely used as a parenterally administered drug; it is also available as an oral tablet or pastille. Nystatin and natamycin are purely topical, either creams, pastilles, suspensions or, in the case of nystatin, as a vaginal tablet, although vaginal preparations are difficult to obtain in some countries. Amphotericin B is metabolised in the liver and penetrates body cavities, cerebrospinal fluid and urine poorly. The polyenes have a broad in vitro spectrum of activity against a wide range of fungi including the major systemic pathogenic fungi such as *Aspergillus* and *Candida* species. Amphotericin B is widely used for the treatment of deep mycoses. The mode of action of the polyenes appears to involve inhibition of sterol synthesis in the fungal cell membrane. Polyenes function, though, by binding onto the sterol membrane and causing cell leakage.

Combinations of amphotericin B with a lipid, for instance, in a liposome, have been developed as a means of reducing the nephrotoxicity of the intravenous drug. The main commercial "lipid-associated amphotericins" are AmBisome (a true liposome), amphotericin B lipid complex (ABLC) or Abelcet (a ribbon-like lipid binding amphotericin B). It does not appear that these combinations have different modes of action, but in the case of AmBisome, there is evidence that the active drug, i.e. amphotericin B, is directly transferred from the lipid droplet to the fungal cell membrane. These formulations are comparatively expensive and are not used for superficial infections.

Indications and Other Uses

The polyene antifungal, amphotericin B, is widely used as a systemic agent for the treatment of systemic mycoses such as aspergillosis and candidosis. The newer lipid-associated amphotericins are used for similar indications including the treatment of the febrile neutropenic patient.

Amphotericin B is also used in the topical treatment of oropharyngeal candidosis as a lozenge; this treatment is not available in certain countries. It is given four times daily for 7–19 days.

Nystatin likewise is used for topical treatment generally for oral candidosis in lozenge or suspension form or as a vaginal tablet, where available, for vulvovaginal candidosis. It is also available as an ointment for skin disease. It is used twice daily for at least 14 days for these indications.

Natamycin is not used for the treatment of skin disease.

Side Effects, Contraindications and Drug Interactions

It is beyond the scope of this article to discuss the side effects of intravenous amphotericin B although it is recognised that the use of this drug is associated with a high frequency of side effects such as potassium loss, renal failure and renal tubular necrosis as well as anaemia. By contrast, the use of the topical preparations, either on the skin or orally, is seldom associated with any problems apart from the bitter taste of some of the oral preparations.

Allylamine Antifungals

Mechanism of Action

The allylamine drugs comprise a smaller group of compounds. There are two related compounds naftifine and terbinafine. There is also a related compound, the benzylamine, butenafine, which is available in some countries. These drugs inhibit squalene epoxidase which is active in the early part of the pathway for the biosynthesis of ergosterol in the fungal cell membrane. They are fungicidal compounds. The antifungal activity appears to depend on two events – the accumulation of squalene, which disrupts intracellular membranes, and the depletion of ergosterol in the membrane. Cidal activity resides mainly with the former property. The allylamines are available as topical agents (naftifine, terbinafine), but terbinafine is also an oral drug. Terbinafine has a very high level of in vitro activity against a number of different fungi such as dermatophytes where minimum inhibitory concentrations (MICs) lie between 0.01 and 0.001 μg/ml. The minimum fungicidal concentrations (MFCs) are usually at the same or within a single dilution of these MICs which explains the high fungicidal activity in vitro. Terbinafine is also very active against some mould fungi such as aspergilli, dimorphic pathogens, e.g. *Sporothrix schenckii*, and pigmented fungi. It is somewhat less active against yeasts such as *Candida* species and is only fungistatic against *C. albicans*. Terbinafine is lipophilic and well absorbed (70 %) after oral administration. After oral administration, it has a large peripheral volume of distribution and is bound in tissue rich in lipid or keratin. This provides a great advantage for dermatophytosis but less for yeast infections such as those caused by *Malassezia* species where terbinafine is active clinically after topical administration but not after oral treatment.

Indications and Other Uses

Terbinafine is mainly used against all dermatophyte infections, and it also has activity against a range of infections due to mould fungi including some superficial *Aspergillus* infections, chromoblastomycosis and sporotrichosis; it is less effective against yeasts such as *Candida albicans* although it can be used topically to treat superficial candidosis. Terbinafine is available as a cream or in tablet form (250 mg). The topical preparation can be used for the treatment of dermatophytosis such as interdigital tinea pedis, superficial candidosis of the skin and pityriasis versicolor. It is clear that treatment periods may be very short, and there is a single application film forming topical treatment for tinea pedis.

Oral treatment is mainly aimed at dermatophyte infections including onychomycosis due to dermatophytes. The oral compound is not clinically effective at normal doses in superficial *Candida* or *Malassezia* infections. The dose is 250 mg for adults. In some countries, a paediatric tablet is available (125 mg). In children, the regimen used is based on weight: <20 kg 62.5 mg/day, 20–40 kg 125 mg/day and >40 kg 250 mg/day. The responses of dermatophyte infections to oral terbinafine are excellent. In most tinea infections, the duration of oral treatment is 1–2 weeks. In onychomycosis, the drug is given for 6 weeks for fingernail infections and 12 weeks for toenails (Evans and Sigurgeirsson 1999). The results are good with remission rates of 70–80 % being achieved even after long-term follow-up of over 1 year (De Cuyper and Hindryckx 1999). There has been some work carried out on reducing drug exposure by using a pulsed course of treatment with 1 month on terbinafine, 1 month off and then a second month on with good results. In tinea capitis, it is effective against a range of organisms, and there are a number of studies comparing terbinafine with griseofulvin. However, there are several points to note. The treatment period is usually 4 weeks – although there are some data to show that shorter periods of treatment may be effective, e.g. 2 weeks for infections due to *Trichophyton* species. The responses of *Microsporum* species causing scalp disease are generally slower than those of *Trichophyton*, and in some patients, there is treatment failure; often a doubling of the normal dose is advised. A new granule form terbinafine has been assessed in scalp disease and has also been shown to be effective, again with the best responses in *Trichophyton* infections (Gupta et al. 2009). Terbinafine is also used in some deep infections notably sporotrichosis and chromoblastomycosis in doses of 250 mg daily.

Naftifine is a related allylamine similar to terbinafine but only available for topical usage in some countries. It is effective is dermatophytosis and other superficial mycoses. It has a similar spectrum and mode of action as terbinafine and is given for 1–2 weeks.

Side Effects, Contraindications and Drug Interactions

Terbinafine is associated with a low level of adverse effects after topical use – occasional reports of irritation. After oral treatment a variety of minor problems may occur such as nausea and dyspepsia. More serious events are occasionally seen. For instance, alteration of taste or even loss of taste may occur. It is expected to return to normal after 4 weeks. Rare instances of hepatic dysfunction presenting with jaundice have been reported. Other very rare drug side effects such as erythema multiforme, including major forms, have also been reported. Drug interactions are shown in Table 132.2; they are not common.

Griseofulvin

Mechanism of Action

Griseofulvin is an orally active compound derived from the organism, *Penicillium griseofulvin*. It is fungistatic in vitro, and its mode of action is through the inhibition of intracellular microtubules. This prevents the formation of the mitotic spindle. Griseofulvin is active in vitro against dermatophyte fungi, but few other organisms respond to the drug. In addition to its antifungal properties, it inhibits leucocyte movement.

Indications and Other Uses

The traditional treatment for many dermatophyte infections was oral griseofulvin given in a dose of 500–1,000 mg daily (adults) or 10 mg/kg daily for a period of 4–8 weeks for superficial infections apart from nail disease and for 6–18 months for onychomycosis. The drug is ineffective in *Candida* or *Malassezia* infections, and it cannot be given by topical route. There are both tablet and, in some countries, liquid formulations of griseofulvin. Griseofulvin appears slower in action than the newer azole and allylamine antifungals and, in most instances, has been superseded by the newer compounds such as itraconazole or terbinafine. However, it is effective for most organisms causing tinea capitis, although there are some patients with *M. canis* infections who require longer courses of treatment, e.g. 12 weeks. Since the earliest clinical studies, patients with *T. tonsurans* infections have been reported to have a variable response to griseofulvin, and, again, the duration of therapy may have to be increased. In some countries, griseofulvin is not available either as a tablet or as a paediatric liquid formulation.

Side Effects, Contraindications and Drug Interactions

Some patients experience gastrointestinal discomfort or nausea on griseofulvin, but generally these are tolerable. But occasionally headache may be chronic and severe, and it may be necessary to stop the drug. Other side effects include urticaria and photosensitivity – the latter may present with onycholysis. Griseofulvin may also precipitate systemic lupus erythematosus and acute intermittent porphyria. As it may cause abnormalities in sperm, its use is not advised in adult males of reproductive age in many countries. Griseofulvin may also cause hepatic dysfunction such as cholestasis. A number of interactions are described which include phenobarbitone and phenytoin that inhibit absorption (Table 132.2).

Amorolfine

Amorolfine is a morpholine antifungal available as a topical treatment for nail disease in a specially formulated nail lacquer. It has broad-spectrum antifungal activity and is fungicidal in vitro. Its mode of action is via inhibition of two enzymes, 14-reductase and the β 7, 8-isomerase, involved in ergosterol biosynthesis in the cell membrane. It is not clear how this leads to cidal activity. Amorolfine nail lacquer has been assessed as a once or twice weekly treatment for dermatophyte nail infection of limited extent and not involving the nail matrix. Treatment results suggest that it is effective as sole therapy in a smaller proportion of nail infections than would be expected with oral therapy but that it is effective as an adjunct to oral treatment. Studies show that the combination with terbinafine or pulsed itraconazole is as or more effective in onychomycosis particularly where there is nail matrix involvement.

Side effects are seldom problematic. Itching and local irritation occur in a small proportion of treated cases.

Ciclopirox Olamine (Ciclopirox)

Ciclopirox olamine is a hydroxy-pyridone derivative. It functions probably through inhibition of iron-containing mitochondrial enzymes. It has broad antifungal activity, particularly against dermatophyte fungi as well as some non-dermatophyte mould fungi, and is active topically. As with amorolfine, its minimum cidal concentrations are close to the minimum inhibitory concentrations. As ciclopirox, it has been developed as an antifungal nail lacquer; the drug is incorporated at a strength of 8 % into a transungual delivery system which allows evaporation of the solvent to provide a much higher terminal drug concentration in contact with the nail plate. While cure rates are lower than with oral therapies in nail disease, some studies indicate that it is effective in about 50 % of cases (Seebacher et al. 1993).

Flucytosine

Flucytosine (5-fluorocytosine) functions through the inhibition of fungal thymidylate synthetase. It is active against yeast fungi including *Candida glabrata* and is chiefly used with amphotericin B as a combination therapy because of its high level of synergistic activity with this polyene drug. It has been used in chromoblastomycosis in this combination. It is more generally given as treatment in systemic mycoses such as cryptococcosis. The drug is excreted in urine, and dosage should be reduced in patients with renal impairment. Resistance is also seen amongst *Candida* and *Cryptococcus* species.

Other Topical Antifungals

A number of other antifungal compounds are used in many European countries. Their availability will vary, though, across the continent. Most are sold as over-the-counter (OTC) preparations. Some of these antifungal preparations are listed here.

Tolnaftate is a tolcyclate compound used topically as a treatment for dermatophytosis. It is active against a range of dermatophyte species but cannot be used for scalp or nail disease. Undecenoic acid and zinc derivatives are used either alone or in combination as topical treatments for dermatophytosis. Whitfield's ointment, a combination of salicylic acid (keratolytic) and benzoic acid (antifungal), is available for dermatophyte infections in many European countries. The relative proportions of these two main ingredients used in the formulation may vary between countries.

Despite a number of studies aimed at evaluating new topical agents either for use in superficial mycoses (e.g. abafungin) or new formulations of topical agents for nail disease (e.g. terbinafine nail lacquer), at present none has been approved for therapeutic use. Amongst the new nail treatments is a new product combining urea ointment followed by topical bifonazole and topically applied terbinafine in transfersomes.

Treatment Regimens

General Guidelines

As a general principle, it is important to select an appropriate formulation and drug for each purpose. In practice, superficial infections of limited extent and not involving structures such as hair can be treated with topical therapy, but where the infections are more extensive or more severe oral therapy is given. It is important when giving an oral treatment to ensure that the infection is likely to be responsive. In fact the majority of superficial infections are easily treated with most of the oral agents apart from griseofulvin which is only active in dermatophytosis. Terbinafine is not active clinically in *Candida* or *Malassezia* infection by oral route although it works when given topically. For many oral compounds, it is important to understand the potential interactions and to ask patients about any concomitant medications. These interactions are listed in Table 132.2.

Adjunctive Treatments

Surgical removal of whole or parts of fungal infected nails either by laser or chemical ablation has been recommended. The usual approach to chemical nail removal has been to treat the affected nail under occlusion with topically applied urea 40 % paste for 7–10 days before removing the softened nail segments with clippers. A formulation combining urea and bifonazole is available in some countries, and the treatment pack contains a scraper for removing the soft nail. At present, there is little comparative or scientifically assessed data on laser treatment of nails, including long-term relapse rates, and reaching a valid judgement on its efficacy is not possible at present (Kimura et al. 2012; Landsman et al. 2010).

Dosages

The dosages of the main antifungal preparations are listed in the table below (Table 132.4).

Table 132.4 Antifungal drugs and their dosages

Family of antifungals	Name	Route of administration	Suggested dose
Polyenes	Amphotericin B	Oral (lozenges)	1–2 qid
		Intravenous	1 mg/kg/day
	Lipid-associated amphotericin B		3 mg/kg/day
	e.g. AmBisome (liposomal AMB)		
	Nystatin	Oral (pastilles)	1–2 qid
Azoles	Azole antifungals topical (bifonazole, clotrimazole, econazole, miconazole, sulconazole, ketoconazole, tioconazole)	Topical	Twice daily (for some once-daily therapy has been shown to be sufficient). 2–4 weeks
			Bifonazole/urea preparation is available for nail disease
	Ketoconazole	Oral	200 mg daily
	Itraconazole	Oral	200 mg bid for 1 week in tinea corporis/cruris but repeat ×2 for fingernail, ×3 for toe nails
			100–200 mg daily oropharyngeal candidosis
	Fluconazole	Oral	100–200 mg daily for continuous therapy or 150–300 mg weekly pulses
Terbinafine		Oral	250 mg daily
		Topical	Usually 7 days once daily
Griseofulvin		Oral	500–1,000 mg daily or 10 mg/kg/day
			20 mg/kg daily in *T. tonsurans* infections
Topical nail treatment	Ciclopirox nail lacquer	Topical	Daily (some studies suggest 2–3 times weekly)
	Amorolfine nail lacquer	Topical	2–3 times weekly
Flucytosine		Oral/intravenous	Daily. In patients with normal renal function, 120 mg/kg daily in four divided doses. Check serum levels in patients with renal impairment (normal 40–60 g/l)
Other antifungal compounds	Undecenoates	Topical	Different compounds usually containing zinc undecenoate/undecenoic acid. Daily use for dermatophytosis
	Benzoic acid compound (Whitfield's ointment)	Topical	Daily treatment for dermatophytosis. As it is irritant, care should be taken in using in the groin area

Further Reading

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Antihistamines

133

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Key Points

- The anti-H1 antihistamines are one of the most commonly used drugs in dermatology, especially for itching dermatitis.
- Antihistamines inhibit the effects of histamine, e.g., localized vasodilation and transudation of fluid.
- They represent the first-line treatment for urticaria-angioedema, pruritus, allergic rhinitis, allergic conjunctivitis, mastocytosis, itch from mosquito bites, and prevention of adverse reaction to insect venous immunotherapy.
- The second-generation antihistamines have replaced the first ones in the dermatological treatment due to their more safe profile and their lack of both sedative and anticholinergic effects.
- The most common side effect of first-generation H1 antihistamines is drowsiness. This side effect is much lower during the therapy with the second-generation H1 antihistamines.
- A patient suffering from urticaria may profit from up-dosing of second-generation H1 antihistamines.

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General Principles

The function of histamine and its receptors are known from several times.

The histamine receptors can be classified into four types: H1, H2, H3, and H4.

The H1 receptors mediate the following effects: vasodilatation of small blood vessels resulting in increased permeability and pruritus. The H2 receptors are known for mediating the effects on gastric acid production. The H3 receptors have been found in the brain and peripheral neurons and are responsible for autoregulation of histamine production and release.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_133, © Springer-Verlag Berlin Heidelberg 2015

The H4 receptors have been discovered recently. They are expressed in the skin from Langerhans cells, DCs, fibroblasts, and T cells.

Classification

The antihistamines have been used in the dermatological practice since the 1950s.

The histamine-receptor antagonists or antihistamines are classified into two classes:

- H1-type antihistamines
- H2-type antihistamines

The H1-type antihistamines can be further divided into:

- First generation – sedating, old, or classic H1-type antihistamines
- Second generation – low-sedating or new H1-type antihistamines

The H1- and also H2-type antihistamines are considered as first-line medication and can be used either in children or in adults.

The role of H3 and H4 receptors has been investigated in the last years. No agents are approved to date yet but some clinical studies are in progress. There is a considerable interest and optimism on efficacy and safety of H3 and H4 antihistamines in allergic disorders as allergic rhinitis, asthma, pruritus, atopic dermatitis, and other chronic inflammatory disorders.

The first-generation H1 antihistamines have in common with histamine a substituted ethylamine moiety as an integral part of their molecule (Fig. 133.1).

The activity of an H1 antihistamine is increased if a halogen is substituted in the *para* position of the phenyl or benzyl group of R1.

The first-generation H1 antihistamines have been divided into six chemical classes on the basis of a substitution at the X position with the nitrogen, oxygen, or carbon. The six chemical classes (and the corresponding most commonly used antihistamines) are shown in Table 133.1.

The first-generation H1 antihistamines are the first ones commercialized. They are widely used in the treatment of allergic and nonallergic

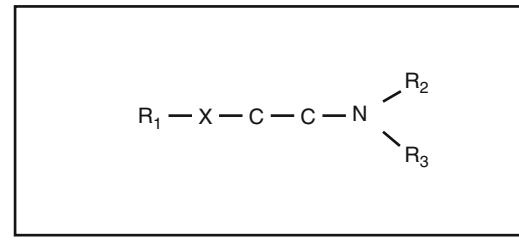

Fig. 133.1 Ethylamine moiety of H1 antihistamine

Table 133.1 Different chemical classes of first-generation antihistamines. Some of them either are not yet approved or have never been approved. Some others, such as astemizole and terfenadine, have been withdrawn from the market in the 1990s because of rare but potentially fatal side effects

	Molecules	
Chemical class	First-generation (old) H1 antihistamines	Second-generation (new) H1 antihistamines
Alkylamine (propylamine)	Brompheniramine maleate, chlorpheniramine maleate, dexchlorpheniramine maleate, dimethindene, pheniramine, triprolidine	Acrivastine
Aminoalkyl ether (ethanolamine)	Celestamine, diphenhydramine hydrochloride, carbinoxamine, doxylamine	–
Ethylenediamine	Tripelennamine citrate, tripelennamine hydrochloride, antazoline,	–
Phenothiazine	Methdilazine, methdilazine hydrochloride, promethazine hydrochloride	–
Piperidine	Azatadine maleate, cyproheptadine hydrochloride, ketotifen, diphenylpyraline	Astemizole, bilastine, desloratadine, ebastine, fexofenadine, loratadine, mizolastine, rupatadine, terfenadine, levocabastine
Piperazine	Hydroxyzine hydrochloride, hydroxyzine pamoate, oxatomide, cyclizine	Cetirizine, levocetirizine
Others	Doxepin	Azelastine, emedastine, epinastine, olopatadine

Doxepin has dual H1- and H2-antihistamine activities and it is classified as an antidepressant

disorders. These drugs, binding also other receptors such as muscarinic, serotonin, and α-adrenergic, are associated with diverse side effects. Moreover they can cross the blood-brain barrier causing sedation of varying intensity. These well-known effects can be results useful in the management of itching diseases, for example, in the nocturnal pruritus that annoys the sleep of patients suffering from atopic dermatitis.

The introduction of second-generation or low-sedating H1 antihistamines in the late 1980s was marked by significant improvements in pharmacology and safety. Their pharmacokinetics and pharmacodynamics have been investigated extensively in healthy adults as well as in elderly people, in children, and in patients with severe hepatic or renal dysfunction. Second-generation H1 antihistamines have improved tolerability and drug/food interaction profile versus the first-generation antihistamines. Thus, they have replaced the first-generation antihistamines in the dermatological treatment due to their better binding to peripheral H1 receptors, more safe profile, and lack of both sedative and anticholinergic effects. They minimally cross the blood-brain barrier and they are extensively distributed in body fluids.

Some of the second-generation antihistamines are related with the first-generation antihistamines and each other: for example, cetirizine is a metabolite of hydroxyzine and levocetirizine is an enantiomer of cetirizine.

The second-generation antihistamines are divided into classes according to their chemical structure (Table 133.1). Not all these drugs are available in all European countries.

H2-type antihistamines, as cimetidine, ranitidine, famotidine, and nizatidine, possess an imidazole ring and lack the aryl ring of H1 antihistamines. These therapeutic agents are less lipophilic, which presumably accounts for their lack of central nervous system (CNS) effects. They were developed for use in peptic ulcer diseases and they are used less than H1-type antihistamines in dermatology. However the presence of H2 receptors in the cutaneous microvasculature justified their use. Clinical trials with H3 and H4 antihistamines are in progress.

Most Commonly Used Antihistamines

- First generation – sedating, old, or classic H1-type antihistamines H1 antihistamines:
  - Dexchlorpheniramine, oxatomide, hydroxyzine, and chlorpheniramine maleate
- Second generation – low-sedating or new H1-type antihistamines:
  - Bilastine, desloratadine, ebastine, fexofenadine, loratadine, mizolastine, rupatadine, levocabastine, cetirizine, and levocetirizine
- H2-type antihistamines:
  - Cimetidine and ranitidine
- No H3 and H4 antihistamines are approved to date, yet but some clinical studies are in progress.

Mechanisms of Action

Antihistamines competitively inhibit the action of histamine by blocking its receptors on the vascular endothelial cell surface. As a result, antihistamines prevent the effects of histamine, e.g., localized vasodilatation and transudation of fluid, leading to the formation of a typical weal.

Moreover histamine is one of the mediators in the pruritus signal.

Indications and Other Uses

Antihistamines are usually used for itching dermatitis. They represent the first-line treatment for urticaria-angioedema, allergic rhinitis, allergic conjunctivitis, mastocytosis, pruritus from mosquito bites, and adverse reaction to insect venous immunotherapy. The recommendation regarding the last three is supported by smaller randomized controlled trials. Comparative studies of the subgroups of traditional H1 antihistamines have shown the drugs to be almost of equal efficacy. Their use is going to decrease. Their side effects (mainly sedation) can be useful in the management of itching disease. They can be combined with other H1 antihistamines, mainly with the low-sedating ones.

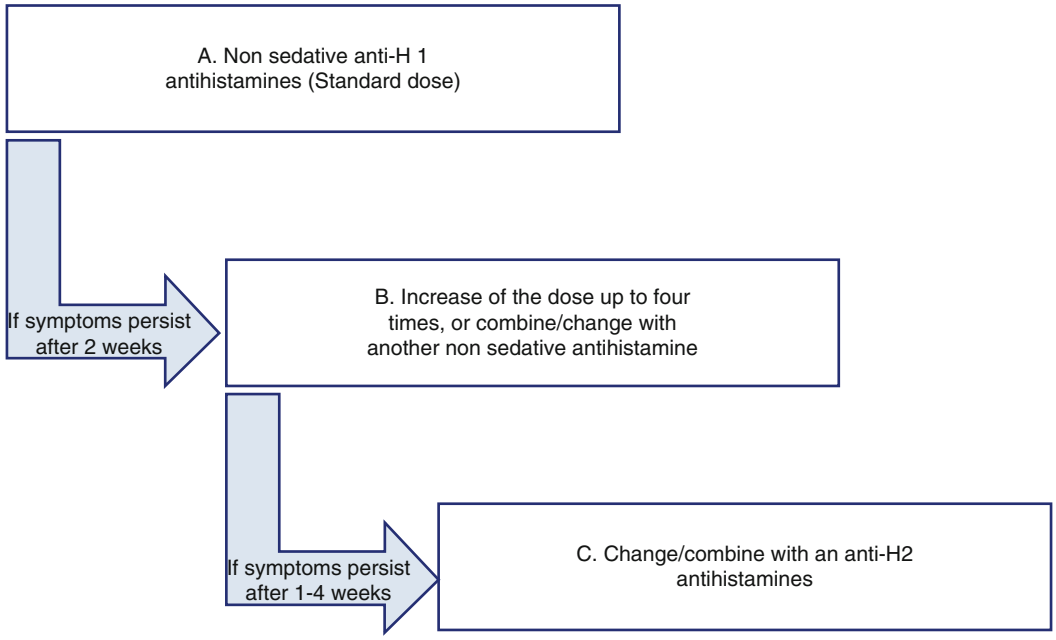

Fig. 133.2 Treatment algorithm for the use of antihistamines in urticaria (From Zuberbier et al. (2009a, b), modified)

The latter have been studied longer in the treatment of acute and chronic urticaria and angioedema and a lot of their use recommendations are derived from urticaria and pruritus guidelines.

In randomized studies, in which low-sedating H1 antihistamines have been compared with each other and with sedating H1 antihistamines, no statistically significant differences in efficacy have been proven. However, due to some important differences between all these agents in terms of dosing, convenience, and side effects, the guidelines for diverse diseases have suggested to use a class respect to another. For example, the European guidelines (Zuberbier et al. 2009a, b; Maurer et al. 2013) on urticaria highlighted the use of low-sedating antihistamines in the treatment of the diseases (Fig. 133.2). Due to the sedation and anticholinergic effects, the guidelines strongly discouraged the use of sedating H1 antihistamines in the treatment of urticaria-angioedema (Church et al. 2010).

Pruritus of various causes and atopic dermatitis are commonly treated with H1 antihistamines, both the first and second generations. In these diseases, even if a rationale of the use of antihistamines has been documented, evidence base for efficacy and safety is missing. As reported by recent atopic dermatitis guidelines (Ring et al. 2012a, b), there is not enough evidence to support the general use of both first- and second-generation antihistamines for treatment of pruritus in atopic eczema.

Molecules as hydrochloride, doxepin, and ketotifen have dual H1 and H2 activities and are classified as tricyclic antidepressant drugs. They have been used successfully to relieve the symptoms of pruritus, diffuse cutaneous mastocytosis, and asthma. Their sedation and other adverse effects are comparable with those of first-generation antihistamines.

Indication of Use

- Allergic diseases in which H1 antihistamines are medications of choice:
  - Urticaria, allergic rhinitis, allergic conjunctivitis, mastocytosis*, pruritus from mosquito bites*, and to reduce adverse reaction to insect venous immunotherapy* (*supported by smaller randomized controlled trial)
- Diseases in which H1 antihistamines are not medications of first choice:
  - Atopic dermatitis, asthma, anaphylaxis, and nonallergic angioedema

Side Effects

The most common side effect of first-generation H1 antihistamines is drowsiness. It is common, varies from patient to patient, and interests mainly the first days/weeks of the therapy; during the continuation of the therapy, it can completely disappear. If the classic H1 antihistamines are given in the evening, the resulting somnolence can be adequately tolerated.

This side effect is much lower during the second-generation H1-antihistamine treatment. The use of first-generation H1 antihistamines can be particularly useful when an itching dermatitis disturbs the sleep of the patient.

Moreover the majority of first-generation H1 antihistamines show an accentuation of the central depressive effect.

Due to their anticholinergic effect, the first-generation and not the second ones should not be administered to patients with glaucoma or urinary retention.

Prolongation of the cardiac QT interval and arrhythmias, mainly ventricular, have been reported after standard or higher doses of first-generation H1 antihistamines for their binding with muscarinic, α-adrenergic receptors and for the blockade of ion currents.

Convulsions, appetite stimulation, weight gain, dry mouth, blurring of vision, difficulty in micturition, and impotence are rare side effects with the sedative ones.

It has well-known the photo-contact dermatitis due to the application of topical antihistamines, as topical promethazine.

An overdose can cause drowsiness, confusion, hallucinations, respiratory depression, cardiotoxicity, and fatality.

Contraindications

In patients with hepatic or kidney dysfunction, epilepsy, prostatic hypertrophy, glaucoma, porphyries, urinary retention, and cardiac diseases, the use of antihistamines should be limited/avoided, especially the first-generation ones. Patients should not drink alcohol after their drug intake.

Drug Interactions

The ingestion of first-generation H1 antihistamines in combination with central nervous system antidepressant may determine an accentuation of the central depressive effects. In particular they should not be administered with the monoamine oxidase inhibitors: their anticholinergic side effects (e.g., dryness of mucosae, urinary retention) may be prolonged and accentuated.

Side Effects

- Common: drowsiness
- Less common: decrease of alertness, dry mouth, glaucoma, urinary retention, arrhythmias, and appetite stimulation (especially the first-generation antihistamines)
- Contact dermatitis (when applied topically)
- Hyperdosage: confusion, hallucinations, convulsions, blurring of vision, difficulty in micturition, impotence, respiratory depression, cardiotoxicity, and fatality
- Drug interaction: central nervous system antidepressant, mainly monoamine oxidase inhibitors

Pregnancy and Breast-Feeding

The first and second generations seem to be quite safe in pregnancy. If possible, the avoidance of all antihistamines is suggested in pregnancy, especially during the first trimester, although none of them have been shown to be teratogenic in humans. No relation between the H1 antihistamines and the development, even minor, of fetal malformations has been established. It is worthy to remember their wide use in allergic disease also in women before discovering to be pregnant.

First-generation H1 antihistamines (chlorpheniramine and diphenhydramine) and second-generation H1 antihistamines (loratadine) have a favorable category B rating.

First-generation H1 antihistamines should be avoided before parturition because they can cause contractions because of oxytocin-like effects. Moreover the neonate may exhibit withdrawal symptoms, as irritability and tremulousness,

when a large dose has been taken before the delivery.

Extremely small amounts of loratadine are excreted in breast milk.

Pregnancy and Breast-Feeding

- First-generation H1 antihistamines (chlorpheniramine and diphenhydramine) and second-generation H1 antihistamines (loratadine) have a favorable category B rating.
- The use of antihistamines should be limited in pregnancy.
- First-generation H1 antihistamines should be avoided before parturition because they can cause contractions because of oxytocin-like effects.

Use in Infants and Children

Most of the antihistamines are allowed to be used in infants and children. Some others have indications in patients older than 12 for the lack of study in this age. It has been recently shown that the first-generation H1 antihistamines can cause in infant and children drowsiness and diminution of REM phase. Recently a lot of pediatric oral formulations containing first-generation H1 antihistamines have been withdrawn from the market.

For these reasons a recent GA^{2}LEN position paper (Church et al. 2010) strictly discourages the use of the first-generation antihistamines in this age, especially in the treatment of urticaria-angioedema.

Use in Elderly People

The use of H1 antihistamines should be limited in elderly people because they often have cognitive dysfunction and they are particularly vulnerable to the adverse effects of these drugs.

Use in Infants and Children

- Most of antihistamines are allowed to be used in infants and children.
- First-generation H1 antihistamines can cause in infant and children drowsiness and diminution of REM phase, and their use is discouraged in this age.

Treatment Regimen and Dosage

The dosage and frequency of administration of antihistamines are recommended by the manufacturers and are usually based on the inhibition of experimental histamine weal.

However recent studies in urticaria-angioedema have shown that the single dose is not sufficient to treat efficiently the diseases.

In these cases, after an insuccess of 15-day treatment of single dose, patients with urticaria may profit from up-dosing with second-generation H1 antihistamines up to four times.

Studies on loratadine, desloratadine, and rupatadine have shown an increase of the efficacy of the drug in the treatment of urticaria without an increase of the side effects. Further researches are needed for predicting markers in different subtypes of urticaria.

It is worthy to remember that this recommendation represents an off-label use of the drug: it is also true that physicians are becoming familiar with an increase of the antihistamines dose.

In the urticaria treatment, when an increase of the antihistamines dose is not sufficient to treat sufficiently the disease, a combination of non-sedative H1 antihistamines and H2 antihistamines is beneficial in patients with (chronic) urticaria-angioedema.

The urticaria guidelines do not suggest the use of first-generation antihistamines (Zuberbier et al. 2009a, b; Maurer et al. 2013). Their use may be useful for some forms of urticaria (e.g., cholinergic or solar urticaria) when the cholinergic receptors are involved (Fig. 133.2).

A lot of suggestions for the use of antihistamines in other itching skin diseases are derived from the urticaria guidelines. In many itching diseases, the evidence base for the efficacy and safety of antihistamines is weak, and it is not supported by large and randomized study. Similarly, there are no data regarding the efficacy and safety of up-dosing of antihistamines. Patients with pruritus or with atopic dermatitis may benefit from the treatment with the first generation of sedative antihistamines. These drugs may allow a better sleep pattern in acute situations with exacerbations of eczema. The evidence of this recommendation is low. The dose and the period treatment have to be personalized to the patient and his/her skin disorder.

Dosage

Traditional H1 antihistamines		
Drug	Adult dose	Children dose
Dexchlorpheniramine	6 mg every 12 h	
Diphenhydramine hydrochloride	25–50 mg every 4 h	Under 12 years of age: 5 mg/kg per 24 h in divided doses
Tripelennamine hydrochloride	25–50 mg every 6 h	Under 12 years of age: 5 mg/kg per 24 h in divided doses
Promethazine hydrochloride	25 mg 3 times a day	Under 12 years of age: 6.25–12.5 mg three times a day and 25 mg at bedtime
Cyproheptadine hydrochloride	4 mg 3 times daily	7–14 years: 4 mg 3 times a day
		2–6 years: 2 mg 2–3 times a day. (0.25 mg/kg daily)
Oxatomide	30 mg 2 times a day	Older than 1 year: 1 drop (2.5 mg)/2 kg two times a day
Hydroxyzine hydrochloride	25 mg 2–3/day	Older than 12 months: 10–20 mg/day in divided doses
Second-generation (new) H1 antihistamines		
Cetirizine	10 mg daily	2–12 years: 5 mg daily
		1–2 years: 2.5 mg daily
Loratadine	10 mg daily	2–12 years: 5 mg daily
Fexofenadine	180 mg daily	–
Mizolastine	10 mg daily	–
Ebastine	10–20 mg daily	–
Bilastine	20 mg daily	–
Desloratadine	5 mg daily	1–5 years: 1.25 mg daily
		6–11 years: 2.5 mg daily
Levocetirizine	5 mg daily	Children 6–12 years: 5 mg daily
		2–6 years: 1.25 mg twice a day
Rupatadine	10 mg daily	–
H2 antihistamines		
Cimetidine	200 mg two to three times daily	Intramuscularly, 2 mg/kg every 6 h
Ranitidine	150 mg twice a day or 300 mg daily	2 mg/kg twice a day
Famotidine	20–40 mg daily	–

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Antiviral Drugs

134

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Abbreviations

5-FU	5-Fluorouracil
HHV	Human herpesvirus
HPV	Human papillomavirus
HSV	Herpes simplex virus
IN	Intraepithelial neoplasia
MC	Mollusca contagiosa
MMRV	Measles, mumps, rubella and varicella
STI	Sexually transmitted infection
TCA	Trichloroacetic acid
VZV	Varicella-zoster virus

Key Points

- In spite of some recent advances, the treatment of viral diseases in dermatology and venereology sometimes remains quite challenging and frustrating for both patients and physicians.
- Herpes simplex virus (HSV) infections belong to the rare group of viral diseases with efficient antiviral drugs available. Thus, antiviral (especially oral) treatment should be provided to the patients with HSV infections to a greater extent than it has been generally advised in the "usual and traditional manner".
- The oral treatment for HSV infections can sometimes be initiated whenever the symptoms exist, no matter if this period might be longer than 72 h (as traditionally believed) from the clinical onset of disease.
- Providing the protection against the most common four human papillomavirus (HPV) DNA types, the quadrivalent vaccine has a great target and potential in dermatovenereology. The HPV has overcome the "only sexually transmitted infection (STI)" limitation, and this virus has been associated today with the great spectrum of cancers (not only cervical, but also anal, penile, vulvar, pharyngeal, oral, tonsillar, etc.). Thus, the HPV vaccine might be one of the first

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_134, © Springer-Verlag Berlin Heidelberg 2015

examples how the oncologic disease might be successfully prevented!

- Treatment of mollusca contagiosa (MC) from dermatovenereological point of view depends on the size, number and site of lesions, convenience, cost of treatment, patient discomfort and preference as well as physician's experience. Given the self-limiting course of disease in immunocompetent patients, the span of therapeutic options ranges from attentive "wait and see" approach, assuming patient education and reassurance, to decisive acts directed to destroy cutaneous lesions induced by *Molluscipoxvirus*. The adult patients with MC should be definitely screened for other STIs!

General Principles

In spite of some recent advances during the past few decades, the treatment of viral diseases in dermatology and venereology remains quite challenging on one side and frustrating on the other side for both patients and physicians. However, due to the better insight into the pathogenesis and principles of molecular biology of viral infections, there are ongoing investigations and clinical trials concerning new therapeutic agents and vaccines which would hopefully change current unrewarding state and prognosis of viral diseases. In this chapter, we will primarily focus on antiviral drugs that are most frequently used in dermatovenereological practice.

Classification

Drugs for the Treatment of Human Herpesvirus Infections

Herpesviridae family comprises eight viruses, *human herpesvirus* (HHV) (1–8) which all have double-stranded linear DNA molecule and are capable of causing several different mucocutaneous disorders (Table 134.1). *Herpes simplex virus* (HSV1) (HHV1) and HSV2 (HHV2) infections, either in the form of orofacial or genital herpes and varicella-zoster virus (VZV) (HHV3) known to cause varicella (chickenpox) with primary infection and herpes zoster with recurrent infection, are all rather frequent in dermatologic practice. However, other types of HHV (4–8) infections are less frequently recognized as the aetiological agents in dermatologist's office. In scientific terms, rather than practical aspects in treating patients so far, a special attention should be given to HHV 6 and 7 and their association with pityriasis rosea and exanthema subitum (roseola infantum), as well as to the HHV 8 and its association with Kaposi sarcoma (KS).

Indications and Other Uses

Treatment of HSV infections remains symptomatic in many cases in the everyday practice. We must say that we do not completely agree with such attitude providing that HSV infections belong to the rare group of viral diseases with efficient antiviral drugs available. Thus, antiviral (especially oral) treatment should be provided to the patients with HSV infections to a greater extent than advised in the "usual and traditional manner", so far. It has been generally recommended to treat, first of all, those infections which are protracted, complicated, recurrent and/or affecting the immunodeficient host or a neonate. It is also recommended as prophylactic treatment from 36 weeks' gestation since it has been documented to reduce recurrences, viral shedding and the need for caesarean deliveries.

Acyclovir (9-2-hydroxyethoxymethyl guanine or acycloguanosine) is an acyclic guanosine analogue which in its active form inhibits viral DNA polymerases resulting in highly selective inhibition of further viral DNA synthesis. It is a widely used and well-tolerated drug which can be administered topically, orally and intravenously. In topical preparations, it is available as 5 % ointment with very little systemic absorption resulting in low efficacy; especially in the cases of genital herpes (topical acyclovir has not

Table 134.1 Schematic overview of the treatment dosing regimen for *human herpesvirus* infections in dermatology and venereology

	Acyclovir	Valacyclovir	Famciclovir
First episode of genital herpes	5×200 mg daily for 10 days OR	2×500 mg daily for 10 days	3×250 mg daily for 10 days
	3×400 mg daily for 10 days		
Recurrent genital herpes	5×200 mg daily for 5 days OR	2×500 mg daily for 3–5 days	2×125 mg daily for 5 days OR
	3×400 mg daily for 5 days OR		
	3×800 mg daily for 2 days		2×1 g daily for 1 day
Suppressive therapy	2×400 mg daily	<10 episodes per year: 500 mg daily	2×250 mg daily
		>10 episodes per year:	
		2×500 mg daily OR 1 g daily	
Orolabial herpes	5×200 mg daily for 5 days	2×2,000 mg daily or 1 day	1×1,500 mg single dose OR
			3×250–500 mg daily for 5 days
Herpes zoster	5×800 mg daily for 7–10 days	3×1,000 mg daily for 7 days	3×500 mg daily for 7 days
Chickenpox	4×20 mg/kg (800 mg max) daily for 5 days	3×20 mg/kg (1 g max) daily for 5 days	
Suppressive therapy in pregnancy	3×400 mg daily from 36 we eks' of gestation		

been recommended for genital herpes at all!). Oral formulations are most frequently used and are characterized by low bioavailability (15–30 %). Intravenous administration of acyclovir is indicated in immunocompromised patients and severe illness such as disseminated HSV infection, complicated primary infection, neonatal infection, eczema herpeticatum (eruptio varicelliformis Kaposi) and herpes encephalitis. Indications approved by the FDA for the use of acyclovir in the context of dermatovenereology are: symptomatic primary or recurrent HSV infections in immunocompetent and/or immunocompromised patients, suppression of recurrent HSV infections, prevention of perinatal transmission, treatment of VZV infections (herpes zoster and chickenpox) in immunocompetent or immunocompromised patients and treatment of recurrent erythema multiforme which is most frequently preceded by HSV infection. Acyclovir is approximately ten times more potent against HSV1 and HSV2 than against VZV (due to its more efficient phosphorylation by the viral thymidine kinase). Adverse effects of oral acyclovir reported in clinical trials include malaise, headache, dizziness and lethargy, while other neurologic adverse effects were less frequently reported. Dermatologic adverse effects have been reported for topical, oral and intravenous formulation, including local pruritus, erythema, unspecified rash, hives, Stevens-Johnson syndrome (!) and toxic epidermal necrolysis. The most frequent adverse effect for parenteral acyclovir is inflammation at injection site, also known as phlebitis. Cases of thrombotic thrombocytopenic purpura and haemolytic-uremic syndrome have occurred in immunocompromised patients.

When given for primary genital HSV infection, recommended dose is 200 mg five times daily for 10 days or alternatively 400 mg three times daily for 10 days, whereas for recurrent

genital HSV infection the dose is usually 200 mg five times daily for 5 days or alternatively 400 mg three times daily for 5 days. This alternative therapeutic regimen has, understandably, better compliance rate. However, there are some "shortcuts" in dosing regimen recommendations for genital herpes suggesting that a time shorter than usual 5 days might be as effective. Therapy of HSV infections in general terms should be adjusted to each patient individually, since studies have not shown significant advantage of one therapy over another in terms of drug choice or duration of therapy. Some patients with recurrent genital herpes will benefit from one of short-course therapeutic regimes such as 800 mg of acyclovir three times daily for 2 days or famciclovir 1 g twice daily for 1 day or valacyclovir 500 mg twice daily for 3 days. For others, prolonged treatment will be needed. Nevertheless, we would feel very happy if even "classical" dosing regimen described above would have been largely accepted for the benefit of the patient him/herself and for the benefit of his/her partner(s). Oral acyclovir has also proven effective when administered early in the course of orofacial HSV infection in doses of 200 mg five times daily for 5 days. It has been usually accepted that oral treatment for either oral or genital herpes should be given up to 72 h after the first signs of infection. The usual (but not clearly evidence-based) practice is that "there is no point" of prescribing the oral treatment afterwards. We do not think that this should be so strict, and such an approach should be individualized; the oral treatment can sometimes be initiated whenever the symptoms exist, no matter if this period might be longer than 72 h from the clinical onset of disease. Suppression of recurrent HSV infections can be achieved with 400 mg of acyclovir twice daily and is generally indicated in patients with frequent recurrences, in immunocompromised patients, in recurrent ocular HSV disease and also in patients with recurrent erythema multiforme. In order to prevent perinatal transmission of HSV, daily dose of acyclovir 400 mg three times should be given from 36 weeks' of gestation (Patel et al. 2010). Suppressive oral treatment turned out to be one of the greatest achievements in improving the quality of life of patients with recurrent genital herpes, as well as in significant decreasing of the viral shedding, and such a treatment might be given for several months up to 1 or 2 years.

Therapeutic regime for first episode of VZV in immunocompetent adults is 800 mg five times daily for 7–10 days, whereas primary varicella in children is 20 mg/kg (800 mg max) four times daily for 5 days.

Valacyclovir 2 [2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl-methoxy] ethyl-L-valinate hydrochloride is the valine ester of acyclovir and is, in fact, its oral prodrug sharing the identical mechanism of action, clinical spectrum and similar side effects. The crucial difference between the acyclovir and valacyclovir is greater bioavailability of valacyclovir (55 %) which is also considered generally safe and well-tolerated drug.

Valacyclovir is indicated in treatment of primary and recurrent HSV infections, both in immunocompetent and immunocompromised patients, chronic suppression of HSV infection, herpes zoster in both immunocompromised and immunodeficient patients and recurrent erythema multiforme.

First episode of genital HSV is treated with 1,000 mg of valacyclovir twice daily for 10 days, while the dose for recurrent episodes of genital HSV is 500 mg twice daily for 3 days. For the purpose of suppressive therapy of recurrent HSV infections (<10 episodes per year), valacyclovir is given 500 mg daily, whereas for ten or more episodes dosage is upgraded to 1 g daily or 500 mg twice daily (Corey et al. 2004). Orofacial HSV infection is treated with 2,000 mg twice daily for 1 day.

Dose of valacyclovir for chickenpox when administered orally is 20 mg/kg (1 g max) three times daily for 5 days. For the treatment of herpes zoster, valacyclovir is administered in doses of 1,000 mg three times daily for 7 days. It has also proven to be more effective than acyclovir in relieving postherpetic neuralgia, though certain cases of postherpetic ("postzosteric") neuralgia remain still very resistant to almost any treatment modality whatsoever.

Famciclovir [9-(4-hydroxy-3-hydroxy-methylbut-1yl) guanine is the oral prodrug of an acyclic nucleoside penciclovir. In its active form, famciclovir has 10–20 times longer intracellular half-life than acyclovir and greater bioavailability (around 77 %). It has identical clinical spectrum to valacyclovir, which is, again, very similar to acyclovir.

When given for the first episode of genital herpes, the dose of famciclovir is 250 mg three times daily for 10 days, and the dose for episodic genital herpes is 125 mg twice daily for 5 days. Suppressive therapeutic regimen for recurrent HSV disease which proved to be efficient is 250 mg twice daily. Several other schemes exist for orofacial HSV infections, such as famciclovir given at 1,500 mg single dose or 250–500 mg three times daily for 5 days.

Therapeutic effectiveness of famciclovir in the treatment of herpes zoster in adult immunocompetent patients was demonstrated for doses of 500 mg three times daily for 7 days, with the same dosing regimen prolonged for 3 days more in an immunocompromised patients.

Topical agent *penciclovir*, the active metabolite of the oral drug famciclovir, is approved for topical treatment of HSV infections on the lips and face. Its use on mucous membranes has not been established so far. Main advantage of topical penciclovir over topical acyclovir is the longer intracellular half-life in infected cells. Recommendation is to apply topical preparation of penciclovir every 2 h from the beginning of the symptoms, avoiding area around the eyes. There is lack of data confirming its safety and efficacy in children younger than 12 years and in immunocompromised patients.

In order to summarize the therapeutic options in HHV infections, we would like to acknowledge that all of the three drugs mentioned above are equivalent in their safety and efficacy profile as well as the clinical spectrum. Each of them is declared as category B for use in pregnancy. Nevertheless, clinical practice has not documented any related fetal risk so far. Drug interactions in this drug group are few since none of them is metabolized by hepatic microsomal enzymes. In general terms, the acyclovir and its derivates mentioned above are effective in HSV and VZV infections in both immunocompetent and immunocompromised patients, with the latter group being more likely to develop resistance against acyclovir in which case it can be substituted with intravenous foscarnet or cidofovir. Among other reasons, viral resistance against acyclovir is most commonly caused by loss of thymidine kinase activity. Since both foscarnet and cidofovir display more toxicity, they are not recommended as first-line therapy in HSV infections (Mendoza et al. 2012). There are, however, some new and potentially effective drugs on the horizon, currently under investigations. These include helicase-primase inhibitors which seem to be capable of addressing the emerging resistance to oral nucleoside analogues. Efficacy of treatment with acyclovir, valacyclovir and famciclovir is demonstrated in several clinical studies where it was measured by shortening of duration of disease and its overall severity, by their ability to inhibit viral shedding and frequency of outbreaks as opposed to placebo.

Vaccine for varicella-zoster virus has been on the market for 18 years since its first official approval, and since then, this live attenuated VZV vaccine has significantly improved quality of life around the world. Varicella vaccine is indicated for all adults without evidence of immunity to varicella, and it is given in two doses. Children receive the first dose of vaccine at the age of 12–15 months and the second at the age of 4–6 years. At age of 12–47 months, either a dose of combined measles, mumps, rubella and varicella (MMRV) vaccine or separate MMR vaccine and varicella vaccine can be given as the first dose. If the first dose is given at ≥48 months of age, CDC recommends combined MMRV vaccine (Klein et al. 2010). Second dose is also preferably combined MMRV vaccine at any age (15 months–12 years). Vaccine is, however, contraindicated for use in pregnancy and immunosuppressed patients. For these groups of patients, there is varicella-zoster immune globulin that can be given within 96 h postexposure to varicella as a passive prophylaxis aid (Marin et al. 2007). Year 2006 remains

important in the history of VZV vaccine since it then became the first approved vaccine for prevention of herpes zoster in patients who are 60 years old or older (Harpaz et al. 2008). It is recommended as a single dose for immunocompetent individuals 60 years of age or older regardless of their history of varicella or herpes zoster. Important contribution of this vaccine is its ability to reduce the incidence of herpes zoster and the severity of postherpetic neuralgia, while those unfortunate patients who still develop the disease after vaccination displayed less pain and discomfort. Although the duration of this vaccine has not been established yet, it is perceived to last for at least 5 years.

Unlike vaccine for VZV, the ongoing search for effective and safe vaccine for HSV has not been completely successful so far. Despite the fact that several different formulations of vaccine have been offered, yet none of them has managed to meet the requirements. Given the impact this vaccine would have on medical practice, global economy and society in general, great efforts are currently being implemented in its development.

Drugs for the Treatment of Human Papillomavirus (HPV) Infections

Treatment of HPV infections to date remains symptomatic since there is no real causative therapeutic option. Bearing that in mind, it is implied that such therapeutic approach to infection as common as HPV in general population is subjected to frequent and multiple doctor's office visits, repeated trials of accessible therapeutic options and at times dissatisfying results. The recurrence rate is generally significant, and the majority of treatment options for the HPV genital infections is associated with pain, discomfort and irritation and can be sometimes very frustrating for both patient and physician. However, given that most HPV infections are self-limited in nature and general lack of evidence to support favourable long-term outcome of treatment, it is considered unjustified to treat them overagressively (Wolf et al. 2007) (Table 134.2).

Indications and Other Uses

Physical destruction of HPV-induced lesions is one possible approach. Purpose of these methods is to voluntarily inflict injury to the skin infected by the HPV with the goal of eliminating the viral-induced skin or mucosal lesion. *Cryotherapy*, perhaps the most frequently tried and inexpensive method, is applied in weekly or biweekly intervals and still remains the mainstay of the routine treatment. Other approaches include surgical removal by tangential excision, *curettage* and/or *electrosurgery*, photodynamic therapy with topical aminolevulinic acid and laser vaporization which is especially suitable for certain localizations of typical lesions such as nailbed (common warts) or urethral meatus (genital warts). Keratolytic agent trichloroacetic acid (TCA) or bichloroacetic acid 70–90 % is also included in the spectrum of local destructive measures, whose topical application results in tissue destruction without systemic toxic effects making it thus applicable for use in pregnancy. TCA can be applied once a week with strict precautions concerning its caustic properties. Various salicylic acid preparations, another yet milder keratolytic agent, for local use can also be tried. It is, of course, possible and often seen in clinical practice that some of these methods are used in various combinations (sometimes following each other after a few minutes) for better clearance rate. There are reports of effectiveness of 5 % potassium hydroxide solution, a strong alkali agent, for at home use as another locally destructive approach.

Cytotoxic therapy both local and intralesional assumes application of several different agents. Podophyllin is used as 10–25 % solution for genital lesions once weekly or once biweekly, often in combination with cryotherapy. It should be washed off 1–4 h after application to avoid local irritation and treating large areas and at once should be avoided. Also, it is recommended for use up to 6 weeks. Due to its sometimes low efficacy, potential systemic toxicity and unstable formulation, it has been slowly replaced by other options, and it has been omitted from certain guidelines. However, we think that it should not be completely banned providing that if only

Table 134.2 Schematic and simplified overview of the treatment options for HPV genital infections and common warts

Regimen	Physical destruction	Cytotoxic therapy	Topical immunomodifiers	Antiviral drugs	Vaccines
Office therapy	Cryotherapy once weekly or biweekly	Podophyllin solution 10–25 % once weekly or biweekly up to 6 weeks (*rarely, but still possible*; *please, see in the text*!)			Gardasil™, Silgard™ quadrivalent (HPV6/11/16/18) for females and males 9–26 years of age at 0, 2 and 6 months
	Tangential excision				
	Curettage				
	Electrosurgery				
	PDT (ALA)				Cervarix™, bivalent (HPV 16/18) for females 9–26 years of age
	Laser therapy				
	Bichloroacetic/trichloroacetic acid once weekly or biweekly				
Patient-applied therapy		Podophyllotoxin solution or gel 0.5 % twice daily for 3 consecutive days followed by 4 days break up to 4 cycles	Imiquimod cream 5 % 3 times weekly up to 16 weeks	Cidofovir gel, cream or ointment 1–3 %	
	Salicylic acid	5-FU 5 % cream or solution 1–3 times weekly for several weeks	Sinecatechins ointment 10–15 % 3 times daily for 16 weeks		

For use in pregnancy

office applied by a skilled professional, and properly washed out, it might be still sometimes an efficient option, especially if the other treatment modalities could not be afforded. Podophyllotoxin, a podophylline derivative known as an antimitotic agent that arrests mitosis in metaphase, used by patient at home as a 0.5 % solution or gel twice a day for three consecutive days followed by 4 days break has proven to be more effective and less toxic according to some trials. This scheme can be repeated for up to four cycles. Both podophyllin and podophyllotoxin are contraindicated in pregnancy. Another cytotoxic agent less frequently used is 5-fluorouracil (5-FU) in formulation of 5 % cream. It is known to interfere with DNA and RNA synthesis resulting in cellular death. 5-FU cream is effective when used one to three times weekly for several weeks especially for troublesome intraurethral (meatal) or perianal condylomata or intraepithelial neoplasia (IN) of external genitalia. It should be washed off 3–10 h after application. When used on genital area, it (often) causes inflammation accompanied by pain, burning and possibly ulceration. However, for cutaneous warts, it can be used daily under occlusion and/or in combination with up to 10 % salicylic acid.

Antiviral agent cidofovir has been used as intralesional injection or 1–3 % topical preparation (gel, cream and ointment) for both cutaneous and genital (especially hyperkeratotic) lesions as well as intraepithelial neoplasia. Its systemic use for HPV mucocutaneous manifestations is, even though proven successful, limited by its toxicity and reserved for immunocompromised patients.

Topical immunomodifiers are another group of drugs used for HPV infections in dermatovenereology that has imposed itself among other therapeutic options. Most commonly used agent in this group is *imiquimod* which will be discussed in more details in separate chapter. The use of *sinecatechins*, extracts derived from green tea leaves, as 10 % (Europe) or 15 % (USA) ointment three times daily for 16 weeks in treatment of anogenital condylomata, offers yet more reason for excitement since clinical studies have demonstrated their ability to induce complete clearance with a low recurrence rate. Adverse effects include erythema, pruritus and pain. The use of *interferons*, topical, intralesional and systemic, has displayed contradictory results so far. Systemic therapy, burdened by high cost and adverse effects, is not recommended for routine use (Kirnbauer et al. 2012). Studies demonstrating satisfying results of *zinc sulphate* 10 mg/kg up to 600 mg daily have been published but still awaiting confirmation from clinical practice (Yaghoobi et al. 2009).

Topical (tretinoin, tazarotene) and systemic (acitretin, isotretinoin) *retinoids* seem to interfere with HPV replication and virions assembly through their effect on keratinocyte proliferation and differentiation, thus expanding their clinical spectrum.

Immunotherapy in the context of HPV infections has not been routinely used, but evidence of its efficacy is well documented. Agents such as diphenylcyclopropenone 0.5–4 % and squaric acid dibutyl ester were given intralesionally at various interval rates producing high percentage of clearance rate. Intralesional application of *Candida*, *Trichophyton* and/or mumps skin test antigens has also been used with certain success in immunocompetent patients.

Recommended approach for the treatment of genital warts in pregnancy includes cryotherapy, trichloroacetic acid, surgical and laser treatment since all of these options are considered generally safe. Several therapeutic modalities are, as mentioned, designed for at home use by patient alone in cases/circumstances where compliance is expected and lesions clinically visible and accessible. These modalities include podophyllotoxin 0.5 % solution or gel, imiquimod 5 % cream and sinecatechins 15 % ointment. Same therapeutic regimes, with perhaps some minor modifications, are foreseen both for immunocompetent and immunocompromised patients regarding HPV infections, although closer monitoring of precancerous lesions is mandatory in the latter group of patients. However, despite seemingly broad therapeutic options, recurrence rate remains relatively high and further aggravated by the questionable reduction of transmission to new sexual partners.

Currently there are two *HPV vaccines* commercially available on the market: quadrivalent vaccine (Silgard™, Gardasil™, Merck, MSD) and bivalent vaccine (Cervarix™, GlaxoSmithKline). These vaccines consist of the virus-like particles of the L1 major capsid protein, but do not contain viral DNA, and so far extensive studies have proven their efficacy in inducing high-titre, long-lasting and type-specific neutralizing antibodies. Their (primary) role is prophylactic as quadrivalent vaccine prevents HPV types 6, 11, 16 and 18, whereas bivalent vaccine prevents HPV types 16 and 18. Providing the protection against the most common four HPV DNA types, the quadrivalent vaccine has a greater target in dermatovenereology. It has been licenced for use in females and males 9–26 years of age, preferentially before beginning of sexually active period, hence before exposure to HPV. Vaccines are administered as intramuscular injections given in three series at 0, 2 and 6 months. Adverse effects include erythema, oedema, itching and pain at the site of injection. These types of vaccines have not been theoretically designed as therapeutic measures since they have no ability to prevent disease progression nor induce disease regression. However, there have been some anecdotal reports about the therapeutic efficacy of the quadrivalent HPV vaccine suggesting that immunity induced by vaccination is four to five times superior to that induced by natural infection, but, definitely, more consistent studies are required. Therapeutic success of Gardasil has also been demonstrated in conjunction with local application of imiquimod. In spite of the fact that the vaccines have been commercially available for relatively short period of time (depending on the geographical distribution and the economy income of the different countries worldwide), quite encouraging conclusions can be made (so far, of course) about the great impact of the HPV vaccine on the reduction of HPV-induced anogenital diseases and the HPV oncogenic potential. Moreover, the HPV has overcome the "only sexually transmitted infection (STI)" limitation, and this virus has been associated today with the great spectrum of cancers (not only cervical but also anal, penile, pharyngeal, oral, tonsillar, etc.). Thus, the HPV vaccine might be one of the first examples how the oncogenic disease might be successfully prevented! Future perspective concerning HPV infection seems to be grounded on further development of preventive and curative vaccines, as currently several such vaccines are being engineered.

Drugs for the Treatment of Mollusca Contagiosa

Treatment of mollusca contagiosa from dermatovenereological point of view depends on the size, number and site of lesions, convenience, cost of treatment, patient discomfort and preference as well as physician's experience. Given the self-limiting course of disease in immunocompetent patients, the span of therapeutic options ranges from attentive "wait and see" approach, assuming patient education and reassurance, to decisive acts directed to destroy cutaneous lesions induced by *Molluscipoxvirus*. Former approach is seldom accepted by patients and potentially complicated by the autoinoculation, increasing contagion, risk of scarring and further patient distress. On the other hand, overaggressive treatment is not eligible approach in this case either.

Indications and Other Uses

Local therapy, with its modalities almost identical to those used for treatment of HPV infection, includes mechanical methods such as curettage, cryotherapy, with or without the prior use of local anaesthetic cream (EMLA), and pulsed dye or carbon dioxide laser. Topical application of keratolytics such as bi- and trichloroacetic acid, salicylic, glycolic and lactic acid is also effective approach. Cantharidin solution 0.7–0.9 %, a type of terpenoid known for its chemovesicant properties, is usually applied at 3–4 week intervals, and the area is thoroughly washed 30–60 min after application. It is generally considered safe, effective and well tolerated when used properly even though it has not warranted FDA approval for this indication (Mathes and Frieden 2010). Precaution should be made since its application can be accompanied by pain and skin erosion. Topical application of cidofovir gel 0.1 %, an

antiviral drug, has been reported to inhibit *Molluscipoxvirus* DNA polymerase activity (Skerlev et al. 2011). Cytotoxic therapy is based on successful usage of 0.5 % podophyllotoxin cream. Imiquimod cream, either 1 % applied three times daily or 5 % applied once a day for 4 weeks, is a relatively new therapeutic option representing the topical immunomodifying method by stimulation of cell-mediated immunity. However, significant irritation can sometimes be observed, which together with its (relative) cost makes this therapeutic option less used for this indication. Sinecatechins 15 % ointment is also effective, albeit off-label, approach within the group of topical immunomodifiers. Other options include tretinoin cream 0.05 % or gel 0.025 % applied once or twice a day. Intralesional interferon alpha once a day for 4 weeks is a therapeutic option in immunocompromised (AIDS) patients, in whom satisfying results can be achieved also by laser therapy together with highly active antiretroviral therapy which itself is known to improve mollusca.

Systemic therapy of mollusca contagiosa with retinoids or cimetidine (30–50 mg/kg of cimetidine daily in divided doses for up to 3 months) is supported by the assumption that it stimulates cell-mediated immunity by increasing the number of CD4+ lymphocytes. For the same reason, it can be used for HPV infection.

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Beta-Blockers for Hemangiomas

135

Carlo Gelmetti and Riccardo Cavalli

Key Points

- Infantile hemangiomas (IHs) are the most common tumors of infancy. Their typical natural history is characterized by an early rapid growth in the first months of life and by a slow spontaneous involution in the first years of life.
- Even though spontaneous regression of IHs could suggest therapeutic abstention, systemic treatment is the therapy of choice in many patients in which these situations occur: (1) rapid growth of IHs; (2) location of IHs in aesthetically critical areas; (3) recurrent hemorrhages, ulcerations, or infections of IHs; (4) IHs interfering with important physiological functions (breathing, feeding, vision, hearing, etc.); and (5) large or multicentric IHs that can cause heart failure.
- Since 2008, systemic administration of propranolol, an old nonselective beta-blocker, was found, serendipitously, to improve the treatment of IHs replacing older and more dangerous therapies like oral steroids, vincristine, interferon-alpha, or vascular lasers. At present, oral propranolol has dramatically changed the approach of IHs because its efficacy is almost 100 % and its action is rapid, without important side effects. The formal approval by the FDA and EMA has been declared in 2014.

General Principles

Infantile hemangioma (IH) is the most common tumor of infancy ranging from a tiny red papule to a giant mass. Its typical natural history is characterized by an early rapid growth following birth and a slow spontaneous involution which is complete before puberty but almost complete within the first 3–6 years of life. The cause underlying IH is still unknown, but the role of fetal hypoxic stress is strongly suggested as a triggering signal. A different hypothesis suggests that IH can be derived from embolized placental progenitor cells that lodge in privileged sites of the developing embryo. Alternatively, IH has been reported as an aberrant proliferation and differentiation of a primitive mesoderm-derived hemogenic endothelium regulated by the renin-angiotensin system

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_135, © Springer-Verlag Berlin Heidelberg 2015

(RAS) leading to propose angiotensin-converting enzyme (ACE) as a potential therapeutic target. While some angiogenic factors have been identified (e.g., mast cells, heparin), there are no data demonstrating a hereditary component. Immunohistochemical studies of IH confirm their vascular origin. During the proliferative phase, IH shows a high expression of cell proliferation nuclear antigen, vascular endothelial growth factor (VEGF), type IV collagen, urokinase, basic fibroblast growth factor (bFGF), and von Willebrand factor. These data demonstrate active angiogenesis and are not observed in vascular malformations.

IHs occur in up to 4–5 % of neonates, although up to 30 % in premature babies with low birth weight (<1 kg). They are significantly more frequent in females, with a 3:1 to 5:1 female/male ratio. The majority of IHs are noticed in the postnatal period more often during the first to second week, even though few of them may already be visible at birth, although usually with very different clinical features. IHs are distinguished from other less common vascular malformations of infancy by their characteristic clinical course. Although each lesion may have a distinct growth pattern, most follow a typical course divided into four stages: (1) nascent, (2) proliferative, (3) steady state, and (4) involution.

The first stage is the newborn stage prior to emergence of lesions, which typically lasts a few days. In fact, when IH is present at birth as a precursor, it is very small and flat, usually represented by an erythematous dot or patch or, paradoxically, by an ischemic patch ("herald patch") mimicking "nevus anemicus," or by telangiectasias surrounded by an ischemic halo. The majority of IHs appear as a single lesion; although there is no limit to their numbers, it is very rare to see more than five or six lesions. Equally rare are visceral IHs, usually hepatic. Topographically, the head is the most affected region, accounting, alone, for about 50 % of total lesions. History and phenotype allow, in most cases, diagnosis of IHs without the need for additional intensive investigations.

During the following 3–6 months, proliferation occurs in an early proliferative stage which brings rapid growth in the first few months of life, followed by a late proliferative stage with less rapid growth. As compared to superficial or localized lesions (the so-called "strawberry angiomas"), deep or segmental lesions, as those affecting the parotid region, appear to have a mysterious and prolonged proliferative phase extending beyond 6 months and rarely beyond the first year of life; in addition, in these phenotypes, the precursors and the first steps of the proliferative phase cannot be clinically observed. However, most lesions still cease growth by 9 months of age. The steady state or stabilization phase is of variable duration, usually a few months. Involution is typically heralded by a change in color from bright red to gray or purple, as well as a softening texture and flattening or diminution in size. Thermographic studies show a higher temperature of IHs, rising in the proliferative phase and fading in the evolution stage. Approximately most of IHs involute by 5–7 years of age, but smaller lesions are not noted any more at the time of primary school.

It should be noted that the deep localization of IHs, in the absence of a superficial "sentinel" IH, delays greatly the observation of the lesion, which is not usually discovered until after its full proliferative stage. The spontaneous regression of IH leaves minimal sequelae in about half the cases; it can result in various degrees of lesions (scars, telangiectasias, yellowish hypoelastic patches, etc.), especially on the head. It is difficult to predict the quality of the final regression, which is not influenced by gender, race, site or size of the lesion, presence or absence at birth, and duration of the proliferating phase. Of course, usually, smaller lesions have a better outcome and deeper lesions more rarely produce sequelae that alter the skin surface.

In addition to the aesthetic changes, IHs may ulcer, producing hemorrhages that can obstruct the respiratory and digestive tract. Big IHs with rapid regression may form a scab with cicatricial sequelae. In periocular localizations, impaired vision may occur. Amblyopia and astigmatism are the most common ophthalmic complication of IHs. Orbital lesions are less common, but, secondary to their mass effect, they may result in

strabismus, proptosis, exposure keratopathy, or compressive optic neuropathy.

Histologically, IHs are composed of a complex mixture of cells including multipotent stem cells, a majority of immature endothelial cells, pericytes, dendritic cells, and, in the late stage, adipocytes. In the proliferating phase, there is a new production of capillaries, sometimes mixed with larger vascular lacunae due to proliferation and swelling of endothelial cells, and mast cells are greatly increased in number. In the involuting phase, the cellular component becomes scarce, and vascular lakes regress and are replaced by fibroadipose structures. In the stable phase, under electron microscopy, the endothelial cell shows swollen mitochondria and activity of the rough endoplasmic reticulum; additionally, there is thickening of the basement membrane.

A critical consideration concerns the treatment of IH. Spontaneous regression of IHs could suggest therapeutic abstention but this attitude is not wise in the majority of cases. We agree with those authors who recommend therapeutic abstention, but only for very small IHs (<3 cm by the 3rd month of age, <6 cm by the 6th month of age) and for those whose locations do not create problems either objectively or subjectively. Otherwise, we recommend treating IHs, because, first, by limiting the expansion we can limit the symptoms, and, second, a small IH will have, in any case, a negligible fibroadipose residue. Finally, it should be considered that even a small IH located in an exposed site can cause variable psychological damage from the time of socialization onward. An early intervention is, therefore, recommended also in this case. In short, and especially after the rediscovery of propranolol, the sentence: "Leave it alone; it will go away" is no longer a universally acceptable advice for IH (Requena and Sangueza 1998). It is, however, better to continue to follow up the patients and their parents, reassuring them of the favorable outcome, with the aid of illustrations and photographs that show the evolution of these lesions. Local treatments (e.g., elastic compression, cryotherapy, laser therapy, ultra-potent topical corticosteroids, etc.) are often disappointing or impossible for various practical reasons, so that systemic treatment remains the therapy of choice in some situations: (1) rapid growth of the lesion; (2) location of the lesion in aesthetically critical areas; (3) recurrent hemorrhages, ulcerations, or infections; (4) in lesions interfering with important physiological functions (breathing, feeding, vision, hearing); and (5) large or multicentric IH that can cause heart failure.

To answer the question that parents have regarding the current stage of IH growth or involution, it is important to consider all available data: anamnestic, photographical, morphological (usually, IHs that are easily and frequently compressed against a bony surface, such as the back, stop earlier, while those that occur in very extensible areas, such as parotid, lateral-cervical, or mammary regions, expand much more), and especially the three parameters of color, temperature, and consistency. The color (not detectable only in subcutaneous IH) is connected with the temperature (that is related with metabolic activity) and with the consistency (in the proliferating phase, most of the mass is formed by endothelium that proliferates and forms solid cords with a small lumen and therefore difficult to compress). The increase of color, temperature, and consistency therefore indicates the proliferating phase of IH, while their reduction indicates the beginning of the involuting phase.

Infantile Hemangiomas and Beta-Blockers

Infantile hemangiomas (IHs) are vascular tumors expressing intrinsically benign proliferations with a spontaneous tendency to regression. So, when lesions are small and located in body regions that are aesthetically indifferent, a "wait-and-see" policy is the best management (Chandran et al. 2013). In many cases, the size and/or the localization of the lesion cause significant cosmetic deformity or functional compromise requiring a prompt treatment. Unfortunately IHs are mainly located in the head and neck area. In any case, besides aesthetic risks, the main indications for treatment of IHs are: life-threatening conditions (heart failure, respiratory distress),

functional risks (amblyopia, swallowing disorders, etc.), and painful ulcerations.

For almost half a century, corticosteroids have been the first-line therapy for complicated IHs. Fortunately, this treatment was effective in the majority of patients affected by IHs and led to a progressive disappearance of older and more dangerous treatments like radiotherapy, cryotherapy, chemotherapy (like vincristine or cyclophosphamide), interferon-alpha 2a, therapeutic embolization, laser, and surgery.

Systemic corticosteroids, however, have a low safety profile, especially in infancy. Parents of children with IHs under treatment with systemic steroids are more worried during treatment and perceive a negative impact on normal life issues, including work and vaccination of their child. Not enough, the response to treatment is not homogenous, and rebound growth upon cessation of treatment is quite common.

At the end of 2007, by serendipity, the pediatric dermatologist Christine Léauté-Labrèze who works in the team of Professor Alain Taïeb in Bordeaux (France) realized that a common beta-blocker, the propranolol, could be used in the treatment of IHs. Indeed the propranolol was prescribed to treat hypertrophic obstructive cardiomyopathy, in a young infant with coexisting nasal IH, and the IH regressed rapidly. In the following year, she published the first two observations together with nine additional cases. Let's quote the original text (Leauté-Labrèze et al 2008):

> The first child had a nasal capillary hemangioma. Despite corticosteroid treatment, the lesion was stabilized but obstructive hypertrophic myocardiopathy developed, so the patient was treated with propranolol. The day after the initiation of treatment, the hemangioma changed from intense red to purple, and it softened. The corticosteroids were tapered, but the hemangioma continued to improve. When the corticosteroids were discontinued, no regrowth of the hemangioma was noted. When the child was 14 months of age, the hemangioma was completely flat. The second child had a plaque-like infantile capillary hemangioma involving the entire right upper limb and part of the face. At 1 month of age, a subcutaneous component developed, and despite corticosteroid treatment, the hemangioma continued to enlarge. Magnetic resonance imaging revealed intraconal and extraconal orbital involvement, as well as an intracervical mass causing compression and tracheal and esophageal deviation …. Ultrasonography showed increased cardiac output, and treatment with propranolol, at a dose of 2 mg per kilogram of body weight per day, was initiated. Seven days later, the child was able to open his eye spontaneously, and the mass near the parotid gland was considerably reduced in size. Prednisolone was discontinued …. without any regrowth of the hemangioma; at 9 months of age, the eye opening was satisfactory, and no major visual impairment was noted. After …, propranolol was given to nine additional children who had severe or disfiguring infantile capillary hemangiomas….. In all patients, 24 hours after the initiation of treatment, we observed a change in the hemangioma from intense red to purple; this change was associated with a palpable softening of the lesion. After these initial changes, the hemangiomas continued to improve until they were nearly flat, with residual skin telangiectasias. Ultrasound examinations in five patients showed an objective regression in thickness associated with an increase in the resistive index of vascularization of the hemangioma…

Mechanism of Action, Indications, and Other Uses

Propranolol is a member of a class of medications called beta-blockers. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure. Propranolol is an old drug classically used for decades to treat high blood pressure, abnormal heart rhythms, heart disease, pheochromocytoma, and certain types of tremor but also to prevent angina and migraine headaches and to improve survival after a heart attack. Several mechanisms may be involved in the control of IH growth by propranolol. Propranolol is responsible for a vasoconstriction of the microvessels of the IH resulting in a rapid change in color and softening. It lowers the rate of renin and thus has a modulating effect on angiotensin II. In addition, β-adrenergic receptors belong to the family of G-protein-coupled receptors, which, when activated by adrenergic catecholamines, can promote a series of intracellular signal transduction pathways including that of angiogenic factors such as VEGF or bFGF and some metalloproteinases such as

MMP2 and MMP9. Finally, propranolol could lead to an early apoptosis of endothelial cells that make up the majority of IHs.

Propranolol seems to act with a dose-dependent cytotoxic effect in IH endothelial cells with decreased cell viability, migration, and tubulogenesis. This cytotoxic effect has shown to be VEGF dependent. Decreased VEGF activity is mediated through the hypoxia-inducible factor (HIF)-1α pathway but not through NF-κβ signaling. Alternatively, propranolol may suppress IH growth by inhibiting expression of eNOS (endothelial nitric oxide synthase) protein and subsequent production of nitric oxide.

More recent investigations (Tu et al. 2013) demonstrated that propranolol induces apoptosis of IH endothelial cells through typical apoptotic changes, including shrinkage, formation of apoptotic bodies, and retention of plasma membrane integrity. The molecular and genetic mechanisms underlying the therapeutic effects of propranolol revealed that this beta-blocker drug led to a marked increase in the expression of caspase-8, cytochrome *c*, apoptosis-inducing factor, caspase-3, and poly(ADP-ribose) polymerase 1, as well as a concomitant reduction in lamin B1 expression. In short, these data demonstrate that propranolol induces apoptosis of IH endothelial cells through activation of the intrinsic and extrinsic apoptotic pathways, explaining its therapeutic effects against IHs. Nevertheless, some molecular mechanisms that could induce resistance to apoptotic stimuli and, therefore, justify the possible insensitivity of some IHs to propranolol have already been described (Caussé et al. 2013).

Treatment Regimen and Dosage

Most of the patients with IHs respond to propranolol more satisfactory and more quickly than systemic corticosteroids at 2 mg/kg per day in two divided doses. The average treatment duration with beta-blockers is 6 months continuously. However, the treatment can be more prolonged when the situation of the IH is problematic (Parikh et al. 2013). The latest available meta-analysis (Lou et al. 2014) concerning the efficacy of propranolol for IHs reviewed 35 studies involving 324 patients and 248 controls, comparing propranolol with steroids, vincristine, and laser in treating cutaneous IHs, periocular IHs, infantile airway hemangiomas, and infantile hepatic hemangiomas. The conclusions of these studies provide a strong evidence for propranolol as a first-line therapy for IHs.

Rebound growth, although mild, can occur in some patients. Late rebound can also be observed indicating a prolonged proliferation IHs even after the first year of age. Late proliferation can occur also after several months of a positive response to propranolol. However, a second course of propranolol is readily able to control the recurrence (Shehata et al. 2013).

In addition to propranolol, which is a lipophilic nonselective beta-blocker, other beta-blockers have been used in the treatment of IHs. Oral atenolol, a hydrophilic selective beta-1 blocker, compared with a control group treated with propranolol, seems to be equally effective and safe (de Graaf et al. 2013).

Topical propranolol in ointment or in gel and topical timolol have also been used with satisfactory results on superficial IHs (Mouhari-Toure et al. 2013).

In the last 5 years, some authors are evaluating whether IH treated with pulsed dye laser (PDL) and propranolol displayed more rapid and complete clearance than IH treated with propranolol alone. In a retrospective and blind review of facial-segmental IHs, those cases treated with a combination of propranolol and PDL displayed more rapid and complete clearance and required a lower cumulative propranolol dose to achieve near-complete clearance (Vigone et al. 2012).

Contraindications and Side Effects

While cardiovascular diseases and asthma are absolute contraindications for propranolol therapy, relative contraindications include: hypersensitivity to propranolol in first-degree relatives, diabetes mellitus, chronic renal insufficiency, and cerebrovascular anomalies. Adverse events

(hypotension, somnolence, wheezing, insomnia, agitation and/or nightmares, hypoglycemia) are rare and uneventful and do not require, usually, treatment suspension. As far it concerns the frequency of side effects, a systematic review of 1,264 patients treated with propranolol for IHs showed (besides a high rate of efficacy) a low rate of serious adverse events with reports of symptomatic hypotension in five patients (0.39 %), hypoglycemia in four (0.31 %), and symptomatic bradycardia in one (0.079 %). The milder and most common adverse events were changes in sleep ($n=136$; 10.75 %) and acrocyanosis ($n=61$; 4.8 %) (Marqueling et al. 2013).

Propranolol has also been proposed as a first-line therapy of thyroid dysfunction associated with IHs. Consumptive hypothyroidism is a rare condition related to massive IHs producing an excess of the thyroid-hormone-inactivating enzyme type 3 iodothyronine deiodinase. While corticosteroid treatment showed only partial benefit in a large parotid IH, introduction of propranolol instead led to normalization of thyroid hormones along with a dramatic involution of the hemangioma (Vigone et al. 2012). A similar positive result was observed in thyroid dysfunction associated with severe infantile hepatic hemangiomas (Vergine et al. 2012).

Discussion and Final Remarks

Even though some authors think that, despite the numerous papers already published, more reliable prospective studies are still needed in the field of IHs treated with beta-blockers, we think that the efficacy coupled with the safety of oral (and probably topical) beta-blockers in the treatment of IH is now a matter of fact: propranolol is the first-line treatment of most IHs.

We are aware that the vast majority of the published literatures concern case reports and that there is a lack of well-designed, high-quality randomized control trials (e.g., beta-blockers versus corticosteroids), and we consider also that the updated knowledge of the broad spectrum of vascular anomalies described by Mulliken and Glowacki (1982) and Enjolras et al. (2007) and better detailed by the International Society for the Study of Vascular Anomalies (ISSVA) in 2014 is not universal. In other words, it is likely that, in some cases, the selection of the patients has not been optimal or it will not be optimal in the next future. However, we agree that the present availability of the big international study on propranolol in IH (the HEMANGIOL® study; ClinicalTrials.gov Identifier: NCT01056341) will confirm the experience of hundreds of doctors that treated thousands of patients. The final approval of beta-blockers for the treatment of IH by the FDA and EMA in 2014 has been a major step for the medicine, allowing all the physicians and the pediatricians (not only the academic doctors!) to prescribe this treatment for the most common tumor of infancy: the IH. In addition, it is not surprising that beta-blockers have already been used successfully in other vascular proliferations such as pyogenic granulomas (Wine Lee et al. 2014).

Our protocol for the management of complicated IHs is summarized in Table 135.1a–c. Obviously, when a complex syndrome is suspected, e.g., PHACES and PELVIS or SACRAL or LUMBAR,[1] additional investigations should be considered such as eye examination, head ultrasound, MRI/CT scan of the brain, etc. Ultrasound examination of the abdomen for hepatic hemangiomas should be advised in case

1 PHACES is an acronym: P, posterior fossa malformation (brain); H, hemangiomas; A, arterial anomalies; C, coarctation of the aorta along with cardiac defects; E, eye abnormalities; and S, sternum and/or supraumbilical abdominal raphe clefts. PELVIS, SACRAL, and LUMBAR are acronyms that denote the association of local hemangioma and malformation in the pelvic region, e.g., PELVIS = perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag. SACRAL = spinal dysraphism, anogenital anomalies, cutaneous abnormalities, renal and urologic anomalies, and angioma of lumbosacral localization. LUMBAR = lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies.

Table 135.1 Practical approach to treatment of IHs with beta-blockers

(a) Inclusion criteria
Patient with IH in cosmetically or functionally relevant areas
Patient with IH in growing or stable phase
Normal lab tests: full blood count, blood glucose, and urea
Normal pediatric evaluation
Normal cardiac evaluation
Parent counseling and consent for propranolol treatment
Direct access to the hospital in case of any emergency
(b) Exclusion criteria
Patient
Cardiovascular disorders
Asthma
History of transient or prolonged hypoglycemia in neonatal period
History of seizures, dizziness, somnolence, and/or restless sleep or nightmares
Severe atopic disorders
Children with low caloric intake
Known allergy to the drug
Coexisting treatments[a]
Family
History of cardiac arrhythmia
Autoimmune disease, i.e., SLE
(c) Dosing oral propranolol
Initial dose – 0.5 mg/kg every 12 h for the first week
If vital signs and general mood are not affected, the dose can be doubled – 1 mg/kg every 12 h for 6 months (average)
If vital signs and general mood are not affected but IH does not respond in 1 week's time, the dose can be raised up to 1.5 mg/kg every 12 h
Follow-up – first review after 1 week and subsequent visits every month
Final dose – 0.5 mg/kg every 12 h for the last week of treatment

This protocol does not apply to complex and/or multisystemic syndromes

[a]Theoretically cimetidine and other medications for heart disease or high blood pressure such as reserpine are contraindicated. In practice, given the typical age of patients with IHs, this event does not occur. For the same reasons, other recommendations concerning propranolol ("Do not drive a car or operate machinery" or "do not take alcohol" until you know how this drug affects you) do not apply to infancy

of neonatal diffuse hemangiomatosis or when cutaneous IHs are more than five.

In the meantime and in the next future, besides for a formal approval of the use of beta-blockers for the treatment of IHs by health authorities, we must always consider the potential side effects of this class of drugs. Thus, parents and caregivers should check the possible appearance of the following items:

- Allergic reactions such as skin rashes (itching or hives), swelling in the face or hands, swelling or tingling in the mouth or throat, and chest tightness
- Mood change, unusual tiredness or weakness, trouble sleeping (nightmares), trouble awakening, or losing consciousness
- Cold sweats and/or bluish-colored skin
- Slow, fast, or uneven heartbeat

In order to prevent hypoglycemic status (check: coldness, shakiness, and sweating), it is wise to give propranolol during mealtime or right after your child has eaten. In our experience (more than 200 children with IHs treated with oral propranolol from 2008 to 2013 – unpublished data), the side effects have always been mild, and in just two cases, the treatment has been stopped prudently and in no case severe side effects have been observed while the efficacy has always been good and, in some cases, spectacular (Fig. 135.1a–d). In addition, we were able to rule out hyperkalemia from the list of possible side effects. Indeed hyperkalemia and hyperphosphatemia observed in a 33-day-old female with an ulcerated IH undergoing oral therapy with propranolol were finally linked with tumor lysis syndrome that was diagnosed after excluding other causes of electrolyte imbalance in the diagnostic workup (Cavalli et al. 2012).

Conclusion

The serendipitous discovery of the efficacy of beta-blockers in the treatment of IHs has been a milestone in pediatric and in dermatologic practice and has revolutionized the approach to these neoplasms. Fortunately, this drug is

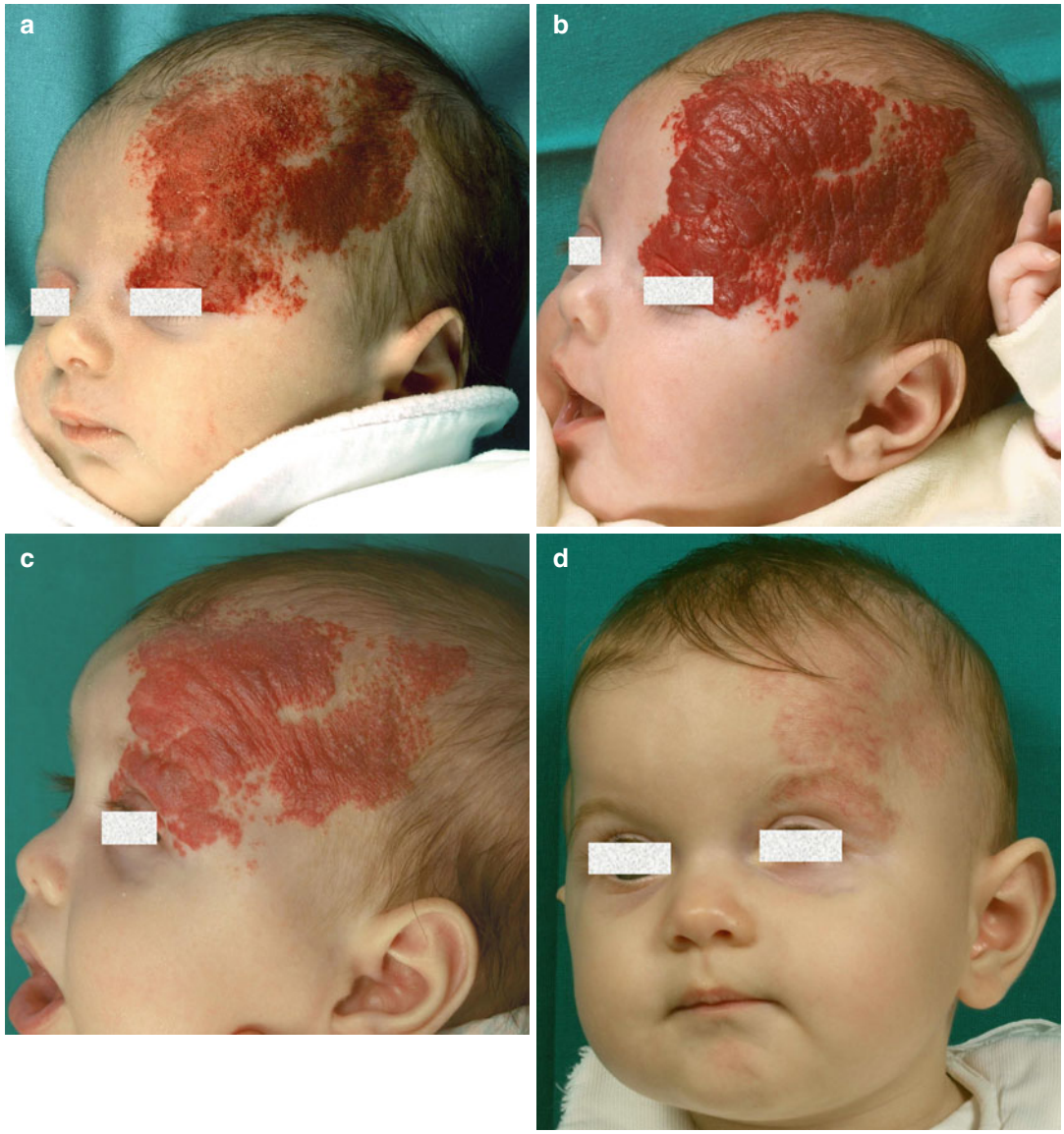

Fig. 135.1 (**a**) This newborn, 17-day-old girl, presented with a large plaque-like IH showing a rapid enlargement with the involvement of the first trigeminal branch causing eye obstruction. (**b**) A cycle of oral corticosteroids for 1 month was almost ineffective and the left eye was still closed. (**c**) A cycle of oral propranolol was greatly effective within the first week of treatment. (**d**) At 6 months of life, the IH showed a complete regression with mild slack skin and fine telangiectasias

now an approved therapy for IHs. There is great debate regarding appropriate monitoring protocols for initiating and maintaining propranolol therapy in infants with IHs as well as right parameters to follow, including the possible hospitalization of the patient. We are happy that precise treatment guidelines have recently come to help doctors and caregivers in this field. However, we strongly suggest, for the present time but also for the future, the constant need of a multidisciplinary approach for all vascular anomalies.

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Biofeedback

136

Jacopo Lotti and Alberto Cossidente

Abbreviations

AAPB	Applied psychophysiology and biofeedback
BCIA	Biofeedback certification international alliance
BFB	Biofeedback
CBT	Cognitive-behavioral therapy
EEG	Electroencephalography
EMG	Electromyography
GSR	Galvanic skin resistance
HRV	Heart rate variability
ISNR	International Society for Neurofeedback and Research

Key Points

- Biofeedback is a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance.
- Biofeedback training may resolve dysfunctional thought patterns, actions, or habits that may damage the skin or interfere with dermatologic therapy.
- Dermatologic disorders that have an autonomic nervous system component can be successfully diagnosed and improved using biofeedback as a complementary approach.
- Biofeedback is an active training, not a passive treatment.
- Biofeedback is a nondrug, noninvasive, and side effect-free approach.

General Principles

In 2008, the Association for Applied Psychophysiology and Biofeedback (AAPB), Biofeedback Certification International Alliance (BCIA), and International Society for Neurofeedback and Research (ISNR) – three international biofeedback organizations – reached a consensus definition of biofeedback: "Biofeedback is a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_136, © Springer-Verlag Berlin Heidelberg 2015

instruments measure physiological activity such as brainwaves, heart function, breathing, muscle activity, galvanic skin resistance, and temperature. These instruments rapidly and accurately 'feed back' information to the user. The presentation of this information – often in conjunction with changes in thinking, emotions, and behavior – supports desired physiological changes. Over time, these changes can endure without continued use of an instrument."

Biofeedback (BFB) is the process of gaining greater awareness of many physiological functions primarily using instruments that provide information on the activity of those same systems, with a goal of being able to manipulate them at will. Some of the processes that can be controlled include brainwaves, muscle tone, skin conductance, galvanic skin resistance, heart rate, and pain perception.

BFB may be used to improve health, performance, and the physiological changes that often occur in conjunction with changes to thoughts, emotions, and behavior. Eventually, these changes may be maintained without the use of extra equipment, even though, once the know-how is learned, no equipment is necessarily required to practice biofeedback.

Classification: Disciplines and Approaches Behind Biofeedback

Biofeedback (BFB) is a procedure – still considered experimental, even after 50 years from its invention – that consists mainly in providing the subject with information, with the assistance of appropriate instruments, regarding neurovegetatively (autonomic nervous system) controlled biological functions. The procedure provides a sort of biological mirror insofar as it furnishes the conscious mind with an idea of the functioning or misfunctioning of certain "visceral activities." For a long time, experimental and clinical psychology taught that learning through "operant conditioning" was possible only in relation to behavior therapy or, in any case, through the mediation of behavioral conditioning. Learning related to visceral functions controlled by the neurovegetative system was considered possible only via "classic conditioning."

The essential difference between the two above theories is that operant conditioning requires the active intervention of the individual. It is inherent in the learning scheme of this method that when there exist different possible alternative responses to a particular stimulus, then by rewarding a certain response one increases the possibility that this response will follow when the specific stimulus presents. A well-known example is Pavlov's dog, who salivated whenever he saw food; by ringing a bell when the food appeared, Pavlov managed to condition the dog to salivate when the bell was rung, even if no food appeared.

In the 1960s, a group of investigators furnished "experimental proof" that visceral control could be learned, thus opening new roads for the systematic application of methods for learning operant conditioning of functions considered autonomous in humans (Miller et al. 1960) .

These studies stimulated research leading to elaboration/development of reliable methods, using appropriate instruments, to render sensorially perceptible changes in functions controlled by the autonomic nervous system (Miller et al. 1960). Thus it became possible to reward a specific response such that the subject was able to associate with certainty the reward with that specific response. In such cases the recompense was symbolic and consisted in the individual's capacity to influence an autonomous organic function.

The new technique was called biofeedback, a combination of the words biology and feedback, meaning literally "biological return information." The biological information, regarding vital functions, such as heartbeat, muscle tone, skin temperature and resistance, electric potential of the brain registered by electroencephalogram, and others, are recorded by special instruments and evidenced to the subject in the form of visual signals or sounds with parallel indications for any variations in the emotional state, all in real time. In very few years the use of BFB spread rapidly in the United States and then in Europe, and it soon became one of the most important new methods of investigation and treatment in psychophysiological medicine and psychiatry.

The rapid development and diffusion of BFB were due principally to the progress in electronics, with the continual production of more precise, reliable, and inexpensive instruments, associated with the affirmation of a new concept of many diseases that have been traced back to functional disturbances rather than to precise anatomic-pathological substrates (Sarti 1998).

Neither the technique nor the underlying BFB concept has been fully developed and classified. In fact, they are the objects of both facile and extreme enthusiasm and equally unjustified skepticism. Biofeedback proposes two very distinct subjects to psychiatrists and psychologists: one is the speculative and heuristic concept/subject involving relevant problems of self control, mind-body equilibrium, and individual responsibility in recovery or maintenance of someone's health; the other is the more practical aspect regarding the actual clinical efficacy of BFB training. In regard to the former, biofeedback as a concept is of undeniable importance, whereas the efficacy of clinical BFB training depends largely on the preparation and skill of the BFB operator who applies the technique, just as the actual therapeutic effects of a drug depend in each case upon both the drug's intrinsic pharmacodynamics and pharmacokinetic properties and, above all, its correct administration in the treatment strategy. The international literature on this topic allows us to conclude that, when correctly applied in the proper setting and in appropriate cases, BFB is a reliable and efficacious therapeutic measure. Cognitive-behavioral methods may resolve dysfunctional thought patterns (cognitive) or actions (behavioral) that damage the skin or interfere with dermatologic therapy. Responsive diseases include acne excoriée, atopic dermatitis, factitious cheilitis, hyperhidrosis, lichen simplex chronicus, needle phobia, psoriasis, onychotillomania, trichotillomania, prurigo nodularis, and urticaria.

BFB is a procedure of training as opposed to a treatment. Much like being taught how to tie their shoes or ride a bicycle, individuals undergoing biofeedback training must take an active role and practice in order to develop the skill. Rather than passively receiving a treatment, the patient is an active learner. It's like learning a new language.

The protocol calls for a preliminary meeting between the patient and the BFB operator before the first treatment session to identify the type of disturbance, establish the appropriate procedure, and explain it and its aims to the patient. During the first session the therapist records the patient's baseline psychophysiological parameters.

Mechanism of Action

Instrumentation that can measure manifestations of autonomic nervous system activity in the skin and then display it in a visual, auditory, or kinesthetic mode gives the individual sensory biofeedback. With training, individuals may learn consciously how to alter the autonomic response and with enough repetition may establish new habit patterns. Components of the instrumentation include detectors, amplifiers, processors, recorders, and visual displays, auditory tone or signal devices, or tactile signal devices.

The most commonly used biofeedback techniques measure and provide auditory or visual feedback of galvanic skin resistance (GSR), skin temperature, electromyography (EMG), and electroencephalography (EEG). The polygraph is a combined instrument that can measure these simultaneously along with heart rate variability (HRV) and respiratory rate.

Cutaneous problems that have an autonomic nervous system component can be improved by biofeedback. Examples include biofeedback of GSR for hyperhidrosis and biofeedback of skin temperature for Raynaud's disease. With training, individuals can learn how to consciously alter the autonomic response and with enough repetition may establish new habit patterns.

A young man with hyperhidrosis, described in Panconesi (1998) as reported by Sarti, had a very low initial GSR at the beginning of treatment and improved slowly over 20 sessions combining GSR biofeedback with autogenic relaxation training. Follow-up at 3 and 6 months after treatment, during which the patient continued to practice the autogenic training exercises, showed a continued reduction in palmar sweating (GSR) to near-normal levels. Systemic sclerosis patients with Raynaud's disease have been able to increase

finger skin temperature by an average of about 4 °C. Two of six patients using autogenic training in addition to biofeedback reported that they could shorten the duration of Raynaud attacks by autogenic training. Measurement of finger blood flow in another study with venous occlusion plethysmography, finger temperature, and GSR in patients with Raynaud's disease showed significant elevations in finger blood flow, finger temperature, and GSR conductance level in those given finger temperature biofeedback compared with those who received autogenic training but no biofeedback. A recent large study of Raynaud's patients compared learned hand-warming results using different biofeedback methods and found that attention to emotional and cognitive aspects of biofeedback training was important (Shenefelt 2003).

The opinion that biofeedback, hypnosis, and cognitive-behavioral techniques are branches of alternative medicine in this particular case in dermatology is surely debatable, but also interesting. We believe that these techniques are now a well-accepted part of official, evidence-based medicine, even in relation to dermatology.

Leaving aside discussion of the boundaries between "official" and "alternative" medicine, let us focus on the main problem, the patient, in our case the dermatologic patient who, in cases involving psychosomatic affections, can benefit greatly from the techniques outlined in this section.

Counseling is a task for and must be undertaken by the dermatologist (in the case of skin disorder patients): he/she is the partner and caretaker chosen by the patient who, at least initially, does not want to be referred to other specialists.

Indications and Other Uses

The use of biofeedback to investigate and complementary treat dermatologic problems is quite recent, being dependent on instrumentation to measure such parameters as galvanic skin resistance (GSR), muscular tension (EMG), heart rate variability (HRV), and skin temperature. Skin problems that have an autonomic nervous system component can be successfully assisted by biofeedback. Numerous dermatologic disorders may be improved using biofeedback as a complementary treatment, for example, acne excoriée, alopecia areata, atopic dermatitis, congenital ichthyosiform erythroderma, dyshidrotic dermatitis, erythromelalgia, glossodynia, recurrent herpes simplex, hyperhidrosis, ichthyosis vulgaris, lichen planus, nummular dermatitis, postherpetic neuralgia, pruritus, psoriasis, rosacea, trichotillomania, urticaria, viral warts, and vitiligo (Shenefelt 2002).

Using biofeedback, individuals may learn to consciously change their autonomic responses. In one report, a man increased his galvanic skin resistance after 20 sessions of biofeedback with autogenic relaxation training (Shenefelt 2005). Cognitive-behavioral therapy (CBT) plays a role in skin conditions that involve dysfunctional thought patterns that result in actions that cause skin damage. Examples include atopic dermatitis, factitious cheilitis, lichen simplex chronicus, prurigo nodularis, and acne excoriée. The therapy is designed to break the cycle of anxiety associated with the dysfunctional thought that is relieved by the destructive action. In one study, patients with atopic dermatitis scored higher in levels of anxiety and suppressed hostility compared with control patients with normal skin (Jordan and Whitlock 1972). In a variety of studies, CBT appears to be beneficial when used in combination with other therapies. One patient with acne excoriée improved with CBT, biofeedback, minocycline, and sertraline (Fried 2002). Factitious cheilitis responds to a combination of topical anti-inflammatory medications with CB. A 6-year-old child with vulvar lichen simplex chronicus improved within 13 weeks when the mother rewarded non-scratching behavior and ignored scratching (Bar and Kuypers 1973). These psychocutaneous therapies are all noninvasive and given their potential for efficacy may be beneficial when used in combination with other therapies (See Table 136.1).

In 2001, a Task Force of the Association for Applied Psychophysiology and Biofeedback and the Society for Neuronal Regulation outlined criteria for levels of evidence-based clinical efficacy of psychophysiological interventions (Moss and Gunkelman 2002). More recently, Yucha and

Table 136.1 Cutaneous affections reported to have high incidence of psycho-emotional factors (Panconesi 1998)

Hyperhidrosis	Telogen effluvium
Dyshydrosis	Alopecia areata
Pruritus sine material	Psoriasis
Urticaria	Seborrheic dermatitis
Lichen simplex	Nummular dermatitis
Atopic dermatitis	Lichen planus
	Herpes
	Warts
Acne	
Rosacea	
Perioral dermatitis	Vitiligo

Montgomery rated the current evidence on the efficacy of biofeedback training on various diseases and reported this in 2008. These ratings are summarized in Table 136.2 (See Table 136.2).

It appears that if a condition has a lower efficacy rating, this does not suggest that biofeedback is not helpful in that condition, but rather that relevant research has not yet been conducted. Also, when combined with conventional medical management, an individual may very much benefit from a "possibly efficacious" biofeedback application.

Table 136.2 Efficacy ratings for biofeedback training on various medical conditions (ratings were made by Yucha and Montgomery (2008) based on data from the cited references)

Level of evidence	Diseases	References
Level 5 Efficacious and specific	Urinary incontinence (females)	Burgio et al. (1998)
Level 4 Efficacious	Anxiety	Rice et al. (1993)
	Attention deficit hyperactivity disorder	Monastra et al. (2005)
	Chronic pain	Corrado et al. (2003)
	Constipation (adult)	Bassotti et al. (2004)
	Epilepsy	Sterman (2000)
	Headache (adult)	Arena et al. (2001)
	Hypertension	Linden and Moseley (2006)
	Motion sickness	Stout et al. (1995)
	Raynaud's disease	Karavidas et al. (2006)
	Temporomandibular disorder	Crider et al. (2005)
Level 3 Probably efficacious	Alcoholism/substance abuse	Sokhadze et al. (2008)
	Arthritis	Young et al. (1995)
	Diabetes mellitus	Jablon et al. (1997)
	Fecal incontinence	Solomon et al. (2003)
	Headache (pediatric)	Arndorfer and Allen (2001)
	Insomnia	NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia (1996)
	Traumatic brain injury	Hammond (2007)
	Urinary incontinence (males)	Van Kampen et al. (2000)
	Vulvar vestibulitis	Glazer et al. (1995)
Level 2 Possibly efficacious	Asthma	Ritz et al. (2004)
	Autism	Coben and Padolsky (2007)
	Bell's palsy	Dalla Toffola et al. (2005)
	Cerebral palsy	Bolek (2003)
	Chronic obstructive pulmonary disease	Giardino et al. (2004)
	Coronary artery disease	Del Pozo et al. (2004)

(continued)

Table 136.2 (continued)

Level of evidence	Diseases	References
	Cystic fibrosis	Delk et al. (1994)
	Depressive disorders	Karavidas et al. (2007)
	Erectile dysfunction	Van Kampen et al. (2003)
	Fibromyalgia/chronic fatigue syndrome	Mueller et al. (2001)
	Hand dystonia	Deepak and Behari (1999)
	Irritable bowel syndrome	Schwarz et al. (1990)
	Post-traumatic stress disorder	Silver et al. (1995)
	Repetitive strain injury	Peper et al. (2004)
	Respiratory failure: mechanical ventilation	Holliday and Lippmann (2003)
	Stroke	Woodford and Price (2006)
	Tinnitus	Heinecke et al. (2008)
	Urinary incontinence (children)	Khen-Dunlop et al. (2006)
Level 1 Not empirically supported	Eating disorders	Pop Jordanova (2000)
	Immune function	Gruber et al. (1993)
	Spinal cord injury	Brucker and Bulaeva (1996)
	Syncope	McGrady et al. (2003)

An initial evaluation can usually reveal whether physiology monitored by biofeedback is outside normal limits and whether correcting it is likely to help the symptoms or disorder. In the latter case, BFB is used as a diagnostic tool to quantify the gap between standard values in body-mind relax condition and patient recordings. The more measured values are far from standard ones, the higher the probability that skin disorder has a psychophysiological component.

Conclusion

Skin disorders can have a significant effect on the psyche, and the psyche through psycho-neuro-immuno-endocrine and behavioral mechanisms can have a significant effect on skin disorders.

Because many inflammatory dermatologic disorders are triggered or aggravated by stress and/or anxiety, investigation and teaching patients to practice safe stress using non-pharmacological methods deserve more attention in treatment planning. Adding nondrug physiological awareness training such as biofeedback often enhances the effectiveness of pharmaceutical, psychiatric, or psychological treatment. A multidimensional approach often enhances and optimizes the treatment response. Much additional research is needed to compare the single mode and multimodal treatment effectiveness of drugs, drug combinations, and non-pharmacological methods for modulating and improving skin disorders that have a significant psychological component.

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Biologic Agents for Psoriasis

137

Marina Papoutsaki and Christina Antoniou

Key Points

- The choice of treatment for psoriasis depends on the severity of the disease.
- The severity of psoriasis is not always easy to define as it depends both from the extension of the disease as well as its impact on the quality of life of the patients.
- The main target of almost all systemic treatments for psoriasis is the immune system.
- The introduction of biologics has brought an important therapeutic improvement for psoriasis.
- Biologics are a heterogeneous group of monoclonal antibodies, fusion proteins, and recombinant cytokines that modify and regulate pivotal and specific mechanisms involved in psoriasis' immunopathogenesis.
- At present, there are four biologics available for the treatment of psoriasis: three antitumor necrosis factor alpha (TNFα) agents, namely, adalimumab, etanercept, infliximab, and one anti-IL12/23 monoclonal antibody (mAb), ustekinumab.
- Patient candidates for a biological treatment need to undergo a detailed screening and a regular follow-up, in order to guaranty a good safety profile.
- Biologics show high efficacy both in the short and in the long term and a good safety profile.
- The better understanding of the pathogenetic mechanisms of psoriasis leads to continuous development of new therapeutic agents with very promising results.

General Principles

The choice of treatment for psoriasis depends on the severity of the disease; nevertheless, the evaluation of its severity may result difficult in some cases as not only objective parameters (extension, erythema, infiltration, etc.), but also the impact on the quality of life of the patients must be taken into consideration. Indeed smaller lesions may cause a higher psychological or physical discomfort for the patient depending on their localization.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_137, © Springer-Verlag Berlin Heidelberg 2015

Given the well-established role of the immune-mediated inflammation in the pathogenesis of psoriasis, the immune system is the main target of almost all systemic treatments available for this disease.

Systemic agents, including cyclosporine, methotrexate, and acitretin, or phototherapy, are usually prescribed in patients affected by moderate to severe plaque-type psoriasis or psoriatic arthritis. However, various factors may limit their long-term use, in particular the risk of serious cumulative organ toxicity and the lack of efficacy over time. Furthermore, underlying diseases, such as hypertension as well as renal and/or hepatic alterations, may represent contraindications to the abovementioned systemic treatments. Thus, effective drugs with less long-term toxicity are needed.

An excellent therapeutic improvement has been recently obtained by the introduction of the "biological response modifiers" or more commonly defined as "biologics." Biologics are a heterogeneous group of monoclonal antibodies, fusion proteins, and recombinant cytokines, designed to modify and regulate pivotal and specific mechanisms involved in psoriasis immunopathogenesis. To date, biologics have been suggested to have a more favorable side effect profile than conventional treatments.

Biological Agents for the Treatment of Psoriasis

Numerous biologics are approved by FDA or EMA and are actually being used for the treatment of psoriasis. These biologics include three antitumor necrosis factor alpha (TNFα) agents, namely, adalimumab, etanercept, infliximab, and one anti-IL12/23 monoclonal antibody (mAb), ustekinumab. All three anti-TNFα agents and the anti-IL12/23 agent, ustekinumab, are now commercially available for the treatment of both psoriasis and/or psoriatic arthritis.

Anti-TNF-a Agents

Etanercept

Mechanism of Action

Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand-binding domain of the human TNF receptor 2 and the Fc domain of human IgG1 antibody (including the hinge and CH2 and CH3 regions but not the CH1 region). Because of its structure, etanercept binds and neutralizes the inflammatory cytokines TNF-α and lymphotoxin-alpha (TNF-beta). As a soluble receptor, etanercept binds free but not transmembrane TNF-α and therefore blocks the inflammatory cascade triggered by TNF-α leading to anti-inflammatory and immunosuppressant activity.

Its terminal elimination half-life is about 4–5 days.

Indications

Etanercept has been approved for moderate to severe plaque-type psoriasis and psoriatic arthritis, in whom other systemic therapies and phototherapy have failed, are contraindicated, or not tolerated. Moreover, etanercept is the only anti-TNFα agent approved for the treatment of childhood psoriasis (in children over 6 years of age) and psoriatic arthritis (in children over 12 years of age) nonresponsive or intolerant to traditional systemic therapies or phototherapy.

Dosage and Mode of Administration

Etanercept is self-administrated subcutaneously.

Initial dose: 25 mg twice weekly or 50 mg once weekly or 50 mg twice weekly for the initial 12 weeks and then reduce to 25 mg twice weekly or 50 mg once weekly. However, the 50 mg/twice weekly seems to have stronger clinical activity. Pharmacokinetic modeling and simulation, as well as clinical studies, suggest that the systemic exposure is equivalent for the 25 mg twice weekly and the 50 mg once weekly regimens. Its efficacy and safety for the different dosing have been demonstrated in several randomized clinical trials.

For childhood psoriasis, the suggested dosage regimen is 0.8 mg/kg (up to a maximum of 50 mg of a single dose) once weekly.

Maintenance dose: 25 mg twice weekly or 50 mg once weekly after 12 weeks of treatment.

Combination Therapy

Etanercept is usually used in monotherapy. Nevertheless, the concomitant use of topical antipsoriatic therapies (topical steroids, vitamin

D_3 derivatives, tazarotene, dithranol) may be feasible and advisable especially in the early stages of treatment or in the cases of mild recurrences of the disease during the maintenance period.

Regarding its combination with other systemic antipsoriatic agents, MTX is an established association in the treatment of psoriatic arthritis, and it can be used also in plaque-type psoriasis. Successful association also with acitretin has been reported in the literature, while there are as yet no validated data on combination therapy with fumaric acid esters or cyclosporine.

Side Effects

The most commonly reported side effects reported are local reactions in the injection site. In patients receiving anti-TNFα agents, as etanercept, there is a higher risk of developing infections. The most common infections observed are these of the upper respiratory tract, bronchitis, and skin infections. Severe infections including sepsis, tuberculosis, demyelinating processes, vasculitis, pancytopenia, anemia, leukopenia, lupus erythematosus, thrombocytopenia, and urticaria are rare.

Drug Interactions

The use of etanercept is not advised in patients who are treated with anakinra (IL-1 R antagonist) or abatacept as an increased number of serious infections and neutropenia have been reported.

Infliximab

Mechanism of Action

Infliximab is a chimeric (25 % mouse, 75 % human) monoclonal IgG1 antibody able to bind TNF-alpha (transmembrane and soluble form) and, consequently, to inhibit TNF-alpha activity. In particular its binding blocks soluble TNF-α, neutralizing this way its proinflammatory activity, while binding to membrane cell-bound TNF-α leads to cell elimination, possibly as a result of complement activation and/or antibody-dependent cellular toxicity or induction of apoptosis.

Infliximab was the first anti-TNF-alpha therapy successfully used in psoriasis, in a woman affected also by refractory inflammatory bowel disease, and therefore treated with infliximab 5 mg/kg. Several studies show that infliximab acts on multiple steps of the pathogenic process of psoriasis.

Indications

Infliximab is approved for the treatment of psoriatic arthritis and plaque-type psoriasis.

Dosage and Mode of Administration

Infliximab is administered intravenously, and the dosage used for the treatment of plaque-type psoriasis is weight dependent.

Initial dose: There is an induction period with the dose regimen of 5 mg/kg at weeks 0, 2, and 6, followed by a maintenance dose.

Maintenance dose: The dose regimen is of 5 mg/kg every 8 weeks. This interval may be temporarily shorten up to every 6 weeks in these patients that present a time-related recurrence of the disease, in order to regain the efficacy.

The efficacy and safety of infliximab has been evaluated in several clinical trials. Infliximab shows a fast efficacy in the treatment of plaque and psoriatic arthritis.

Combination Therapy

Infliximab is usually used in monotherapy in plaque-type psoriasis. Nevertheless the concomitant use of topical antipsoriatic therapies (topical steroids, vitamin D_3 derivatives, tazarotene, dithranol) may be feasible and advisable especially in the early stages of treatment or in the cases of mild recurrences of the disease during the maintenance period.

Regarding its combination with other systemic antipsoriatic agents, MTX is an established association in the treatment of psoriatic arthritis, and it can be used also in plaque-type psoriasis. There are reports in the literature regarding its association also with acitretin (in particular in the case of recurrence of pustular forms of psoriasis) and cyclosporine.

Side Effects

Acute infusion reactions are a commonly reported side effect of infliximab, but usually these reactions are mild and transitory and

include chills, headache, flush, nausea, dyspnea, or infiltration at the infusion site. Due to this, it is advisable to monitor carefully the patient during the infusion and for 1 h afterward. Serum sickness may occur 3–12 days following the infusion. The probability of an infusion reaction is higher in patients that have developed infliximab-specific antibodies and in patients receiving the drug after a long treatment-free interval. The administration of an antihistamine can help reduce or prevent a moderate infusion reaction. Other common reactions are exanthema, pruritus urticaria, and increased liver transaminase. In patients receiving anti-TNFα agents, as infliximab, there is a higher risk of developing infections. The most common infections observed are these of the upper respiratory tract, bronchitis, and opportunistic infections. Severe infections including sepsis, tuberculosis, demyelinating processes, vasculitis, pancytopenia, anemia, leukopenia, lupus-like syndrome serum sickness, onset or exacerbation of psoriasis (often pustular forms of the disease), thrombocytopenia, anaphylactic shock, and liver cell damage are rare.

Drug Interactions

Based on the present information, no drug interactions of infliximab with other medications have been described. Nevertheless based on the reports that combination of etanercept with anakinra leads to a higher rate of serious infections, the combination of infliximab and anakinra is not advised.

Adalimumab

Mechanism of Action

Adalimumab is a fully human monoclonal antibody, genetically engineered using phage display technology, and it is structurally and functionally analogous to naturally occurring human immunoglobulins G1 (IgG1). This monoclonal antibody demonstrates a high specificity and affinity for TNFα but not other cytokines, such as lymphotoxin (LTβ).

Indications

Adalimumab is approved for the treatment of psoriatic arthritis and plaque-type psoriasis.

Dosage and Mode of Administration

Adalimumab is self-administrated subcutaneously.

Initial dose: The recommended dosing of adalimumab for the treatment of plaque-type psoriasis and psoriatic arthritis is an initial dose of 80 mg, followed by 40 mg the week after.

Maintenance dose: The maintenance dose is 40 mg/every other week starting from week 2. In some high-need patients, a dose regimen of 40 mg/weekly may be considered in order to enhance its efficacy.

The efficacy and safety of adalimumab has been evaluated in several clinical trials. Moreover, adalimumab was the first biological drug for which a comparative study with a conventional drug (methotrexate) has been performed.

Combination Therapy

No controlled studies on combination therapy have been performed, and adalimumab is usually used in monotherapy in plaque-type psoriasis. Nevertheless the concomitant use of topical antipsoriatic therapies (topical steroids, vitamin D_3 derivatives, tazarotene, dithranol) may be feasible and advisable especially in the early stages of treatment or in the cases of mild recurrences of the disease during the maintenance period.

Regarding its combination with other systemic antipsoriatic agents, MTX is an established association in the treatment of psoriatic arthritis, and it can be used also in plaque-type psoriasis. There are anecdotal reports in the literature regarding its association also with acitretin (in particular in the case of recurrence of pustular forms of psoriasis) and cyclosporine.

Side Effects

The most common adverse event reported from placebo-controlled clinical trials was injection site reactions, such as erythema, itching, pain, and swelling. Adalimumab can be associated with infectious adverse events, mainly of the upper respiratory tract, bronchitis, and urinary tract infections. Severe infections such as pneumonia, septic arthritis, postoperative infections, erysipelas, phlegmonous infections, diverticulitis, and pyelonephritis have also been described.

Thrombocytopenia and leukopenia have been rarely reported. Treatment with adalimumab may result in the formation of autoantibodies and infrequently in the development of lupus-like syndrome. Severe allergic reactions are rare and include exanthem, urticaria, pruritus, respiratory distress, tightness in the chest, as well as swelling of the mouth, face, lips, or tongue. Malignancy, especially lymphoma, is a very rare side effect.

Drug Interactions

The combination therapy with anakinra and abatacept may lead to serious infections, without any additional clinical benefit; therefore, their combination is not recommended.

Anti-IL12-23 Agents

Ustekinumab

Mechanism of Action

Ustekinumab is a human monoclonal antibody that binds to the shared p40 protein subunit of human interleukins 12 and 23 with high affinity and specificity, thereby preventing interaction with their surface IL.12Rβ1 receptor. In a population pharmacokinetic analysis based on data obtained from two pivotal large-scale phase III studies (PHOENIX 1, PHOENIX 2), different factors such as body weight, diabetes, and positive immune response (antibodies to ustekinumab) seem to be important covariates affecting the apparent clearance and/or apparent volume of distribution of ustekinumab.

Indications

Ustekinumab is approved for the treatment of psoriatic arthritis and plaque-type psoriasis.

Dosage and Mode of Administration

Ustekinumab is self-administrated subcutaneously at a dose of 45 or 90 mg according to the patient's weight (<100 kg or ≥100 kg).

Initial dose: The recommended dosing of ustekinumab for the treatment of plaque-type psoriasis and psoriatic arthritis is an initial dose of 45 or 90 mg, according to the patient's weight, at week 0 and 4.

Maintenance dose: The maintenance dose is 45 or 90 mg, according to the patient's weight, every 12 weeks.

The efficacy and safety of ustekinumab has been evaluated in several clinical trials.

Combination Therapy

There are no controlled studies on combination therapy; nevertheless, combination with topical antipsoriatic agents may be beneficial for the patient.

Side Effects

Infections are the most important side effect occurring with this drug. The most common infections observed were nasopharyngitis and upper respiratory tract infections, while the rate of severe infections was low. The data from the main clinical studies of ustekinumab (PHOENIX-1 and PHOENIX-2) show no association with lymphocytopenia nor any toxic cumulative effects. Moreover, the rate of reported malignancies was low and comparable either with the ones of the placebo population or the general population. The same applies also to the serious cardiovascular events observed, mainly during the first phase of the studies.

Drug Interactions

No chemical or via the cytochrome P450 system interactions are expected for ustekinumab.

Patient Candidates for Biological Treatments

Candidates for biological treatments are patients affected by moderate to severe psoriasis (PASI >10 or BSA >10 and DLQI >10) for at least 6 months that fulfill one of the following criteria:

- Nonresponsive or intolerant to traditional systemic treatments (cyclosporine, methotrexate, acitretin, fumaric acid)
- Nonresponsive or intolerant to phototherapy (PUVA, UVB)
- Affected by instable or life-threatening forms of psoriasis

- Patients with severe impact on their quality of life
- Patients affected by psoriatic arthritis independently of the severity of their skin lesions

Nevertheless and according to the new concept of treatment goals in psoriasis, there are special clinical manifestations that may change the definition of a mild psoriasis into moderate to severe psoriasis leading to a significant impairment of their quality of life. These manifestations can include the following:

- Involvement of visible areas
- Involvement of major parts of the scalp
- Involvement of the genitals
- Involvement of the palm and/or soles
- Onycholysis or onychodystrophy of at least two fingernails
- Pruritus leading to scratching
- Presence of single recalcitrant plaques

Patient's Screening and Follow-Up

Biological treatments have demonstrated a rather good safety profile in the long-term treatment compared with the traditional therapies. These drugs seem to lack specific organ toxicity unlike conventional treatments. Nevertheless due to their mode of action, adverse events may arise. In order to minimize their side effects, a careful screening of the patient prior to treatment is required.

Patient's Screening

Medical History and Physical Examination

Prior to treatment with a biological agent, a detailed medical history needs to be taken, and the following conditions need to be investigated:

- Presence of chronic or acute infections (tuberculosis, hepatitis B, hepatitis C, HIV)
- Presence or history of malignancies or lymphomas
- Presence of other autoimmune diseases
- Signs or positive family history of demyelinating diseases (especially in candidates of anti-TNFα agents)
- Presence or history of cardiovascular events
- Presence of comorbidities such as arthritis, diabetes, hypertension, obesity, hyperlipidemia, and depression

A list of the absolute and relative contraindications is given in Tables 137.1 and 137.2.

Physical examination is important in order to evaluate the severity of the disease as well as the presence of psoriatic arthritis. In order to evaluate the severity of the disease before treatment as well as to evaluate its efficacy during treatment, the following scores need to be assessed:

- BSA (Body Surface Area)
- PASI (Psoriasis Area Severity Index)
- NAPSI (Nail Area Psoriasis Severity Index)
- DLQI (Dermatology Life Quality Index)

Table 137.1 Absolute contraindications of biological treatments

	Adalimumab	Etanercept	Infliximab	Ustekinumab
Cardiac insufficiency (III or IV)	Yes	Yes	Yes	No
Active chronic infections including TB or HBV	Yes	Yes	Yes	Yes
Pregnancy or nursing	Yes	Yes	Yes	Yes
Known hypersensitivity to mouse proteins	No	No	Yes	No

Table 137.2 Important relative contraindications of biological treatments

	Adalimumab	Etanercept	Infliximab	Ustekinumab
Demyelinating diseases	Yes	Yes	Yes	No
Malignancy (with the exception of BCC) and lymphoproliferative diseases or history of such disease	Yes	Yes	Yes	Yes
Use of live vaccines	Yes	Yes	Yes	Yes
Autoimmune diseases	No	No	Yes	No
HIV or AIDS	No	No	Yes	No

Laboratory Parameters

The laboratory parameters include the following exams:

- Full blood count
- Biochemical analysis (including liver enzymes, creatinine, uric acid, cholesterol, triglycerides, glucose)
- ESR/CRP
- Urine analysis
- Pregnancy test (urine)
- Hepatitis B (HBsAg, anti-HBs, anti-HBc) and C screening
- ANA/anti-dsDNA
- Mantoux test and/or QuantiFERON® Gold test

Imaging

The imaging should include the following:

- Chest X-ray (in order to exclude active or latent tuberculosis)

In case of latent tuberculosis, the patient is not necessarily excluded from the biological treatments. A specialist needs to be consulted and the patient put under prophylactic anti-TB treatment prior to the beginning of biologics. The time of the prophylactic therapy varies according to the drugs used.

Patient's Follow-Up

During treatment, it is very important to monitor the efficacy and safety of the therapy.

Clinical and standard laboratory evaluation needs to be repeated more closely during the beginning of the treatment (after 2 and 6 weeks for infliximab and after 4 weeks for adalimumab, etanercept, and ustekinumab) and then every 2–3 months following the administration schedule of each drug.

Chest X-ray, Mantoux skin testing and/or QuantiFERON® Gold test, and hepatitis B and C and HIV screening should be repeated once a year. Nevertheless we need to take into consideration that further specific testing might be needed according to clinical signs, risks, and exposure of each patient. Moreover, there may be some conditions that may require a more frequent laboratory monitoring. The most common of these conditions are the following:

- Presence of comorbidities
- Contemporary administration of prophylactic therapy for tuberculosis
- Contemporary administration of other systemic conventional drugs for psoriasis (methotrexate, retinoids, cyclosporine)
- Exacerbation and/or persistence of the disease

During treatment, it is also recommended to advise the patient to undergo regular cancer screening exams according to his age, sex, and family history (pap test, mammography for women, PSA for men).

Efficacy and Long-Term Treatment with Biologics

All biological therapies have shown a rather fast onset of action, and the clinical improvement is usually visible within the first 4–8 weeks of treatment. The time of evaluation of their efficacy varies from 10 weeks of infliximab to 16 weeks in case of adalimumab and ustekinumab and 24 weeks of etanercept. More detailed information on their efficacy is shown in Table 137.3.

Regarding the long-term data on psoriasis therapy, their analysis is limited mostly due to different clinical trial designs and statistical methodology used for their interpretation. Adalimumab showed (REVEAL study) that the patients who had achieved a PASI 75 response at weeks 16 and 33 maintained that response for 100 weeks in 83 % and for 160 weeks in 76 % of the patients.

Etanercept in a post hoc analysis that included patients treated with different doses over a period of up to 4 years showed that 67 % of the patients that had a good response during the induction period (PGA 0/1) maintained the response at 24 weeks and showed only a slight variation through week 48.

Infliximab has no data of open-label extension trials available. In the EXPRESS II study, 71 % of the patients maintained PASI 75 until week 50 of continuous treatment.

Table 137.3 Efficacy of different biological agents

Therapeutic agent	Dose	PASI 75/(week 12) (%)	PASI 75/(6 months) (%)
Etanercept	2×25 mg/week	34	44
Etanercept	2×50 mg/week	49	59
Ustekinumab	45 mg/12 weeks (body weight <100 kg)	67	70
Ustekinumab	90 mg/12 weeks (body weight >100 kg)	68–71	79
Adalimumab	40 mg/eow	71–80	71
Infliximab	5 mg/kg	≥80	82

Biologic agent	Dosage	PASI 75 at week 12 (%)
Etanercept	2×25 mg/week	34
Etanercept	*2×50 mg/week*	*49*
Ustekinumab	45 mg/12 weeks (<100 kg BΣ)	*67*
Ustekinumab	90 mg/12 weeks (>100 kg BΣ)	*68–71*
Adalimumab	40 mg eow	*71–80*
Infliximab	5 mg/kg	*≥80*

Ustekinumab showed (PHOENIX I study) that 79 and 81 % for the doses of 45 and 90 mg, respectively, maintained their PASI75 at 5 years (244 weeks).

Given the good safety profile of the biologics, the therapeutic schema proposed is that of a continuous treatment, and treatment discontinuation is not advised with the exception of etanercept where also a discontinuous schema is also proposed.

According to the "new" for dermatology concept of treatment goals, a treatment is successful and should be continued if it results in a reduction of PASI ≥75 % or PASI ≥50 to <75 % combined with a DLQI ≤5. When the reduction in PASI is <50 % or PASI ≥50 to <75 % combined with a DLQI >5, treatment modifications should be considered. These treatment modifications include the following:

- Increase of drug dose
- Reduction of the intervals between drug doses
- Combination of therapies, either by adding topical treatment or a conventional systemic treatment (MTX, cyclosporine, acitretin)
- Change of the drug (usually done when all the above measures fail)

New Biologics

In the last few years, a great progress has been achieved in identifying some of the risk genes for psoriasis leading to a better understanding of the pathogenetic pathways of the disease. This increased understanding of the immunogenetic pathways has led to the development of more targeted biological therapies. In fact, multiple new treatments are currently in development for the treatment of psoriasis and their preliminary data seem to be very promising.

Table 137.4 Some of the new biological treatments currently under investigation for the treatment of psoriasis

Class	Agent
Anti-TNF inhibitors	Certolizumab pegol
	Golimumab
	ART621
Anti-IL23	BI655066
	SCH900222
Anti-IL-17	Brodalumab
	Secukinumab
	Ixekizumab
Anti-IL-20/22	Fezakinumab
Phosphodiesterase 4 inhibitors	Apremilast
JAK inhibitors	Tofacitinib (JAK1/JAK3)
	Baricitinib (JAK1/JAK2)
	ASP-015K (JAK3)

Among the new classes of targeted biological agents for psoriasis, the agents targeting the Th17/Il-23 axis will likely represent an important new therapeutic approach. These drugs by specifically targeting the IL-23/Th17 axis are likely to have a more targeted effect and an improved safety profile. Also the family of Janus kinases (JAK) inhibitors as well as the phosphodiesterase 4 inhibitors seems to show promising preliminary results.

An overview of some of the new biological treatments is shown in Table 137.4.

Conclusions

Psoriasis is a chronic systemic inflammatory disease with a complex pathogenetic mechanism that involves interactions between the innate and adaptive immune systems, genes, and environment. Being a systemic inflammatory disease, psoriasis is associated with a number of comorbidities that include psoriatic arthritis, cardiovascular disease, metabolic syndrome, and depression. In addition, psoriasis is also associated with a significant impairment of quality of life, as it affects relationships, social activities, work, and emotional well-being. Moreover due to the chronic nature of the disease, often treatment options can be limited either because of their efficacy or because of their safety.

The introduction of the biological agents, such as adalimumab, etanercept, infliximab, and ustekinumab, has provided dermatologists with more options for the short- and long-term treatment of patients with psoriasis. With the use of biological therapies, it is now possible to achieve and maintain effective disease control with a good safety profile in the long term compared to the conventional treatments. Nevertheless, the careful screening and regular follow-up of the patients that undergo biological treatments are of great importance in order to avoid side effects and guaranty the patient efficacy and safety in the long term.

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Bleaching Agents

138

Agustin Alomar and Elena Manubens

Key Points

- Before starting treatment, the nature of lesions should be evaluated: potential malignancy, colour, size and pattern are characteristics that need to be taken into consideration.
- Not all of the hyperpigmentation disorders are candidates for bleaching treatments. Melasma, solar lentigines and postinflammatory hyperpigmentation are the most relevant indications.
- Sunscreen use during daytime is both effective for avoiding worsening of the lesions and enhancing the effect of bleaching compounds.
- Hydroquinone is the most studied and used of the bleaching agents. Several trials demonstrate its efficacy and safety.
- Retinoic acid results in good response rates; however, longer time of treatment is needed and it can induce more irritation.
- Combination formulas such as the Kligman-Willis formula have obtained better results than monotherapies or other therapies in many clinical trials.
- Other compounds used are azelaic acid, arbutin, ascorbic acid and kojic acid.

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General Considerations

Hyperpigmented lesions are common in a dermatologist's practice. They are usually an important reason of concern, especially when they involve the face, but also other common areas such as the forearms and upper chest are frequent.

The first thing to evaluate is the nature of the lesion. Physicians should be able to differentiate between benign and potentially malignant conditions as the last ones should be removed and examined microscopically. Once malignancy is discarded, the next step is to decide whether bleaching is a suitable approach or not, and in order to determine that, the colour of the lesion should be examined. In general terms, skin colour is determined by several components, the main ones being: thickness, blood vessels and its oxygen concentration, pigments such as carotenes and the most important one being melanin.

Melanin can be deposited in the upper layers of the skin (epidermis) or in deeper ones (papillary and reticular dermis). The more superficial, the more susceptible to topical bleaching agents it should be. Wood light may help us localise the height of the pigment, as when it is disposed in the epidermis, the light highlights the contrast between the affected and the normal skin.

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_138, © Springer-Verlag Berlin Heidelberg 2015

The size and pattern of disposal should also be evaluated as some skin problems appear as dark blotches, uneven distribution of pigment or uniform hyperpigmentation.

Finally, other conditions should be evaluated such as ethnicity, hormonal and genetic factors or sun exposure.

All of them are elements that should be taken into consideration in choosing the appropriate agent and technique.

Pigment lightening has always been a challenge for dermatologists. The wide range of treatment options and the lack of quality studies supporting their efficacy and safety make it difficult to take a decision when the patient asks for a solution for his hyperpigmentation.

Topical Bleaching Agents: Indications

Solar Lentigines

Also called "sunspots" or "old-age spots", these dark spots are one of the commonest reasons of consultation. They affect 90 % of white patients older than 50 years and their incidence increases with age and sun exposure.

They are well-defined hyperpigmented macules with sizes varying from a few millimetres to 1 or 2 cm and usually round shaped. The lightest ones are more homogeneous than the darkest ones, which tend to be spotted. They appear in severely sun-damaged areas such as the face, upper chest, back, hands and arms. They can appear at any age, normally over 40s, and can lighten with cession of sun exposure.

Microscopically they appear as ridge hyperplasia of melanocyte with or without proliferation. There is an increase of the melanogenesis that determines a rise in the number of the keratinocyte melanosomes.

This kind of pathology is so histologically structured that bleaching agents are usually not enough; they have a mild lightening effect but more invasive treatments are necessary such as chemical peelings or lasers to completely remove them.

Melasma

This hypermelanosis, commonly affecting women, is also called "chloasma" or "pregnancy mask" when it appears during pregnancy. It is defined by its characteristic pattern of distribution on the face, and it is associated with darker skin phototypes (Asian and Hispanic).

The lesions appear as light brown to grey macules in sun-exposed areas with irregular margins and shapes. We can differentiate three patterns depending on their distribution. The "centrofacial pattern" is the most common one (two-thirds of the patients), and it affects the forehead, nose, chin and medial cheeks. "Malar pattern" affects 20 % of the patients and is circumscribed to the nose and cheeks. The other 15 % of the patients have a "mandibular pattern". All of them can have macules in other sun-exposed areas. It can also be classified as epidermal, dermal or mixed melasma depending on the skin level where pigment is disposed.

Even though melasma's pathogenesis is not well known, it has been associated with many factors. Genetic predisposition and sun exposure are two of the most important ones. Hormonal factor also has to be taken into consideration as pregnancy and the use of contraceptives can also contribute to its appearance. If melasma occurs during pregnancy, it is likely that the lesions become lighter in the months following the pregnancy.

Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation is a common disorder that may occur after practically any kind of skin inflammation, especially the ones with lichenoid pattern such as lichen planus or cutaneous lupus. Other conditions that may lead to hyperpigmentation are acne, atopic dermatitis, irritant and allergic contact dermatitis, phytophotodermatitis, pyodermas, burns and many others. Darker skin phototypes are more likely to develop more intense and durable lesions, causing important aesthetic traumas.

It presents with dark macules of irregular shapes and sizes that appear after the resolution of the inflammatory erythema and oedema. In the following months, the lesions may get lighter but sometimes they are permanent. The evolution depends mostly on the level of the pigment deposit in the skin; if it gets phagocyted by the macrophages, lesions are unlikely to disappear.

General Principles

All the treatments with any topical bleaching agent should be combined with a series of measures that may help improve their results.

The first and most important advice that should be given to the patient is to avoid sun exposure before, during and after the treatment as it stimulates melanogenesis. The bleaching agent should be applied at night and sunscreen should be worn when going outdoors; if the bleaching preparation incorporates sun protection, it could be used during daytime as well. Most physicians prefer to start the treatment after summer time, especially in sunny regions, as very little improvement may be achieved if the patient is exposed to high-intensity sun radiation.

Before starting the treatment, the patient should apply it on a small area of the skin as some of them may cause irritation that could lead to a counterproductive effect. If erythema appears, the physician should consider using a lower concentration of the bleaching compounds of the formula.

The preparation must be used on cleaned skin which is not dry, irritated or sunburnt; one should wait until inflammation goes down in order to avoid its worsening.

During the treatment, the patient must be aware that only pigmented patches need to be treated. If the preparation is used in normal skin, the contrast between normal and affected skin may not get better.

The physician must also advise that it may take months to achieve visible results. If no improvement is achieved during the first 3–4 months, he should consider increasing the concentration of the preparation if possible, as well as changing or combining its compounds.

Topical Bleaching Agents

Hydroquinone

Hydroquinone is probably the most popular and well-studied bleaching agent. It is a phenolic organic compound also known as benzene-1, 4-diol that inhibits the enzymatic oxidation of tyrosine and phenoloxidases. It also inhibits DNA and RNA synthesis of the melanosomes leading to melanocyte damage. All of these actions end up reducing gradually the melanin production.

In a 2010 Cochrane Review of the interventions in melasma treatment, hydroquinone was the one with more randomised controlled trials. Most of the trials compared hydroquinone to other bleaching agents and not placebo, making it difficult to obtain statistically significant results. Hydroquinone may be formulated at many concentrations from 2 % to 5 %, with 4 % being the most commonly used. When compared to 20 % azelaic acid, neither physicians nor patients found significant difference in skin lightening. The same happened with physicians' assessment in the 5 % ascorbic acid comparison, although patients did find significant improvement.

When lower concentrations of hydroquinone were used, other treatments such as 20 % azelaic acid got better results.

Higher concentrations up to 8 % could be used, but they are unstable formulations and get oxidised rapidly. At any concentration, darkening of the preparation reflects oxidation of the product, and if seen, it should be discarded as it may be more active and irritating.

Although it is a widely used compound, there is still some controversy around it.

The biggest one is the risk of developing exogenous ochronosis after its use for long periods of time. This side effect appears as brown, grey or blue hyperpigmentation in the areas of application of the product and has been well established in the literature. Although the exact incidence remains unknown, high rates have been reported in the South African population, with lower rates among Hispanics and Caucasians and rare cases in the USA. Physicians should also be careful

in cases of skin irritation, lack of sun protection and the use of concentrations higher than 3 % for more than 6 months.

Regarding its potential for malignancy, the higher incidence of hepatic adenomas, renal adenomas and leukaemia when applied topically in murines with large doses over extended time periods has been well established. However, in humans, absorption varied from 24 % to 45.3 % depending on the areas exposed and generating peak plasma concentrations no higher than the ones obtained after eating some foods containing arbutin (a compound that hydrolyses to yield hydroquinone in weak acid media).

Mode of Use: Hydroquinone should be applied at nights and be combined with a sunscreen agent during daytime. After 5 to 6 months of its use, further improvement should not be expected, and the physician should consider changing the compound or combining it. Patients should be advised that in some cases hydroquinone effect is only temporary and hyperpigmentation could reappear in the affected areas. Contact with nails should be avoided as it may tint them orange.

Nowadays the commercial hydroquinone formulas are always in combination with some other agents for thinning the epidermis and to enhance the action like some acids such as retinoic or glycolic acid.

Topical Retinoic Acid

Tretinoin (all-trans retinoic acid) is a first-generation topical retinoid derived from vitamin A and has been widely used in dermatology. When dermatologists started using it for acne treatment, patients reported lightening of the dark spots on their face. The mechanism of this effect is not well known, but it has been thought that acceleration of cell turnover, by binding specific nuclear proteins, may be implied. Its capacity for inhibiting the UVB-induced tyrosinase and interrupting melanin synthesis has also been demonstrated. Other generations of topical retinoid compounds such as isotretinoin or adapalene have shown milder effect but better tolerance, making them a good option in patients with poor tolerance to retinoic acid.

Many studies have demonstrated tretinoin's benefit over placebo for treating melasma and actinic lentigines at concentrations ranging from 0.025 % to 0.1 %. Creams or gels have been used, but the first ones are considered the best option as the moisturiser component may help with the irritation caused by the retinoic acid.

Tretinoin 0.1 % cream to treat melasma was evaluated in two randomised controlled trials showing a significant improvement in clinical assessment in 68 % and 32 % of the patients compared with 5 % and 10 % in the vehicle control group.

Adverse effects include dryness with light scaling, redness and slight stinging and usually improve after the first weeks of treatment. If the patient refers important discomfort, the preparation could be used on alternate nights.

It is important to note that studies show a slower response, up to 24 weeks, when using tretinoin in monotherapy in comparison with other treatments available such as hydroquinone.

Mode of Use: Treatment should be adapted to individual skin type. Physicians recommend to start with the lower concentration and to increase it gradually in order to minimise the adverse effects. A small amount of product should be applied nightly and cleaned up before sun exposure since it increases sensitivity. In cases of sensitive skin, it would be better to start applying it on alternate nights for 2–3 weeks. During daytime, sunscreen plus moisturiser should be worn, and aggressions to the skin such as smoking avoided. A physician should supervise combination with other cosmetic products, as retinoic acid is not stable when combined with some other compounds.

Kligman-Willis Formula

In 1975, Kligman and Willis published a new formula for lightening human skin. Their

research found that the combination of 5 % hydroquinone, 0.1 % tretinoin and 0.1 % dexamethasone applied twice daily was the one with better results and less irritation. It is thought that the retinoid prevents the hydroquinone from oxidising, improving its absorption through the epidermis. The point of adding a topical corticosteroid was to reduce the inflammation caused by the other two compounds for increasing tolerability and reducing possible postinflammatory hyperpigmentation.

Since then many other dual or triple combinations have been studied. Using hydroquinone plus retinoic acid alone may be a good option for long-term treatments where use of corticosteroids is generally a big concern.

There are other combined formulations that have proved efficacy. Four per cent hydroquinone, 0.05 % tretinoin and 0.01 % fluocinolone acetonide used nightly showed better results than dual-combination creams containing either hydroquinone plus tretinoin, hydroquinone plus fluocinolone, tretinoin plus fluocinolone and hydroquinone 4 % alone.

Six per cent hydroquinone, 0.05 % tretinoin and 0.05 % triamcinolone acetonide has also obtained good results in some patients.

Other Bleaching Agents

Azelaic Acid

Azelaic acid is a natural compound synthesised by *Malassezia furfur* and it is responsible for the hypopigmentation in pityriasis versicolor. As with other bleaching compounds, its mechanism of action also involves inhibition of the tyrosinase leading to a decrease in melanin production and melanosome formation.

In a randomised double-blind multicentre study comparing 20 % azelaic acid versus placebo in patients with melasma, statistically significant results were found. In comparison to hydroquinone, 20 % azelaic acid has been shown to have greater efficacy than 2 % hydroquinone in a 6-month study and to be equally as efficacious as 4 % hydroquinone in a 24-week double-blind trial.

As with other bleaching compounds, pruritus, erythema and scaling have also been commonly reported when using azelaic acid.

As azelaic acid is also useful for treating mild to moderate acne, it should be considered an interesting option for patients with postinflammatory hyperpigmentation secondary to acne spots.

Mode of Use: Preparations containing up to 20 % of azelaic acid are commonly used. It can be used as monotherapy or combined with other bleaching agents. It can be used up to twice daily, although it is recommended to start with nightly application to assess tolerability.

Arbutin

Technically known as hydroquinone-beta-D-glucoside, it is the natural compound of hydroquinone and it is extracted from the leaves of *Arctostaphylos uva-ursi* (bearberry) and other plants. It can inhibit the tyrosinase activity and the melanosome maturation and is used with concentrations of up to 3 %. Special care needs to be taken with higher doses as it can induce hyperpigmentation.

Ascorbic Acid

Also known as vitamin C, ascorbic acid is a natural compound that can be found in the dermis and epidermis with many properties that have been used for cosmetic purposes since old times.

When administrated both orally and topically, its antioxidant action helps to prevent the damage caused by the UVB-induced free radicals. It is also thought to decrease pigmentation by interacting with copper at the active site of tyrosinase and by reducing dopaquinone by blocking dihydro-chinindol-2-carboxyl acid oxidation. Additionally, it is involved in collagen synthesis, as it is an essential factor for the enzymatic hydroxylation of the amino acids proline and lysine, providing a more lightened and elastic appearance of the skin.

Kojic Acid

Kojic acid is a molecule produced by *Aspergillus oryzae* and *Penicillium* spp. that is a popular bleaching agent in Japan. Its mechanism of action is also through the inhibition of the tyrosinase and it is used at 2 % concentrations. Many studies have tried to demonstrate its equivalent effect to other compounds; however mixed results have been obtained. It is a very unstable molecule that can easily lose its efficacy when exposed to light.

Other Bleaching Techniques

Chemical peelings
Lasers

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Calcineurin Inhibitors: Topical

139

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Key Points

- Topical calcineurin inhibitors are, together with topical corticosteroids and UV light, one of the mainstays of topical anti-inflammatory treatment in dermatology.
- Topical calcineurin inhibitors are currently licensed in Europe for treatment of atopic dermatitis only, but there is extensive off-label use in seborrhoeic dermatitis, lichen planus, lichen sclerosus, eyelid dermatitis, perioral dermatitis, vitiligo and pyoderma gangrenosum.
- Tacrolimus ointment and pimecrolimus cream are the two drugs licensed and available throughout Europe.
- Tacrolimus is also licensed for maintenance use or proactive therapy, which is defined as long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin, together with an ongoing emollient treatment of unaffected skin.
- Topical calcineurin inhibitors have the advantage of not causing skin atrophy, striae distensae, telangiectasia, glaucoma or cataract and are less absorbed than topical corticosteroids.
- Topical calcineurin inhibitors have the disadvantage of an initial burning sensation and a higher cost and less available galenic formulations compared to steroids.
- Legally, topical calcineurin inhibitors are not licensed for use during pregnancy. Scientifically, there is no evidence that they may have teratogenic effects or may otherwise be harmful during pregnancy. There is large experience with calcineurin inhibitors during pregnancy from the systemic use in transplantation medicine.

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General Principles

Calcineurin inhibitors are a functionally defined substance class of molecules and well established as systemic agents in transplantation medicine. They block the induction of proinflammatory cytokines by the nuclear factor of activated T cells (NFAT), thus suppressing T-cell activation. Cyclosporine A is best established but has poor skin penetration and is not suitable for topical

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_139, © Springer-Verlag Berlin Heidelberg 2015

use. Tacrolimus and pimecrolimus have a smaller molecule size and are suitable for topical use in atopic dermatitis and many other skin diseases. Their main advantage is that they do not induce skin atrophy, even with long-term application, and thus they are particularly useful for facial and flexural areas where topical corticosteroids should be avoided.

Classification

The first introduced calcineurin inhibitor was cyclosporine. Although cyclosporine has revolutionized transplantation and proved efficacy in many inflammatory and autoimmune skin diseases, its use is limited by side effects. Despite the fact that it is very lipophilic, cyclosporine is almost ineffective as a topical agent, as it is not able to penetrate skin. Though cyclosporine acts as a calcineurin inhibitor, it is not regarded a member of the substance class of topical calcineurin inhibitors.

In contrast to cyclosporine, the newer calcineurin inhibitors tacrolimus and pimecrolimus have sufficiently low molecular weight to penetrate stratus corneum; thus, they are very effective when applied topically (Fig. 139.1). Tacrolimus and pimecrolimus can be roughly viewed as equivalent, as the wanted and unwanted effects of the medication are substance class effects. Tacrolimus is about fourfold more efficient than pimecrolimus, whereas pimecrolimus is more lipophilic. Pimecrolimus has a considerably higher affinity for the skin but a lower permeation potential. This explains the higher efficacy as well as the more common application site reactions of tacrolimus ointment compared with pimecrolimus cream. Tacrolimus is commercially available as 0.1 and 0.03 % ointment, while pimecrolimus is available as 1 % cream.

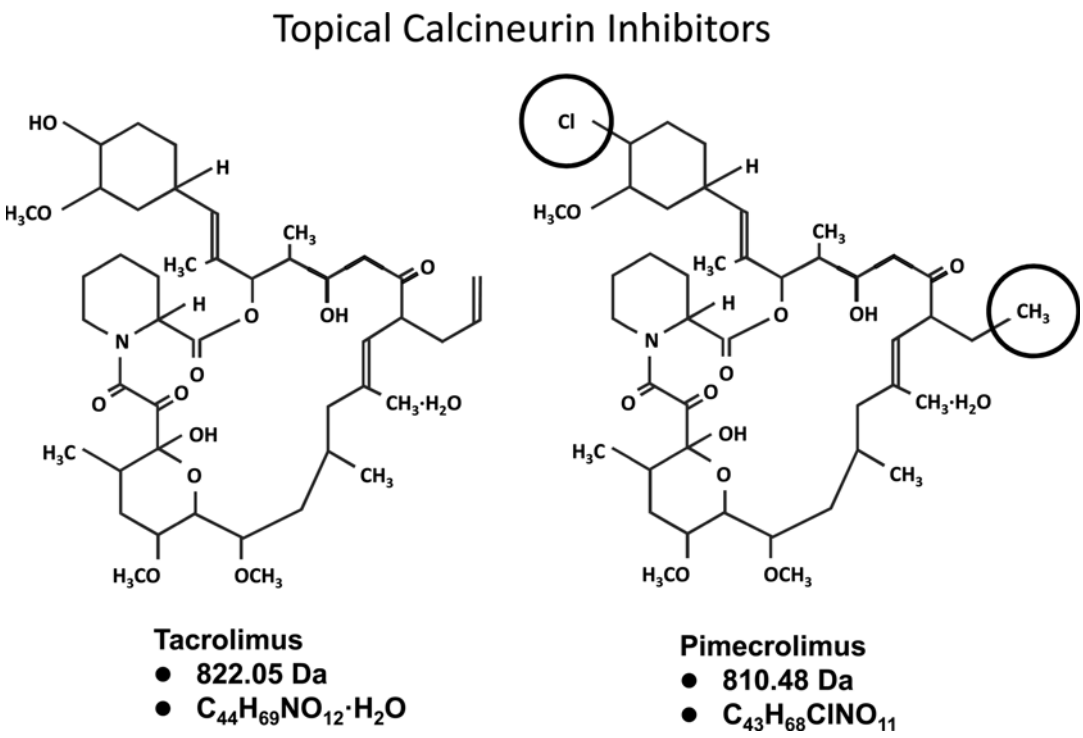

Fig. 139.1 The topical calcineurin inhibitors tacrolimus and pimecrolimus show an almost identical structure and molecular weight.

Mechanisms of Action

Calcineurin inhibitors are a functionally defined substance class of molecules, which are blocking the translocation of calcineurin from the cytosol to the nucleus, thereby inhibiting the translation of proinflammatory cytokines dependent on the nuclear factor of activated T cells (NFAT). This inhibits the activation and maturation of T cells and blocks transcription of several proinflammatory gene products in other cells. In addition, the release of histamine and other vasoactive substances from mast cells is blocked, and the expression of functionally relevant surface molecules on Langerhans cells is altered.

The main advantage of topical calcineurin inhibitors over topical corticosteroids is that they do not affect collagen synthesis by fibroblasts and therefore do not induce skin atrophy, even with long-term application. Hence, they are particularly useful for facial and flexural areas where topical corticosteroids should be avoided as the potential side effects are frequently observed.

Indications and Other Uses

Atopic dermatitis is currently the main and only licensed indication for topical calcineurin inhibitors in Europe. Numerous studies have shown the safety and efficacy in this indication. Traditional atopic dermatitis therapy follows reactive approach with an on-and-off regimen of anti-inflammatory topical treatment of visible skin lesions.

Tacrolimus 0.03 % ointment is approved for treatment of moderate to severe atopic dermatitis skin lesions in children aged 2–16 years, whereas the 0.1 % ointment is licensed for the same indication in patients older than 16 years. Pimecrolimus 1 % cream is approved for treatment of mild to moderate atopic dermatitis skin lesions in all patients aged 2 years and above. Both are routinely used twice daily on all visible skin lesions as a safe and effective therapeutic option for atopic dermatitis patients. Treatment is particularly useful in delicate skin areas where topical corticosteroid side effects are frequently observed.

The reactive treatment concept has been recently challenged by the proactive approach, which is defined as long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin, together with an ongoing emollient treatment of unaffected skin. The immunobiological basis for this approach is the presence of subclinical inflammation and barrier dysfunction in non-lesional atopic dermatitis skin, which is invisible to the naked eye. Proactive therapy is only performed after an intensive, twice-daily therapy has mostly cleared visible eczema. The current ETFAD position paper and EDF guideline for atopic dermatitis recommend the proactive use of tacrolimus ointment. Tacrolimus ointment, but not pimecrolimus cream, is also approved for the proactive therapy of moderate to severe atopic dermatitis to prevent relapses and extend the periods without recurrences in patients with frequent exacerbations (four or more times a year), who are initially treated with tacrolimus ointment two times a day.

Several other varieties of dermatitis and eczema including contact dermatitis, asteatotic dermatitis, irritant dermatitis, chronic actinic dermatitis, eyelid dermatitis and perianal dermatitis can effectively be treated with topical tacrolimus, whereas all topical calcineurin inhibitors are little effective on palms and soles because of the thickness of the stratum corneum in these regions.

Seborrhoeic dermatitis can effectively be treated by topical tacrolimus and pimecrolimus. Both drugs induce marked improvement of erythema and scaling with excellent tolerability in those regions where topical corticosteroid application could be potentially harmful.

Erosive mucosal lichen planus, anogenital lichen sclerosus et atrophicus and cutaneous graft-versus-host disease are other excellent indications for topical calcineurin inhibitors. Cutaneous lupus erythematosus, vitiligo, rosacea and skin lesions of dermatomyositis may also be treated with good response. In vitiligo, early lesions, children and facial lesions show a better response compared to older lesions, adults and

lesions on the extremities. As a rule, tacrolimus tends to be somewhat more effective in these off-label indications due to its higher efficacy and better penetration characteristics. Topical tacrolimus is also a good treatment option for pyoderma gangrenosum patients who are resistant to or intolerant of standard therapy, as long as the total area treated is small, e.g. less than 100 cm^2. Perioral dermatitis responds well to pimecrolimus cream.

Topical calcineurin inhibitors are worthwhile trying in virtually all inflammatory and autoimmune skin diseases in which systemic cyclosporine is effective. Though chronic plaque psoriasis does not respond well due to penetration problems, topical tacrolimus and pimecrolimus may be useful in facial and inverse psoriasis.

Side Effects

Safety data of topical calcineurin inhibitors have been reported in many clinical trials, demonstrating their safety in daily routine use. The most frequent side effect is a transient warmth and burning sensation at the application site that tends to resolve after a few days. Systemic exposition is low, and the blood levels are usually too low to be measured and significantly below the therapeutical level maintained in organ transplant patients.

A number of patients treated with topical calcineurin inhibitors experience a flush phenomenon following alcohol consumption. It is not dangerous, but may be annoying and can be prevented by 500 mg of aspirin taken 30 min before drinking alcohol.

A theoretical concern of an increased risk for cutaneous or haematologic malignancies is derived from the long-term, high-dose, systemic exposure to oral calcineurin inhibitors in transplantation medicine, where these drugs are given in spite of the known risk. Numerous clinical studies failed to demonstrate an increased risk of infections, malignancy or photocarcinogenicity, but some additional long-term safety studies are still running. It is unlikely that topical application of TCI is connected with significant systemic exposure, and they seem to have an excellent safety profile, even in small children. For safety reasons, patients are still advised to avoid excessive intentional UV exposure during the calcineurin inhibitor use.

Contraindications

Drug hypersensitivity against macrolactams and contact allergy against the components of the topical products are the main and obvious contraindications for all topical calcineurin inhibitors. The similar structure of tacrolimus and pimecrolimus may explain the cross reactivity in the patch test observed in a contact allergic patient. Treatment of patients with genetic epidermal barrier defects such as ichthyosis linearis circumflexa with topical tacrolimus may result in systemic toxicity dependent on the surface area treated, which has not been observed for topical pimecrolimus.

Drug Interactions

Treatment of atopic dermatitis with topical calcineurin inhibitors results in low systemic exposure. Those molecules reaching the systemic compartment are mostly inactivated by the cytochrome p450-3A4 isoenzyme of the liver. Known inhibitors of this enzyme such as erythromycin, itraconazole, ketoconazole, diltiazem or even grapefruit juice do increase the drug level of oral cyclosporine or oral tacrolimus, but the effect on blood levels induced by topical calcineurin inhibitor treatment is less relevant because of the generally low systemic exposure.

Use in Infants, Children and Elderly

From a scientific point of view, many published studies confirm the efficacy and safety of topical treatment with pimecrolimus cream and tacrolimus ointment in infants under the age of

2. From a medicolegal point of view, both preparations are licensed throughout Europe from the age of 2 years and above. This constellation has led to frequent off-label use in infants with atopic dermatitis. There are no restrictions or particular features for treating elderly patients.

Pregnancy and Breastfeeding

Scientifically, there is no evidence that topical calcineurin inhibitor use may have teratogenic effects or may otherwise be harmful during pregnancy. There is long-lasting experience with oral calcineurin inhibitors during pregnancy from transplantation medicine, which does not indicate a teratogenic potential for the entire substance class. The expected systemic exposure from topically applied calcineurin inhibitors is even lower, which would further lower any risk if used during pregnancy. Legally, topical calcineurin inhibitors are not explicitly licensed as safe agents for use during pregnancy. This constellation results in the need for an individual decision for each patient.

There is published data from oral tacrolimus use in transplantation medicine that tacrolimus is excreted in human milk, whereas no data is available for pimecrolimus. There is no harmful effect known for topical calcineurin inhibitors during breastfeeding. The expected systemic exposure from all topically applied calcineurin inhibitors is low, which further limits a potential risk if used during breastfeeding. This constellation results in the need for an individual decision for each patient.

Treatment Regimen and Dosage

For traditional reactive treatment, tacrolimus ointment and pimecrolimus cream are applied twice daily to all visible skin lesions of atopic dermatitis or other skin diseases. Tapering of topical calcineurin inhibitors may be helpful but is not as important as it is for topical corticosteroids.

For proactive treatment, topical tacrolimus is applied once a day twice weekly to all clinically normal but usually affected or frequently relapsing "problem zones" of atopic dermatitis. Visible lesions reappearing during the proactive treatment time must be treated twice daily, as usually done with all visible lesions, until these disappear. The frequency of applications may be adjusted according to the severity of the disease.

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Corticosteroids: Topical

140

Alejandro Martin-Gorgojo, Jeanne-Duus Johansen, and Ana M. Giménez-Arnau

Key Points

- Topical corticosteroids (TCS) have a broad treatment spectrum given their multiple actions. Despite their adverse effects, including cutaneous atrophy and the possibility of systemic absorption, they are still the most potent topical anti-inflammatory agents available.
- Though their anti-inflammatory properties are the main reason for their use, other actions such as their lowering the synthesis of macromolecules that form connective tissue, their antimitotic activity, and their symptomatic relief of itching and burning can make them useful in the treatment of multiple skin conditions.
- The choice of topical steroids and their bioavailability must take into account the excipient used. Choosing one formulation or another will depend on the type of disease and on the area of the body and extent to which it will be applied.
- TCS may cause topical or systemic adverse effects, which need to be known and prevented.
- Thoughtful, individualized, and specific regimens should be advised. Combination with emollients, keratolytic agents, or regimens including corticosteroid-saving agents can be helpful.
- Long-term daily treatment of large areas of the skin should be avoided: regardless of the potency, treatment of TCS should not be maintained for more than 2–4 weeks.
- No more than 50 g per week of very potent or potent corticosteroid preparations should be used in the general population, and no more than 300 g of very potent or potent corticosteroid preparations should be administered to women during their entire pregnancy.
- Patients with preexisting renal or hepatic disease should be carefully assessed, since systemic side effects of topical administration seem to be more frequent.

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General Principles, Classification, and Structure

Topical treatment with glucocorticoids began 20 years after the discovery of the basic structure of cholesterol, a precursor in the biosynthesis of

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_140, © Springer-Verlag Berlin Heidelberg 2015

all steroids. The application of cortisone directly on the skin showed disappointing therapeutic results, but the fermentation of this molecule resulted in hydrocortisone, a great therapeutic advance at the time of its introduction in 1952.

Over the years, the activity of topical corticosteroids was improved by several molecular changes, including the introduction of a double bond between the first and the second carbon (C-1 and C-2) in the molecule; the formation of esters in C-17 or C-21 position within fatty acids; the introduction of cyclical acetonides in C-16 and C-17 position, which increases the potency; and the process of halogenation (with fluorine—which tends to protect the steroid ring from being metabolized—or chlorine) in the C-9α (alpha) that enhances the effect of the preparations.

Triamcinolone acetonide was the first active halogenated topical steroid to become commercialized with success, in 1960, after showing a specific, anti-inflammatory effect that proved useful in the management of psoriasis. Flurandrenolone and flumethasone became available at the same time. All three are known as *second-generation* steroids.

The *third-generation* group of steroids includes betamethasone valerate and fluocinolone. Free betamethasone is considered as active as hydrocortisone.

The ester formation in C-17 position proved to be important: in 1962, 17-betamethasone valerate was selected from a wide range of topical steroids due to its good results obtained in the vasoconstriction test designed by Mackenzie-Stoughton. Subsequently, several simple esters in the C-17 position of hydrocortisone were developed, leading to the introduction of hydrocortisone 17-butyrate and hydrocortisone 17-valerate, two molecules designed to obtain the same efficacy as the fluorinated second-generation steroids but which minimized the systemic and topical adverse effects secondary to halogenation. The disassociation between the efficacy and adverse effects can be explained by the hydrolysis of the esters, first at skin level and afterwards in the blood. These non-fluorinated topical steroids are known as the *fourth generation.*

In the 1970s and 1980s, more potent, *fifth-generation* corticosteroids appeared: betamethasone dipropionate and clobetasol propionate. Potent compounds that could help to control certain dermatoses rapidly, they also posed a real risk for the development of topical and systemic adverse effects.

The *sixth generation* of steroids includes budesonide, specifically characterized by lateral chains of butyric acid in the C-16 and C-17 positions. This potent, non-fluorinated steroid can be used topically or inhaled. According to the vasoconstriction tests, its potency ranges between the clobetasol 17-propionate and the betamethasone-17, 21-dipropionate. Its effect on the hypothalamic-pituitary-adrenocortical axis is similar to hydrocortisone 17-butyrate.

Other formulations have aimed to minimize adverse effects while preserving the anti-inflammatory effects: mometasone furoate; prednicarbate; C-21-carboxylates such as the fluocortine-butyl-ester; the diesters 17,21-hydrocortisone aceponate, hydrocortisone 17-butyrate-21-propionate, methylprednisolone aceponate, and aclomethasone propionate; and carbothioates such as the fluticasone propionate have now been on the market for several years.

Mechanisms of Action

Glucocorticoids act on different tissues and types of cells and on tissue, cellular, or molecular levels. Some of the actions attributed to corticosteroids are not caused primarily by their pharmacological effect but by the action on a different level. Corticosteroids have specific and nonspecific actions, which can be explained by several direct and indirect mechanisms.

As small hydrophobic molecules, steroids cross the cell membranes by simple diffusion. Once inside the cell, they bind reversibly to the specific cytoplasmatic protein receptor, which is codified by the GR gene, located in chromosome 5. The glucocorticoid receptor may adopt two isoforms, depending on posttranscriptional processing: alpha, responsible for corticosteroid effects, and beta, with a regulatory role. Therefore, a rise in the beta/alpha isoforms ratio has been linked to glucocorticoid resistance.

Receptor-corticosteroid interaction activates a complex consisting of a binding protein for the hormone, two heat-shock proteins, p23 and an immunophilin. The activation causes the cleavage of these last three components and the dimerization and migration of hormone-receptor complexes into the nucleus (through the pores of the nuclear membrane), which bind to a DNA sequence and modulate the genetic transcription. This results both in the upregulation of the expression of certain molecules (interleukin-1 receptor antagonist, Iκβ-α [kappa beta-alpha], secretory leukocyte inhibitory protein, transforming growth factor-β [beta], lipocortin-1, etc.) and the downregulation of others (multiple cytokines, including interleukins 1, 2, 3, 4, 5, 6, 11, 12, and 13, tumor necrosis factor-alpha, and others; chemokines, comprising interleukin-8, C-C motif chemokine-5, and others; inducible nitric oxide synthase, cyclooxygenase 2, endothelin-I, etc.). However, several co-activators, corepressors, and other factors (such as the interaction of steroid-receptor complexes with nuclear factor-κβ [kappa beta], leading to its transrepression) should be taken into account to fully understand this genomic pathway.

Though gene modulation is considered the most important mechanism explaining the glucocorticoid effects, other mechanisms of action have been described, including a non-genomic pathway, in which corticosteroids may bind on membrane receptors linked to second messenger molecules, altering the sensitivity and activation level of target cells (such as T lymphocytes, platelets, or monocytes), with a rapid-onset effect.

These pathways have been observed and reported in the skin, helping to explain the different properties of topical glucocorticoids:

- *Anti-inflammatory effects*. Achieved by the decrease of inflammatory molecules, such as cytokines (multiple interleukins and tumor necrosis factor-alpha), chemokines (interleukin-8, C-C motif chemokine 5, and others), and inducible nitric oxide synthase, as well as the increase of anti-inflammatory molecules (such as lipocortin-1, interleukin-1 receptor antagonist, Iκβ-α [kappa beta-alpha], secretory leukocyte inhibitory protein, etc.), by modulating the transcription of their codifying genes, or by a non-genomic pathway.
- *Vasoconstrictive effects*. Capillary vasodilation is inhibited by glucocorticoids. Although not completely understood, vasoconstriction is considered to be part of the anti-inflammatory effects: the downregulation of the transcription of cytokine-inducible nitric oxide synthase may be involved in achieving this effect, given its indubitable effect on diminishing erythema and edema.
- *Immunosuppressive effects*. In addition to the inhibition of inflammatory molecules, corticosteroids inhibit leukocyte migration to sites of inflammation and interfere with the proliferation, differentiation, and maturation of all the cells that participate in the immune response. Glucocorticoids have been proven to shift the T-helper reaction pattern, favoring a T-helper type 2 response.
- *Antiproliferative effects*. Antimitotic properties of corticosteroids have been explained partially by the inhibition of the transcription and effect of several cytokines.
- *Apoptotic and antiapoptotic effects*. Glucocorticoids have proven to decrease the survival and lead to apoptosis of lymphocytes, mast cells, eosinophils, and monocytes/macrophages but to increase the survival and reduce apoptosis of neutrophils and erythrocytes.
- *Antipruritic effects*. TCS have been proven effective to alleviate pruritus and the signs of eczema, as a recent trial based on patients with induced allergic eczema to nickel sulfate (a model that has been confirmed valid to assess the efficacy and speed of action of TCS) has confirmed.

Pharmacology

The therapeutic (and adverse) effects of TCS vary according to different factors, including the potency of the molecule. The most important tests used to determine it are:

- The vasoconstriction test (or the blanching test) is based on one of the effects of TCS. Its

results correlate with drug potency, although in an unspecific manner.
- Tests to measure the suppression of the mitotic index.
- Tests for skin atrophy.

Skin pharmacokinetics and pharmacodynamics are studied together. The percutaneous absorption of steroids depends on:
- The preparation: its lipophilicity, solubility, and the drug concentration that may be reached after its application
- The patient: the anatomical location and extension on which the drug is applied, the age of the patient, and preexisting skin diseases
- The pattern of application (e.g., the number of applications per day, open or occlusive therapies, etc.)

Comparing different therapeutic studies is difficult, due to different reasons such as the lack of a standardized method to study the effect in clinical trials. Animal and human models have been used to evaluate the activity of TCS. Special methods to assess adverse effects have also been developed. Animal models include studies about the immunological and non-immunological inflammatory process and about the antimitotic and atrophogenic effects. Human models include the vasoconstriction test, non-immunological inflammatory studies (such as the ultraviolet or pyrexial erythema tests), immunological inflammatory examinations (including the ones based on allergic contact dermatitis), and studies concerning side effects (e.g., the skin atrophy induction and steroid-induced acne tests and the quantification of the endogenous suppression of cortisol).

Indications and Other Uses

There are currently numerous corticosteroid preparations, which are classified in four levels of potency (I–IV) according to the standard European classification system, with level I being the strongest. There are, however, other proposed classifications, such as the German and US systems, that may also be found in Table 140.1, along with the available marketed formulations of different topical steroids.

Table 140.1 Potency of the most commonly used topical steroids and their formulations

Very potent (*Class I Europe/IV Germany/I USA*)
Betamethasone dipropionate 0.05 % *gel* (*o.v.*), *ointment* (*o.v.*)
Clobetasol propionate 0.05 % *cream*, *foam*, *gel*, *lotion*, *ointment*, *shampoo*, *spray*
Diflorasone diacetate 0.05 % *ointment* (*o.v.*)
Diflucortolone valerate 0.3 % *cream*, *ointment*
Fluocinonide 0.1 % *cream*
Fluocinolone acetonide 0.2 % *cream*, *ointment*
Halcinonide 0.1 % *cream*, *ointment*, *solution*
Halobetasol propionate 0.05 % *cream*, *ointment*
Potent (*Class II Europe/III Germany/II/III USA*)
Amcinonide 0.1 % *cream*, *ointment*
Beclomethasone dipropionate 0.025 % *ointment*
Betamethasone benzoate 0.025 % *gel*
Betamethasone dipropionate 0.05 % *cream* (*o.v.*), *gel*, *lotion* (*o.v.*), *ointment*
Betamethasone valerate 0.1 and 0.05 % *ointment*
Budesonide 0.25 % *cream*, *lotion*, *ointment*
Desonide 0.05 %[a] *cream*, *foam*, *gel*, *lotion*, *ointment*
Desoxymethasone 0.25 % *cream*, *ointment*
Diflorasone diacetate 0.05 % *cream* (*o.v.*), *ointment*
Fluclorolone acetonide 0.025 % *ointment*, 0.2 % *cream*
Fluocinolone acetonide 0.25 and 0.2 %[a] *cream*, *ointment*
Fluocinonide 0.05 % *cream*, *gel*, *ointment*, *solution*
Fluprednidene acetate 0.1 and 0.05 % *cream*, *ointment*
Flurandrenolone 0.05 %[a] *cream*, *ointment*
Fluticasone propionate 0.05 %[a] *cream*, *lotion*, 0.005 % *ointment*
Halcinonide 0.01 % *cream*, *ointment*, *solution*
Methylprednisolone aceponate 0.1 % *cream*, *emulsion*, *ointment*
Mometasone furoate 0.1 % *ointment*
Prednicarbate 0.25 % *cream*, *ointment*, *solution*
Triamcinolone acetonide 0.5 and 0.1 % *ointment*
Moderately potent (*Class III Europe/II Germany/IV/V USA*)
Alclometasone dipropionate 0.05 %[a] *cream*, *ointment*
Beclomethasone dipropionate 0.025 % *lotion*
Beclomethasone salicylate 0.025 % *cream*, *lotion*
Betamethasone benzoate 0.025 % *cream*, *ointment*
Betamethasone dipropionate 0.05 % *lotion*
Betamethasone valerate 0.1 and 0.05 % *cream*, *foam*, *lotion*, 0.025 % *ointment*
Clobetasone butyrate 0.05 % *cream*, *ointment*
Desoxymethasone 0.05 % *cream*, *ointment*
Fluocinolone acetonide 0.1 %[a] and 0.00625 %[a] *cream*, *ointment*, *solution*

(continued)

Table 140.1 (continued)

Fluocortin butyl 0.75 % *cream*, *ointment*
Flumethasone pivalate 0.2 % *cream*, *ointment*
Flurandrenolone 0.0125 % *cream*, *lotion*
Halometasone 0.05 % *cream*
Hydrocortisone aceponate 0.127 % *cream*, *ointment*
Hydrocortisone butyrate 0.1 % *cream*, *lotion*, *ointment*
Hydrocortisone valerate 0.2 % *cream*, *ointment*
Mometasone furoate 0.1 % *cream*, *lotion*
Prednicarbate 0.1 % *cream*, *ointment*
Triamcinolone acetonide 0.2 % *spray*, 0.1 and 0.04 % *cream*, *ointment*
Mild (*Class IV Europe/I Germany/VI/VII USA*)
Dexamethasone 0.2 and 0.1 % *cream*, *gel*, *lotion*, *ointment*
Fluocinolone acetonide 0.0025 % *cream*, *foam*, *solution*
Fluocortin butyl ester 0.75 % *cream*, *ointment*
Hydrocortisone/hydrocortisone acetate 1.0 and 0.5 % *cream*
Methylprednisolone acetate 0.25 % *cream*, *ointment*
Triamcinolone acetonide 0.025 % *cream*, *lotion*

o.v. optimized vehicle
[a]Considered the next lowest level of potency according to some authors

Table 140.2 Topographical differences in the management of topical corticosteroids

Treated area	Recommended potency
Mucous membranes	Mild or moderately potent
Scrotum/genitalia	Mild (or moderately potent or potent, short periods of time)
Eyelids	
Face	
Inner thighs	
Perianal area	
Skinfolds	Mild (or moderately potent or potent, short periods of time)
Inner arms	
Scalp	
Thorax and back	Potent or very potent
Arms and thighs	Very potent (short periods of time)
Forearms and legs	
Dorsum of hands and feet	
Elbows and knees	Potent or very potent
Palms and soles	
Nails	

Topical steroids must be chosen according to the patient's age and preexisting skin conditions as well as the diagnosis (the acute or chronic character of the disease, its extent, and its location), as detailed in Table 140.2.

Table 140.3 Skin conditions susceptible to topical steroid treatment

Dermatoses requiring very potent topical corticosteroid therapy
Discoid lupus erythematosus
Granuloma annulare
Hand eczema (severe)
Hyperkeratotic eczema
Keloids
Lichen planus
Lichen simplex chronicus
Necrobiosis lipoidica
Palmoplantar psoriasis
Pompholyx
Sarcoidosis
Dermatoses requiring potent topical corticosteroid therapy
Alopecia areata
Atopic dermatitis (resistant)
Contact dermatitis (irritant or allergic)
Lichen sclerosus (skin)
Mastocytosis
Mycosis fungoides (patch stage), parapsoriasis
Nummular eczema
Subacute lupus erythematosus
Dermatoses requiring moderately potent topical corticosteroid therapy
Anal, vulvar, or scrotal pruritus
Atopic dermatitis (ideally in children)
Flexural (inverse) psoriasis
Flexural dermatitis (severe)
Lichen sclerosus (genitalia)
Perianal inflammation (severe)
Pityriasis rosea of Gilbert
Seborrheic dermatitis
Sunburns
Dermatoses requiring mildly potent topical corticosteroid therapy
Flexural, eyelids, or face dermatitis
Perianal inflammation

Though their anti-inflammatory properties are the main reason for the use of corticosteroids, other actions such as the lowering the synthesis of macromolecules that form connective tissue, their antimitotic activity, and their symptomatic relief of itching and burning can make them useful in the treatment of multiple skin conditions (Table 140.3).

The choice of topical steroids and their bioavailability must take into account the excipient

used. Choosing one formulation or another will depend on the type of disease and on the area of the body and extent to which it will be applied:

- Ointments: More occlusive than other bases, enhancing the penetration of the agent, ointments are ideal for patients with dry skin (such as those with atopic dermatitis or those who live in dry and cold areas). However, they have low cosmetic acceptability, resulting in low patient satisfaction and compliance. Ointments should not be used on hairy areas of the skin, because they can occlude the hair shaft. At the same time, they should be avoided on flexural areas, due to the risk of maceration and folliculitis.
- Creams: Cosmetically more acceptable but less potent than ointments, creams are ideal for exudative inflammatory processes, due to their drying effect, and in flexural areas.
- Lotions, solutions, and gels: Indicated on hairy locations, given their capacity to penetrate easily without leaving much residue, or on very exudative lesions, due to their drying effect. Gels are one of the most cosmetically acceptable formulations and are increasingly used in certain indications.
- Foams and shampoos: As another option for the treatment of scalp conditions, these formulations are also cosmetically very acceptable, maximizing the patient's compliance.

Finally, the combination of topical steroids with other active substances can be considered:

- Antibacterial or antifungal agents may be useful in some cases, taking into account the potential colonization of dermatitis with *Staphylococcus aureus* or *Pityrosporum orbiculare*. However, they can pose the risk of sensitization, and long-term treatment with these combinations should be discouraged.
- Salicylic acid may be another helpful association given its antiseptic and keratolytic properties, facilitating the absorption of topical steroids.
- Urea also enhances the absorption of corticosteroids, acting as a keratolytic agent and favoring water retention in the epidermis.
- The combination of betamethasone and calcipotriol has proven to be effective in the treatment of plaque psoriasis.

Side Effects

Corticosteroids are commonly metabolized in the liver. The study of glucocorticoid metabolism, of their epidermal, upper, and lower dermal concentration after topical application on intact skin, as well as the evaluation of the necessary concentrations to inhibit the synthesis of human connective tissue by the skin fibroblasts, suggests that local and systemic adverse effects could be reduced if extrahepatic transformation occurs more quickly. Therefore, the ideal glucocorticoid should be inactivated immediately after its absorption.

Steroid potency is directly related to the adverse effects; their use should be limited, and a clear and explicit treatment regimen should be indicated to the patient. Factors that may increase the risk of side effects include chronic use (especially of potent steroids), larger quantities of preparation, unclear treatment regimens or incorrect understanding of the regimen, excessive application of the preparation on the skin (which, in most of the cases, has no extra therapeutic benefit), treatment of a greater surface, or treatment of certain anatomical areas (raising the risk of systemic absorption).

Local Side Effects

Cutaneous side effects may result from the presence of corticosteroid preparations on the skin and include:

- Tachyphylaxis: Defined as the progressive lowering of the corticosteroid efficacy (or sensitivity) during chronic treatment, requiring the use of more potent topical molecules, and the subsequent increased risk of side effects.
- Skin atrophy, subsequent alterations in cutaneous mechanical properties and elasticity, and impaired wound healing: TCS can cause epidermal, dermal, and subcutaneous atrophy. Dermal atrophy is the first atrophy that can be detected. The atrophy caused by topical application of these drugs is considered reversible. Albeit less frequent than previously thought, this local side effect may be seen more among older and pediatric patients.

- Hypopigmentation: It has been postulated that melanin synthesis can be decreased in smaller melanocytes, adding up to another effect, which is the reduction amount of melanin transferred from melanocytes to keratinocytes.
- Epidermal barrier alteration: This potential effect, expressed by reduced formation of lipid lamellar bodies and an increased transepidermal water loss, seems paradoxically outweighed by aiding barrier repair and reducing inflammation in atopic dermatitis and psoriasis patients.
- Apparent skin aging, ulcerations, purpura, and stellate pseudoscars: Severe dermal atrophy, along with an increased fragility of the vessels resulting from chronic topical corticosteroid abuse, may be associated with lesions resembling actinic damage, purpuric lesions, hypopigmented and depressed stellate pseudoscars, and ulcers.
- Striae: Potentially caused by corticosteroid abuse, they should not be confused with those resulting from weight gain or pregnancy.
- Acne: Acneiform lesions can be precipitated or aggravated after topical steroid therapy. Although corticosteroids may initially diminish inflammatory papules and pustules, these lesions tend to recur and persist, giving the clinical picture of steroid-induced acneiform eruptions.
- Steroid rosacea: This is seen typically among middle-aged women with a history of rosacea-like lesions treated with mildly potent corticosteroids, which progressively lose efficacy and prompt the need of continued use of more potent steroids.
- Corticosteroid addiction: Seen among patients who, trying erroneously to control the flare-ups of several dermatoses, such as perioral dermatitis, rosacea, or acne, perform an inadvertent long-standing use of TCS mainly on the face. Some of these cases may even develop the so-called red burning skin syndrome: this erythroderma seen after steroid withdrawal can be distinguished from chronic eczema by measuring the serum nitric oxide.
- Telangiectasia: Endothelial cells from the dermal vessels may be stimulated after chronic use of corticosteroids, causing dilatation of the vessels, which can be more evident on the face.
- Perioral dermatitis: Seen mainly among female patients with continued use of potent topical steroids on the face, it is defined by the presence of an erythema along with follicular papules and pustules beginning in a perioral distribution, with a characteristic sparing of the vermilion border-adjacent skin.
- Hypertrichosis: Albeit infrequent with topical but relatively common with systemic corticosteroids, growth of villous hair by an unknown mechanism can be seen and may persist for months even after stopping the application of steroids.
- Mucocutaneous infections: Considered common during (and in some cases prior to) treatment with corticosteroids. The occurrence of the typical tinea incognito (unrecognizable cutaneous eruptions resulting from corticosteroid treatment of tinea infections) has been described, as has herpes simplex, molluscum contagiosum, scabies, reactivation of Kaposi's sarcoma, and the characteristic but rare clinical picture of granuloma gluteale infantum (consisting of persistent granulomatous papulonodular lesions on the inguinal folds, buttocks, or thighs of children that have been treated with TCS of their diaper dermatitis).
- Contact dermatitis: Incidence of contact dermatitis from TCS (excluding the excipients) is variable (ranging from 0.2 to 5 %, with 85 % of these patients having multiple steroid allergies) and depends on the molecules that are available and predominantly used in each country. Relapsing or persistent dermatitis on the face, hands, or lower legs, in older-aged patients showing signs of other side effects of chronic glucocorticoid use or with a repeated occupational exposure to TCS (e.g., nurses, pharmacists), with a lack of improvement or a worsening of the dermatitis despite of an apparently adequate corticosteroid treatment regimen, should trigger the suspicion of topical corticosteroid-induced contact allergy. Corticosteroid contact allergy testing has some specific characteristics that should be

taken into account, such as the need of a delayed reading, on the seventh day, to maximize the diagnosis.

Previously classified in five groups (A, B, C, D1, and D2), corticosteroids were reclassified in 2011 by Baeck et al. into three groups, on a clinical and molecular basis:

- Group 1: encompassing the previous group A (e.g., hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, tixocortol pivalate), group D2 (e.g., hydrocortisone aceponate, hydrocortisone butyrate, methylprednisolone aceponate, prednicarbate), and budesonide
- Group 2: including the previous B group steroids (e.g., triamcinolone acetonide, fluocinolone acetonide, amcinonide, desonide, fluocinonide, halcinonide)
- Group 3: including the previous groups C (e.g., betamethasone, dexamethasone, desoxymethasone, fluocortolone, halometasone) and D1 (e.g., clobetasol propionate, clobetasone butyrate, beclomethasone dipropionate, betamethasone dipropionate, betamethasone valerate)

This study also confirmed that there are two usual subsets of patients with corticosteroid reactivity: patients reacting to molecules from only one group and patients reacting to the whole spectrum of corticosteroids. The European standard series of patch test allergens currently includes two markers of corticosteroid allergy: budesonide and tixocortol pivalate.

Systemic Side Effects

Normally, only 1 % of the applied topical steroid remains therapeutically active (the rest can be easily removed from the skin). Though small, this proportion of steroids may be absorbed and potentially cause systemic adverse effects, which include the following:

- Hypothalamic-pituitary-adrenal axis suppression: Short-term and early increase of plasma cortisol levels after the application of TCS has been seen. The use of more than 50 g of potent topical steroids per week, particularly in patients with impaired barrier function (such as pediatric atopic dermatitis patients), has been associated with an increased risk of iatrogenic Cushing syndrome and Addison crises.
- Hyperglycemia: Especially in patients with liver disorders, glucocorticoids may lead, through a complex mechanism, to hyperglycemia and insulin resistance.
- Other metabolic disorders: Osteoporosis in the elderly or decreased growth rates in pediatric populations, among other disorders, have been described as rare side effects of topical therapy with steroids.
- Electrolyte and water balance disorders: Due to their mineralocorticoid effect, edema, hypocalcemia, and hypertension can be triggered.
- Cataracts and glaucoma: It is possible, but not frequent, that, following long-standing topical therapy with potent preparations on the face, ophthalmologic disorders may occur.

Contraindications

TCS are contraindicated in the following situations:

- Active bacterial, fungal, or viral skin infections without applying specific antimicrobial treatment.
- Most superinfected dermatoses. However, topical steroids may be used for symptomatic relief in some situations if prescribed adequately. Furthermore, growing evidence does not contraindicate proceeding this way: a recently published study observed that, in hospitalized children with eczema herpeticum, the use of TCS during active infection was not associated with poorer outcomes.
- Long-term treatment of extensive skin areas using corticosteroids as the single topical agent for treatment.
- Past personal history of systemic or contact allergy to a molecule or the excipients of a specific preparation.

Drug Interactions

With adequate treatment regimens, it is highly unlikely that TCS could interact with systemic medications.

TCS have been combined with multiple topical treatments with no incidences. Nevertheless, possible contact allergies need to be considered when prescribing any preparation. Specifically, cross-reactions between different molecules should be taken into account when prescribing alternative preparations to patients presenting with systemic or contact corticosteroid allergy.

Use in Infants/Children and the Elderly

As previously stated, pediatric and elderly patients are more prone to suffer systemic adverse effects to TCS. Consequently, treatment regimens in this populations need to be more conservative, explicit, and clearly limited.

Regarding local adverse effects, there is no reason to sustain any concerns about the risk of cutaneous atrophy in children with atopic dermatitis exposed to appropriate long-term treatment regimens with TCS, as a recent observational study shows (in which 70 exposed versus 22 non-exposed children were evaluated for skin atrophy, finding no significant differences).

Even with reassuring evidence supporting the safety of topical corticosteroid therapy in the general population, corticosteroid phobia is a frequent concern in contact dermatitis patients and especially among the parents of these patients. A new scale has been developed to assess corticophobia in these settings.

The best practice in these population groups is described in the "Treatment and dosage" section.

Pregnancy and Breastfeeding

Growing evidence supports that adequate and limited regimens with TCS in pregnant women can be considered safe. A recent study involving 2,658 pregnant women exposed to topical glucocorticoids showed no associations with orofacial cleft, preterm delivery, fetal death, low Apgar score, or mode of delivery. However, it did show a relationship between low birth weight and the use of more than 300 g of potent or very potent TCS during the entire pregnancy. Therefore, limited use of mild to moderate corticosteroids is advised.

Extensive bibliographic searches have yielded no references concerning TCS and breastfeeding.

Treatment Regimen and Dosage

There is no standard topical corticosteroid regimen, and therefore treatments should be individualized. An appropriate treatment would be a topical corticosteroid with sufficient potency to control the disease but with as few local or systemic side effects as possible, in a formulation and excipient according to the site of the lesion, the patient's age, and past medical history.

It is essential to explain and give explicit instructions to each patient concerning the correct dosage, number of applications, and duration of the treatment.

Treatment Duration

Regardless of the potency, treatment of TCS should not be maintained for more than 2–4 weeks. Regimens exclusively with potent or very potent corticosteroids should never exceed 2 weeks and should be tapered progressively to avoid adverse effects.

Frequency of Applications

- *Acute Phase*
- One or two applications per day are recommended for most of the available preparations. Applying the product more frequently has been related with a higher rate of adverse effects, without providing better therapeutic results. However, if we take into account that the stratum corneum acts as a reservoir for TCS (animal models have proved that very potent TCS such as clobetasol propionate may persist up to 4 days in the stratum corneum, yielding a reservoir effect), every-other-day or twice-a-week regimens can be recommended.

- *Maintenance Regimen* (*If Needed*, *Mainly in Inflammatory Dermatoses*)
- Once the dermatosis is under control with the treatment, weekend application (or the minimal frequency with therapeutic effect) of topical corticosteroid along with weekday application of emollients or steroid-sparing agents (such as the calcineurin inhibitors tacrolimus and pimecrolimus) might be optimal in terms of efficacy, safety, and compliance.

Amount of Preparation Needed

The *fingertip unit* (FTU) was proposed in 1991 as a measure of the amount of cream or ointment necessary to treat a specific anatomic area. It is defined as the amount that can be squeezed with a 5 mm-diameter nozzle tube from the fingertip to the fold of the distal interphalangeal joint (with standard tubes, 1 FTU is equivalent to 0.5 g of cream/ointment). The use of FTU has been promoted worldwide to standardize recommendations and encourage compliance. Recommended FTUs depend on the anatomical site being treated (given that, as previously stated, there are certain areas more sensitive to the effects of TC). Following are the FTU recommendations:

- The face and neck would require 2.5 FTU.
- The anterior or posterior aspect of the trunk, 7 FTU.
- Each arm, 3 FTU.
- The whole hand, 1 FTU.
- Each leg, 6 FTU.
- Each foot, 2 FTU.

Specific FTU recommendations for pediatric populations were published by the same group in 1998.

Other formulations such as foam or gel are increasingly more convenient for the patient in terms of dosage, though no standardized system has been proposed to control the amount of product that needs to be applied.

General Recommendations

Though referred mainly to pediatric, elderly, and pregnant patients, the following recommendations can contribute to maximizing the therapeutic benefit and minimizing the possibilities of adverse effects:

- Thoughtful, individualized, and specific regimens should be advised. For example, alternate-day treatment (which may contribute to reducing tachyphylaxis), occlusive therapy with mildly or moderately potent corticosteroids (which has been associated with a lower risk of hypothalamic-pituitary-adrenocortical axis suppression), combination with emollients (which have been proven to reduce the amount of steroids needed), combination with keratolytic agents (lowering the need for more potent formulations), or regimens including corticosteroid-saving agents can be helpful.
- Treatment with very potent or potent corticosteroids should be done for short periods of time.
- Occlusive application of potent or very potent corticosteroids should be avoided in pediatric patients, whereas it should be used only for short periods of time in the general population.
- Long-term daily treatment of large areas of the skin should also be eluded: regardless of the potency, treatment of TCS should not be maintained for more than 2–4 weeks.
- No more than 50 g per week of very potent or potent corticosteroid preparations in the general population and no more than 300 g of very potent or potent corticosteroid preparations in women during their entire pregnancy should be used.
- Patients with preexisting renal or hepatic disease should be carefully assessed, since systemic side effects of topical administration seem to be more frequent.

TCS have a broad treatment spectrum with multiple effects. Despite their side effects, including cutaneous atrophy and the possibility of systemic absorption, they are still the most potent topical anti-inflammatory agents available.

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Glucocorticoids: Systemic

141

Elisa Cinotti and Frédéric Cambazard

Key Points

- Corticosteroids (CSs) still play a major role in dermatology due to their potent anti-inflammatory and immunosuppressive properties.
- They are used as first line in most autoimmune bullous dermatoses, autoimmune connective tissue diseases, neutrophilic dermatoses and vasculitis.
- Adverse effects are mainly due to the alteration of electrolyte and water balance, the inhibition of tissue repair process, the activation of gluconeogenesis, the increase of infection risk, the inhibition of the secretion of ACTH and the risk of growth retardation in children.
- Prednisolone is commonly the oral medication of choice and its daily dose varies from 0.5 to 2 mg/kg/day, depending on the severity of the dermatological condition.
- A gradual tapering of the CSs is necessary for treatments that last longer than 4 weeks (long-term therapy) in order not to precipitate into acute adrenal insufficiency and to avoid a flare of the dermatological condition.

General Principles

Despite numerous therapeutic advances of new biologic agents and immunosuppressive drugs, corticosteroids (CSs) still play a major role in the dermatologist's armamentarium due to their potent anti-inflammatory and immunosuppressive properties.

Cortisone developed as a new compound in 1935. The Nobel Prize for Medicine and Physiology was awarded in 1950 to Edward Calvin Kendall and Tadeus Reichstein, who had independently isolated and synthesised cortisol and the adrenocorticotropic hormone (ACTH), and to Philip Showalter Hench, who had described its dramatic efficacy when injected intravenously in patients with rheumatoid arthritis. The industrial production of cortisone started subsequently.

In dermatology, CSs are widely prescribed in either topical or systemic formulations in various potencies to tailor therapy according to the severity of the underlying condition, anatomic location of application, size of the involved area and patient age. However, CSs are associated with several adverse events (AEs), particularly in cases of high doses and long-term use. The use of these drugs, therefore, requires a deep knowledge of their mechanism of action and their potential complicating factors.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_141, © Springer-Verlag Berlin Heidelberg 2015

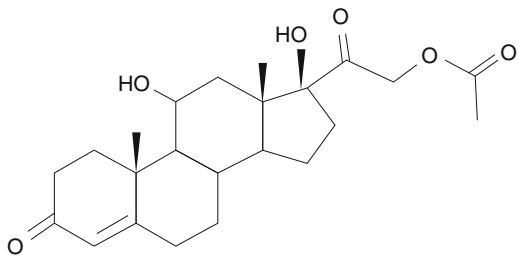

Fig. 141.1 Chemical structure of cortisol

Structure

Glucocorticoids and mineralocorticoids are collectively called CSs. CSs are basic components of the cell membrane, metabolites of the fatty acids and hormones.

The basic structure of all CSs is the cyclopentanoperhydrophenanthrene ring, composed of three hexane rings and one pentane ring (Fig. 141.1). Modifications in this steroid structure result in synthetic agents which have varying anti-inflammatory potency, mineralocorticoid effect and duration of action (related to the biologic half-life) (Table 141.1). Moreover, CSs differ for their metabolism: prednisone and cortisone must undergo conversion by the 11-hydroxylation enzyme in the liver to transform the 11-keto group in 11-beta-hydroxyl group and become activated, whereas biologically active molecules, such as prednisolone and cortisol, have already the essential beta-hydroxyl group at the 11 position. Patients with severe hepatic disease are less able to metabolise CSs, and therefore the administration of already transformed agents (prednisolone or cortisol) is recommended.

Apart from the natural steroids aldosterone, cortisone, deoxycortisone and hydrocortisone, several synthetic steroids have been produced. These analogues try to increase the potency of the drug and to separate the glucocorticoidal effect from the mineralocorticoidal effect. The determination of the potency of glucocorticoids is based on the degree of ACTH inhibition.

Table 141.1 Pharmacology of systemic corticosteroid

Drug	Equivalent dose (mg)	Mineralocorticoid potency
Short acting		
Cortisone	25	1
Hydrocortisone (cortisol)	20	0.8
Intermediate acting		
Prednisone	5	0.25
Prednisolone	5	0.25
Methylprednisolone	4	0
Triamcinolone	4	0
Long acting		
Dexamethasone	0.75	0
Betamethasone	0.6	0

Absorption and Distribution

CSs are absorbed in the jejunum. Concomitant administration with food does not decrease absorption but may delay it. Peak plasma levels are achieved within 30–100 min. Metabolised primarily by the liver, metabolites are excreted by the kidney and liver. Approximately 95 % of endogenous CSs are bound either to cortisol-binding protein (CBP), also known as transcortin, or to albumin in the circulation. The other 5 % free fraction is the steroid that is biologically active, and it is that fraction that enters cells and mediates CSs effects. Many factors influence circulating quantities of CBP. Hepatic failure, renal failure and hypothyroidism decrease CBP levels and, therefore, increase drug toxicity. Synthetic glucocorticoids have less avidity for CBP (estimated at 70 %) and, thus, have a tendency to cause side effects at low doses.

Duration of Action

The plasma half-lives of various glucocorticoids range from 1 to 5 h, but the duration of biologic effect is best assessed by the period of suppression of ACTH secretion after the administration of a single dose of the particular glucocorticoid. Short-acting glucocorticoids have an effect for

8–12 h, intermediate-acting agents for 24–36 h, and long-acting agents for 36–54 h.

Mechanism of Action

The greatest amount of cortisol is released during the early morning hours prior to waking. The basal rate of cortisol (hydrocortisone) production is 20–30 mg daily. The production may increase tenfold in stressful situations.

Cortisol enters the cellular cytoplasm by passive diffusion through the cell membrane and binds to the intracytoplasmic soluble CS receptor. This hormone–receptor complex then translocates to the nucleus either to enhance or to inhibit the expression of target genes by two independent pathways. In the first pathway, it binds to the steroid-responsive genes to induce transcription of annexin I (lipocortin-1) and mitogen-activated protein kinase (MAPK) phosphatase, limiting the formation of prostaglandins and leukotrienes. In the second one, the hormone–receptor complex binds to activator protein 1 (AP1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), two important transcription factors that play a significant role in chronic inflammation, thus inhibiting them. The end result is inactivation of cytokines, interleukins (ILs), adhesion molecules and growth factors. Glucocorticoids inhibit the production of IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, gamma-interferon, tumour necrosis factor-α and the granulocyte-macrophage colony-stimulating growth factor. As a result of the intracellular effects on transcription factor activity and cytokine production, glucocorticoid administration alters the distribution and activity of each inflammatory cell. CSs affect the growth, differentiation and function of monocytes and lymphocytes, the distribution of cellular subsets and the production of cytokines. They decrease the number of circulating monocytes, eosinophils and lymphocytes and they increase the circulating pool of neutrophils by accelerating their release from the bone marrow. Moreover, they decrease some functions of macrophages such as phagocytosis and antigen presentation.

Dermatological Indications

CSs are used to treat a vast group of dermatological conditions (Table 141.2).

Table 141.2 Major indications for systemic corticosteroids in dermatology

Autoimmune bullous dermatoses
Pemphigus vulgaris (all forms)
Bullous pemphigoid
Cicatricial pemphigoid
Linear IgA bullous dermatosis
Epidermolysis bullosa acquisita
Herpes gestationis
Autoimmune connective tissue diseases
Dermatomyositis
Systemic lupus erythematosus
Mixed connective tissue disease
Eosinophilic fasciitis
Relapsing polychondritis
Neutrophilic dermatoses
Pyoderma gangrenosum
Acute febrile neutrophilic dermatoses (Sweet syndrome)
Behçet disease
Vasculitis
Cutaneous and systemic
Miscellaneous dermatoses
Sarcoidosis
Urticaria/angioedema – acute
Type I reactive leprosy
Haemangioma of infancy (in case of beta-blocker failure)
Panniculitis
Linear scleroderma
Short-term treatment for severe eczematous dermatoses
Photodermatitis
Erythrodermas
Controversial use
Erythema multiforme
Toxic epidermal necrolysis
Alopecia areata
Contact dermatitis
Atopic dermatitis
Lichen planus

Contraindications

Absolute contraindications to systemic CSs are systemic fungal infections, herpes simplex keratitis and hypersensitivity. Relative contraindications include tuberculosis, peptic ulcer disease, hypertension, congestive cardiac failure, depression or psychosis, diabetes mellitus, chronic renal failure, osteoporosis, infectious disease, cataracts and glaucoma.

Delivery

Systemic CSs can be administered orally, intravenously and intramuscularly. Oral forms are usually to be preferred.

Intravenous (IV) Therapy

IV CSs are given in two situations: in severe or life-threatening diseases to rapidly gain control and for stress coverage in patients on long-term CSs and with hypothalamic–pituitary–adrenal (HPA)-axis suppression.

Methylprednisolone, devoid of mineralocorticoid activity, is usually preferred. Two methods of administration are available: it can be given either at a total daily dose of 2 mg/kg in divided doses every 6–8 h or as pulse therapy of 500–1,000 mg daily for 1–5 days. Pulse therapy should be given in a monitored setting due to potential serious AEs (i.e. sudden death, atrial fibrillation, anaphylaxis and electrolyte imbalances). Slow administration of pulse steroids over 2 h, along with concomitant infusion of potassium and electrolytes controls before and after therapy, helps prevent these problems.

Intramuscular (IM) Therapy

IM CS therapy is not widely used in dermatology. One advantage is assured compliance since the physician administers the dose. However, there are disadvantages, including the interpersonal variability in absorption and possible lipoatrophy and sterile abscess formation at the injection site.

Choosing and Dosing the Glucocorticoids

Glucocorticoids differ in their relative anti-inflammatory and mineralocorticoid effects and duration of ACTH suppression. CSs with minimal mineralocorticoid effects and an intermediate half-life are usually selected to decrease sodium retention and reduce AEs.

Prednisolone is commonly the oral medication of choice because it has a sufficiently prolonged action (intermediate-acting CSs) to ensure the sustained effectiveness of a single daily dose, has minimal mineralocorticoid activity and is biologically active (differently from prednisone that needs to be transformed into its active form in the liver).

Cortisone and hydrocortisone have a significant mineralocorticoid effect, while prednisone and prednisolone have fewer mineralocorticoids properties. Methylprednisolone, triamcinolone, betamethasone and dexamethasone have negligible mineralocorticoid activity.

The daily dose of prednisone varies depending on the severity of the dermatological condition and ranges from 0.5 to 2 mg/kg/day. When initiating therapy, a single daily dose is preferable, given in the morning when there is maximal adrenocortical cortisol secretion. At this time, the HPA axis is least suppressed by medication since maximal feedback suppression of ACTH secretion occurs from endogenous production. To gain rapid control in severe disease, the dose can be divided and administered from two times per day (avoiding the evening) to maintain a steady plasma concentration. This increases medication efficacy but also increases HPA-axis suppression. Therefore, conversion to a single daily dose should occur as soon as possible. It should be noted that corticosteroids should be taken immediately after the meal to avoid excessive stomach damage.

The dose of systemic corticosteroids should be adapted according to the age of the patient: it should be doubled in newborns and halved in elderly

subjects. For example, a dose of 1 mg/kg/day prednisolone in adults matches to 2 mg/kg/day for a newborn and to 0.5 mg/kg/day for an elderly person.

Use of CSs can be divided into short-term (≤3 weeks) and long-term (≥4 weeks) therapy. The first one is normally reserved for acute conditions (i.e. extensive allergic contact dermatitis), whereas the long-term therapy is necessary in the majority of the other conditions. Corticosteroid-sparing agents are usually added to the regimen, in an attempt to reduce the CSs dose.

Tapering

Tapering of the CSs is necessary for treatments that last longer than 4 weeks (long-term therapy). The reduction of systemic treatment has to be gradual in order not to precipitate into acute adrenal insufficiency and to avoid a flare of the dermatological condition. Tapering should be done in decrements of 10–20 % every 1–2 weeks, taking into account the underlying disease and individual response. Tapering can be faster at the beginning and then must be slowed down with lower doses of corticosteroids. There is a lack of clinical evidence to favour a particular regimen, and various tapering durations have been studied. A peculiar method of CSs dosage tapering is to convert from daily to alternate-day therapy once prednisone dose is 15–20 mg/day. In this regimen, patients are not exposed to high daily glucocorticoid concentrations and, therefore, have less HPA-axis suppression. Conversion from a daily to an alternate-day regimen should be carried out gradually, for example, progressively diminishing the dose on 1 day while building it up the next.

Drug Interactions

Most drug interactions are due to dexamethasone and methylprednisolone, whereas prednisone and prednisolone have fewer interactions.

Inducers of the cytochrome P450 (CYP) hepatic microsomal enzyme system (CYP 3A4), such as rifampin and anticonvulsants (phenytoin and phenobarbital), may decrease serum levels of CSs. Conversely, macrolide antibiotics and azole antifungals may increase serum levels of CSs via cytochrome CYP 3A4 inhibition.

Other effects are due to the rise of intrinsic AEs rather than to true interactions. Coadministration of nonsteroidal anti-inflammatory drugs (NSAIDs) increases gastrointestinal toxicity, additive immunosuppressant drugs enhance immunosuppression, and concomitant diuretics worsen hypokalaemia. Moreover, CSs decrease effectiveness of antidiabetic agents due to induced hyperglycaemia and reduce the serum levels of salicylates so that anticoagulants, such as dicumarol, need to be increased.

Adverse Effects

CS therapy is associated with numerous AEs (Table 141.3). AEs are mainly due to the alteration of electrolyte and water balance, the inhibition of

Table 141.3 Adverse effects of systemic glucocorticoid treatment

Skeletal	Osteoporosis
Gastrointestinal	Peptic ulcer
	Intestinal perforation
Ocular	Glaucoma
	Cataracts
Cardiovascular and fluid retention	Hypertension
	Hypokalaemic alkalosis
	Fluid and sodium retention
Metabolic	Changes in fat distribution
	Hyperglycaemia
	Hyperlipidaemia
Immunological	Increased susceptibility to infections
Endocrine system	Adrenal suppression
	Growth disorders
	Cushing's syndrome
	Secondary amenorrhoea
Cutaneous	Purpura
	Atrophy
	Striae
	Acne
	Folliculitis
	Hirsutism
Hypersensitive reactions	Anaphylaxis
	Urticaria

tissue repair process, the activation of gluconeogenesis, the increase of the risk of infection and the inhibition of the secretion of ACTH.

Short-term therapy is usually well tolerated and has fewer AEs. AEs are typically dose related. However, even low doses for prolonged periods are associated with significant AEs. Clinicians need to thoroughly monitor their patients. Low-fat, low-calorie and low-sodium diets but rich in proteins, potassium and calcium are recommended. Blood pressure should be monitored and an ophthalmologic control should be performed in case of decreased visual acuity. Osteoporosis should be prevented giving calcium and vitamin D supplements (500 mg of calcium and 400 units of vitamin D twice a day for men and for premenopausal women and up to 1,500 mg of calcium and 1,200 units of vitamin D for postmenopausal women). Gastric toxicity should be prevented with the association of proton-pump inhibitors. Moreover, tuberculosis should be excluded before establishing a long-term therapy.

In children there is a risk of growth retardation that requires height and weight chart monitoring. Moreover, parents should be informed of the increased risk of infections, especially chickenpox, and contraindication of live attenuated vaccines (Bacillus Calmette–Guérin; polyomavirus; chickenpox; MMR vaccine against measles, mumps and rubella; etc.).

Pregnancy

In general, CSs do not have teratogenic AEs on the fetus. However, delay of fetal growth and persistent ductus arteriosus have been reported. In animals adverse effects on the growth and development of immature brain and the development of cleft lip and palate have been observed, though these findings are controversial in humans. All exogenous glucocorticosteroids cross the placental barrier but each in a different degree. Prednisolone and methylprednisolone appear to cross the placenta only to a small extent in comparison with prednisone, betamethasone and dexamethasone and should therefore be preferred in pregnancy.

Conclusion

CSs remain useful molecules for the treatment of several dermatological conditions. They often provide rapid and effective response; however, in an era of steroid phobia, dermatologists should be aware of all significant AEs and monitor patients to prevent any serious complication.

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Hormonal Treatment for Skin Androgen-Related Disorders

142

Francesco Lotti and Mario Maggi

Abbreviations

17β-HSD	17β-Hydroxysteroid dehydrogenase
3β-HSD	3β-Hydroxysteroid dehydrogenase
AGA	Androgenetic alopecia
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
DHT	Dihydrotestosterone
FPHL	Female pattern hair loss
MPHL	Male pattern hair loss
OC	Oral contraceptives
PCOS	Polycystic ovarian syndrome
PSA	Prostate-specific antigen
SHBG	Sex hormone-binding globulin

Key Points

- Exposure of the pilosebaceous unit to androgen excess may lead to (1) vellus to terminal/sexual hair transformation in androgen-dependent areas of the female body and hair male-like pattern in females (hirsutism); (2) reversion of terminal hair to villous-like hair (miniaturization), leading to balding scalp (androgenetic alopecia); (3) formation of sebaceous glands with excessive sebum production and, acting in combination with other causative factors, development of inflammatory skin lesions (acne).
- The most common cause of hirsutism and acne in females is polycystic ovarian syndrome.
- Androgenetic alopecia is a common cause of hair loss in both men and women. Its exact pathogenesis is not well understood. As the name implies, the role of androgens and genetic susceptibility predisposes to pattern hair loss due to gradual conversion of terminal hair into vellus hair. Male and female pattern hair loss (MPHL and FPHL, respectively) are clinically distinct entities but histologically indistinguishable.
- Skin androgen-related disorders may depend on excess of androgen: (1) production, (2) peripheral conversion, and (3) local action, alone or combined. For this reason, skin androgen-related disorders may present with high or normal androgen levels; conversely, high androgen levels may not present with skin manifestations.
- The main androgens involved in skin androgen-related disorders are testosterone and its more active metabolite,

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_142,

dihydrotestosterone (DHT), formed by conversion in the pilosebaceous unit by the enzyme 5α-reductase.

- Hormonal treatments are effective in reducing the clinical expression of skin androgen-related disorders and should be started when androgen excess etiological investigations lead to a diagnosis and exclude specific causes which should benefit from other specific therapy/management.
- Hormonal therapy of hirsutism and acne is mainly based on the use of oral contraceptives (OC) and associated antiandrogens. Hormonal therapy of androgenetic alopecia mainly relies on the use of antiandrogens.
- The main difference between different OC is determined by the progestin, according to its chemical derivation and biological activity. Besides progestinic effect, different progestins may exert also antigonadotropic, antiestrogenic, antiandrogenic, or antimineralcorticoid effects or, conversely, estrogenic or androgenic effects. OC-containing progestins with antiandrogenic activity should be preferred in treating skin androgen-related disorders.
- Antiandrogens commonly used for hormonal treatment of hirsutism are competitive antagonists of the androgen receptor (spironolactone, cyproterone acetate, flutamide) or inhibitors of 5α-reductase, which decrease the conversion of testosterone to the more potent androgen DHT (finasteride).
- Spironolactone and cyproterone acetate are the most commonly used oral antiandrogens in the treatment of FPHL. Finasteride is the most commonly used oral antiandrogen in the treatment of MPHL.
- Indications and adverse effects of both OC and antiandrogens should be well known and explained to the patient.

General Principles

It is well known that the pilosebaceous unit is an elective androgen target tissue. In some areas of the skin, pilosebaceous units respond to androgens by forming sexual hair follicles, whereas in other areas they respond by forming sebaceous glands. Excessive androgen levels as well as their excessive local action on pilosebaceous units in different areas of the body may lead to different skin androgen-related disorders: hirsutism, acne, and androgenetic alopecia.

Pilosebaceous units form during fetal development, usually between 9 and 12 weeks gestation, and start producing hair by 16–20 weeks. No new hair follicles form after birth, and a decline in the number of hair follicles begins after age 40. Structurally, there are three types of hair. The first is lanugo hair, which is a soft, fine, lightly pigmented hair that covers the skin of the fetus and is shed between the first and fourth months postpartum. The second type, vellus hair, is also soft, but less fine than lanugo hair and is usually short and nonpigmented. The third type, terminal hair, is coarse, longer, and pigmented. It is the hair that comprises the scalp, eyebrows and eyelashes, and pubic and axillary areas of both sexes, and the majority of body and facial hair of men.

The growth of sexual hair is entirely dependent on the presence of androgen. Before puberty, hair is vellus (small, straight, and fair), and the sebaceous glands in androgen-sensitive follicles are small. In response to the increased levels of androgens at puberty, vellus follicles in specific areas develop into terminal hairs (larger, curlier, and darker, hence more visible), becoming sexual hair follicles; higher androgen levels are required for the growth of beard than for the growth of pubic and axillary hair. In other areas (e.g., the forehead and cheeks), the increased androgen levels dramatically increase the size of the sebaceous glands, but the hair remains vellus; the reason for this differential response is unclear.

Androgens play a major role in determining the type and distribution of hairs. Within the hair follicle, testosterone, under the influence of the enzyme 5α-reductase, gets converted to its more active metabolite, dihydrotestosterone (DHT). In

the pilosebaceous unit, 5α-reductase is expressed in two isoforms: type I, mainly located in the dermal papilla, outer root sheath, and sebaceous gland, and type II, mainly localized in the dermal papilla and inner root sheath. DHT, acting directly on dermal papilla cells and indirectly on hair epithelial cells, melanocytes, and keratinocytes, converts vellus to terminal hair. However, in some subjects, under the influence of androgens, terminal hair may gradually revert to villous-like hair, leading to balding scalp. Finally, pilosebaceous units may also respond to androgens by forming sebaceous glands. An excess of androgen action on these sites may contribute, promoting sebum production and acting together with other factors, to the onset of acne.

Among skin androgen-related disorders, the most frequent is hirsutism, followed by acne and androgenetic alopecia.

Hirsutism

Definition and Epidemiology

Hirsutism is defined as excessive terminal hair that appears in a male pattern (i.e., sexual hair) in women. About 5 % of women of reproductive age in the general population are hirsute. Racial and ethnic differences in the appearance of hirsutism are well known to exist. Especially among young women, hirsutism negatively influences psychological well-being, and this is mainly related and modulated by cultural aspects.

Basic Concepts of Pathogenesis

Hirsutism results from an interaction between the androgen level and the sensitivity of the hair follicle to androgen. Most women with androgen levels that are twice the upper limit of the normal range or higher have some degree of hirsutism. However, the severity of hirsutism does not correlate well with the level of androgen, because the response of the androgen-dependent follicle to androgen excess varies considerably within and among persons. Some women with androgen excess have no skin manifestations, or they may have seborrhea, acne, or alopecia without hirsutism. In other women, hirsutism develops without the presence of androgen excess (idiopathic hirsutism).

Testosterone is the key circulating androgen involved in hirsutism. It arises as a product of ovarian and adrenal function, either by secretion or by the metabolism of secreted precursors (mainly androstenedione or dehydroepiandrosterone sulfate, DHEAS) in peripheral tissues, such as fat. Free testosterone seems to be the main bioactive portion of plasma testosterone. The level of free testosterone is often elevated when the total testosterone level is normal in hirsute women, reflecting the relatively low levels of sex hormone-binding globulin (SHBG) in such women, which determines the fraction of plasma testosterone that is free. The SHBG levels are suppressed by hyperinsulinemia/insulin resistance and by androgen excess itself so that the total testosterone level may be normal despite androgen excess.

Variety of disorders give rises to androgen excess. In reproductive-age women, they can be classified in ovarian, adrenal, pregnancy-related, and other causes. Ovarian causes include polycystic ovarian syndrome (PCOS), hyperthecosis (a severe PCOS variant), and ovarian tumors (i.e., Sertoli–Leydig cell tumors). Adrenal causes include nonclassic adrenal hyperplasia, Cushing's syndrome, glucocorticoid resistance, and adrenal tumors. Specific conditions of pregnancy include luteoma of pregnancy, hyperreactio luteinalis, and aromatase deficiency in fetus. Other causes are hyperprolactinemia, hypothyroidism, acromegaly, idiopathic hirsutism (normal serum testosterone in an ovulary woman), and idiopathic hyperandrogenism (patients who do not fall into any of the categories listed above). In addition, several medications can induce hirsutism. In most hyperandrogenic disorders, androgen originates from more than one source. For example, testosterone secretion is increased from the ovary in PCOS, but the bulk of testosterone comes from the extraovarian conversion of significantly elevated circulating androstenedione of ovarian origin to testosterone.

The most common identifiable cause of androgen excess is PCOS. PCOS is the most common form of chronic anovulation associated with androgen excess, occurring in 5–10 % of reproductive-age women. The diagnosis of PCOS is made by excluding other medical conditions that cause irregular menstrual cycles and androgen excess and the presence of at least two of the following criteria: oligoovulation or anovulation (usually manifested as oligomenorrhea or amenorrhea), elevated levels of circulating androgens (hyperandrogenemia) or clinical manifestations of androgen excess (hyperandrogenism), and polycystic ovaries as defined by ultrasonography. Physiopathology of PCOS is complex, and the syndrome may be associated to several glicometabolic disorders.

Acne

Definition and Epidemiology

Acne vulgaris (acne) is a chronic inflammatory dermatosis that requires chronic treatment. Acne may present as a spectrum of lesions, including non-inflammatory open and closed comedones (blackheads and whiteheads, respectively) and inflammatory papules, pustules, nodules, and cysts. Lesions may be present on the face, neck, chest, or back—areas with the greatest density of pilosebaceous units.

Although often perceived as a self-limited disease of adolescence, acne's prevalence remains high into adulthood. Nearly 90 % of teenagers have acne, and half of them continue to experience symptoms as adults. By age 40 years, 1 % of men and 5 % of women still have lesions. Recent analyses show an increasing prevalence of acne in children, perhaps because of pubertal onset. Acne has clear detrimental psychosocial effects and may lead to permanent scarring.

Basic Concepts of Pathogenesis

Acne is an inflammatory disease of the pilosebaceous duct that results from four primary pathophysiologic processes: (1) abnormal keratinocyte proliferation and desquamation that leads to ductal obstruction; (2) androgen-driven increase in sebum production; (3) proliferation of *Propionibacterium acnes*; and (4) inflammation. Increased androgen production causes abnormal epithelial desquamation and follicular obstruction, which lead to the primary precursor lesion in acne—the microcomedone. Microcomedones are pathological structures not visible to the naked eye that evolve into visible lesions. An increase in circulating androgens also promotes sebum production, causing these obstructed follicles to fill with lipid-rich material and form visible open and closed comedones. Sebum serves as a substrate for bacterial growth, leading to proliferation of *P. acnes*. Finally, *P. acnes* releases chemical mediators that promote inflammation, which is propagated by traumatic rupture of comedones into the surrounding dermis. This inflammation manifests through the development of inflammatory papules, pustules, nodules, and cysts. The successful management of acne requires an understanding of these four facets of the pathophysiology of acne.

The exact mechanisms by which androgens affect sebaceous glands are unknown. There is evidence that both circulating and locally produced androgens play a role. Several, but not all, studies have reported a positive correlation between acne severity and circulating serum androgen levels. However, androgens produced and secreted locally within the sebaceous gland play a major role in acne formation. Type 1 5α-reductase isoenzyme predominately appears in sebaceous glands. Evidence has shown that there are regional differences in type 1 5α-reductase activity. The face, for example, is an area prone to acne because of increased type 1 5α-reductase enzyme activity within sebaceous glands compared to other areas of the skin.

Other enzymes have also been reported to mediate androgen activity within the skin. These include 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD), both of which are part of the steroidogenic pathway that regulates conversion of

testosterone precursors. Within the sebaceous glands, the enzyme 3β-HSD converts DHEAS, the major circulating adrenal androgen precursor, to androstenedione. Subsequently, 17β-HSD controls the reversible conversion of androstenedione into testosterone. The enzyme 17β-HSD has been demonstrated in the pilosebaceous unit and epidermal keratinocytes. Greater 17β-HSD activity has been noted in sebaceous glands from the face as compared to acne nonprone areas.

Androgenetic Alopecia/Male and Female Hair Loss

Definition and Epidemiology

Androgenetic alopecia is a common cause of hair loss in both men and women. Its exact pathogenesis is not well understood. As the name implies, the role of androgens and genetic susceptibility predisposes to pattern hair loss due to gradual conversion of terminal hair into vellus hair. Male and female pattern hair loss are clinically distinct entities but histologically indistinguishable. The role of sex hormones in females is less understood.

Male pattern hair loss (*MPHL*) or *androgenetic alopecia* (*AGA*) is the most common cause of hair loss in men. The incidence of pattern hair loss in men varies from population to population based on genetic background. Hair is an important feature of self-image. Men who suffer from MPHL are 75 % less confident, especially when interacting with the opposite sex, and report loss of self-esteem and introversion. Men who seek medical help and are successfully treated reported psychological benefits with improvements in self-esteem and personal attractiveness.

MPHL occurs in the presence of androgens in genetically susceptible individuals. The disease onset and progression vary from person to person. Initial signs of MPHL usually develop during teenage years, leading to progressive hair loss with pattern distribution. Bitemporal hair loss starts at the anterior hair line, resulting in a receding hair line followed by hair loss over the vertex and midfrontal areas, with sparing of the occipital scalp.

Female pattern hair loss (*FPHL*) is the most common cause of alopecia in women. It affects 6–12 % of women between the ages of 20 and 30 years and more than 55 % of women older than 70 years. FPHL clinically presents with diffuse nonscarring loss of hair, with prominent thinning over the frontal, central, and parietal scalp. The frontal hairline is characteristically retained. A similar pattern of hair loss with follicular miniaturization is seen in male androgenetic alopecia (AGA). Because the role of androgens on alopecia in women remains uncertain, FPHL has emerged as the preferred term rather than AGA in women.

Basic Concepts of Pathogenesis

Male Pattern Hair Loss (MPHL)

Locally and systemically derived testosterone either directly binds to the intracellular androgen receptors mainly expressed within the dermal papilla and the hair bulb or is metabolized by the 5α-reductase into the more potent DHT which, in turn, binds to androgen receptors with an approximately fivefold greater affinity. It is thought DHT to be the key androgen required for the induction of MPHL. Changes in several factors along the androgen-signaling pathway possibly lead to hair follicle miniaturization, including an increase in the expression of androgen receptors, increased androgen sensitivity to bind more steroid ligand, and higher levels of 5α-reductase. The scalp has a combination of androgen-sensitive and androgen-independent hair follicles. Androgen-sensitive hair follicles are located on the frontal scalp and vertex, whereas androgen-independent hair follicles are present on the sides and back of the scalp. This distribution of androgen receptors explains the clinical presentation of pattern hair loss. The dermis of the frontoparietal scalp is derived from the neural crest, whereas the dermis of the occipital and temporal scalp is derived from the mesoderm. This difference in embryonic origin may explain the differential influence of androgens.

Table 142.1 Dosage of systemic hormonal medications commonly used for treatment of skin androgen-related disorders. Suggested duration of treatment is at least 6 months

Hormonal medication	Hirsutism	Acne	FPHL	MPHL
Oral contraceptives (OC)	OC with antiandrogenic progestins are preferred	OC with antiandrogenic progestins are preferred	OC with antiandrogenic progestins are preferred	–
Cyproterone acetate (CPA)[a,b]	50–100 mg/day	50–100 mg/day	50 mg/day	–
Spironolactone[a]	50–200 mg/day	100 mg/day	50–200 mg/day	–
Flutamide[a]	125–500 mg/day	250–500 mg/day	62.5–250 mg/day	–
Finasteride[a]	2.5–5 mg/day	2.5–5 mg/day	1.25–5 mg/day	1 mg/day
Dutasteride[a]	–	–	0.25–0.5 mg/day	0.5 mg/day

FPHL female pattern hair loss, *MPHL* male pattern hair loss
[a]Antiandrogens must be used with OC in premenopausal women
[b]In premenopausal women, CPA should be used on days 1–10 of menstrual cycle with an OC. Note that OC with CPA 2 mg are available

Female Pattern Hair Loss (FPHL)

Androgens and estrogens are the main hormonal regulators implicated in FPHL. The hair follicle is sensitive to alterations in circulating estrogen and androgen levels; these hormones are also synthesized and metabolized locally. The role of androgens in FPHL has not been clearly established, and it does not seem to be as essential as in AGA. Pattern hair loss has been described in cases with complete androgen insensitivity syndromes, suggesting that mechanisms other than androgens may be involved. Although FPHL can be associated with hyperandrogenic states, the circulating testosterone levels do not differ between patients with FPHL and normal controls. Many women with FPHL have low levels of circulating SHBG, which may increase the available free testosterone at the level of the hair follicle. Although it has been postulated that there is an increased peripheral sensitivity to androgens in FPHL, the response to treatment with 5α-reductase inhibitors is unpredictable.

The observed differences between androgen regulation in FPHL and male AGA may lie in the presence of estrogens. Estrogen signaling can modify androgen metabolism at the hair follicle, by unclear mechanisms. Estrogens may positively affect hair loss through inhibition of 5α-reductase. High systemic estrogen levels in pregnancy are implicated in the prolongation of anagen. The sudden loss of estrogen postpartum is believed to lead to shedding, known as telogen gravidarum. Conversely, lower systemic estrogen levels have been implicated in the increase of FPHL after menopause.

Hormonal Therapy: Indications and Other Uses

Hormonal therapy of hirsutism and acne is mainly based on the use of oral contraceptives and associated antiandrogens. FPHL and MPHL hormonal therapy mainly relies on the use of antiandrogens. Dosage of systemic hormonal medications commonly used for the treatment of skin androgen-related disorders is reported in Table 142.1.

Hormonal Therapy of Hirsutism

Since the cycle of the hair lasts about 3–6 months, patient should be advised that results should be observed at least 3–6 months after androgen suppression. The Ferriman–Gallwey score may be used by the clinician to objective the variation of patient's hair distribution. A score >8 indicates mild hirsutism, while a score >15 a moderate–severe form.

Oral Contraceptives (OC)

Estrogen–progestin combination therapy, mainly exerted by oral contraceptives (OC), is the

predominant treatment for hirsutism and acne in PCOS. The estrogenic component of the oral contraceptive suppresses luteinizing hormone and thus ovarian androgen production. Estrogen also enhances hepatic production of SHBG, thereby reducing the free fraction of plasma testosterone available to occupy the androgen receptor.

The main difference between different OC is determined by the progestin, according to its chemical derivation (Sitruk-Ware 2004) and biological activities (Schindler et al. 2003) (Table 142.2). Different progestins may exert, besides progestinic effect, also antigonadotropic, antiestrogenic, antiandrogenic, or antimineralcorticoid effect or, conversely, estrogenic or androgenic effect. In particular, different androgenic effects have to be known to optimize hirsutism and acne hormonal treatment. 19-Nortestosterone derivatives exert androgenic effect. Norgestimate and desogestrel are virtually nonandrogenic progestins. Cyproterone acetate exerts the maximum antiandrogenic activity. Chlormadinone acetate and dienogest exert antiandrogenic activity, as well as drospirenone, an analogue of spironolactone, which shows also antimineralocorticoid activity. Antimineralocorticoid activity is exerted also by gestodene, which however shows androgenic effect. Etonogestrel (Nuvaring) and norelgestromin (Evra patch) have androgenic activity.

The decrease in circulating free androgens results in an improvement in the hirsutism. Even if large long-term placebo-controlled RCTs assessing the actual efficacy of OC for hirsutism are lacking, subjective improvement in hirsutism with OC ranges from 60 to 100 %. Such an improvement may decrease hirsutism scores to within the normal range in women presenting with mild hirsutism, supporting the use of an OC as the single drug in these cases.

Among the different formulations, low-dose OC containing a neutral (low androgenicity) progestin, such as desogestrel or gestodene, or an antiandrogen, such as cyproterone acetate, chlormadinone acetate, or the spironolactone-derivative drospirenone, are the choice for the treatment of hirsutism because all of these drugs provide adequate normalization of testosterone levels. If the clinical response to OC containing a neutral progestin is unsatisfactory, changing the OC formulation to include an antiandrogenic progestin may be useful.

Of note, these low-dose third-generation OC formulations are not associated with the unfavorable metabolic profile of older formulations. However, a mild increase in blood pressure might occur with some of these newer OC formulations. Especially among smokers, the third-generation OC may have deleterious effects on coagulation and may increase the risk of nonfatal venous thromboembolism compared with second-generation OC containing the androgenic progestin levonorgestrel. Aside from the amelioration of hirsutism, OC provide the effective contraception recommended for the concomitant use of antiandrogens and are quite useful for the regularization of menstrual bleeding in women with PCOS, which will also reduce the risk of endometrial hyperplasia. Based on these considerations, a low-dose neutral or antiandrogenic OCP as first-line therapy for hirsutism can be useful as a single drug in women with mild hirsutism, as an adjuvant to antiandrogen administration in women with moderate or severe hirsutism and to provide adequate contraception to these patients, to guarantee regular menstrual bleeding in hirsute patients with PCOS presenting with oligo- or amenorrhea.

Antiandrogens

Antiandrogens can be classified as steroidal (cyproterone acetate and spironolactone) and nonsteroidal (flutamide, finasteride, bicalutamide, dutasteride, GnRH agonists, GnRH antagonists). Among these, cyproterone acetate, spironolactone, flutamide, and bicalutamide are competitive antagonists of the androgen receptor. In addition, steroidal antiandrogens, passing through the blood–brain barrier, exert central inhibitory action on pituitary LH release. Antiandrogens commonly used for hormonal treatment of hirsutism are competitive antagonists of the androgen receptor (spironolactone,

Table 142.2 Biological activities of natural progesterone and synthetic progestins

Progestin	Progestogenic	Antigonadotropic	Antiestrogenic	Estrogenic	Androgenic	Antiandrogenic	Glucocorticoid	Antimineralcorticoid
Progesterone	+	+	+	−	−	±	+	+
Dydrogesterone	+	−	+	−	−	±	−	±
Medrogestone	+	+	+	−	−	±	−	−
17α-Hydroxy derivatives								
Chlormadinone acetate	+	+	+	−	−	+	+	−
Cyproterone acetate	+	+	+	−	−	++	+	−
Megestrol acetate	+	+	+	−	±	+	+	−
Medroxyprogesterone acetate	+	+	+	−	±	−	+	−
19-Norprogesterone derivatives								
Nomegestrol acetate	+	+	+	−	−	±	−	−
Promegestone	+	+	+	−	−	−	−	−
Trimegestone	+	+	+	−	−	±	−	±
Spironolactone derivatives								
Drospirenone	+	+	+	−	−	+	−	+
19-Nortestosterone derivatives								
Norethisterone	+	+	+	+	+	−	−	−
Lynestrenol	+	+	+	+	+	−	−	−
Norethynodrel	±	+	±	+	±	−	−	−
Levonorgestrel	+	+	+	−	+	−	−	−
Norgestimate	+	+	+	−	+	−	−	−
3-Keto-desogestrel	+	+	+	−	+	−	−	−
Gestodene	+	+	+	−	+	−	+	+
Dienogest	+	+	±	±	−	+	−	−

Adapted from Schindler et al. (2003)

Table 142.3 Antiandrogen properties and adverse effects

Antiandrogen	Properties	Common adverse effects
Cyproterone acetate (steroidal)	Progestagenic properties, → decrease gonadotropins, and testosterone levels	Loss of libido in men
	Strong antiandrogen activity	Thrombophilic
	Inhibits 5α-reductase activity	Hepatotoxic
	Inhibits LH	Gynecomastia
Spironolactone (steroidal)	Weak progestagenic properties and diuretic activity	Hyperkalemia
	Androgen antagonist	Hypotension
	Inhibits 5α-reductase activity	Loss of libido in men
	Increases SHBG	Loss of erections
	Inhibits LH	Gynecomastia
	Inhibits steroidogenesis	
Flutamide	Strong antiandrogen activity	Hepatotoxic
Finasteride	Type 2 5α-reductase inhibitor	Loss of libido in men
		Loss of erection
		Gynecomastia
		Ejaculation disorders
		Depression
Dutasteride	Type 1 and 2 5α-reductase inhibitor	Loss of libido in men
		Loss of erection
		Gynecomastia
		Ejaculation disorders
GnRH analogues	Testosterone reduction	Virtually no adverse effects

cyproterone acetate, flutamide) or inhibitors of 5-α reductase, which decrease the conversion of testosterone to the more potent androgen DHT (finasteride) (Table 142.3). In particular, cyproterone acetate is a 17-hydroxyprogesterone acetate derivative with strong progestagenic properties, leading to decrease gonadotropin production and testosterone synthesis and with strong antiandrogen activity, by competing with DHT and testosterone for binding to the androgen receptor. In addition, there is evidence it inhibits 5α-reductase in the skin and increases SHBG. As an adverse effect it may reduce sexual desire, has a thrombophilic and hepatotoxic profile, and may lead to the onset of gynecomastia. Spironolactone has weak progestagenic properties and diuretic activity. It can inhibit steroidogenesis, acts as an androgen antagonist, inhibits 5α-reductase activity, and increases SHBG. Rare adverse effects are hyperkalemia and hypotension and in the male loss of libido or erection and onset of gynecomastia. It has no thrombophilic and hepatotoxic profile. Flutamide is a potent antiandrogen, which could lead to enhanced gonadotropin, testosterone, and estrogen levels and to hepatotoxicity, usually not suitable for the indication of hirsutism. Finasteride and dutasteride inhibits 5α-reductase. In particular finasteride primary inhibits type 2 isoform. As hirsutism results from a combination of effects of type 1 and type 2, this agent is only partially effective. Dutasteride inhibits the two isoforms, and anyway it has not demonstrated a positive effect on hirsutism. GnRH analogues are effective in reducing testosterone and do not have virtually side effects, but they are expensive.

Antiandrogens (androgen receptor blockers and 5α-reductase inhibitors) are possibly the most effective drugs for hirsutism, although the evidence supporting this statement is relatively weak. Several RCTs support the use of antiandrogens for hirsutism. All these drugs ameliorate hirsutism compared with placebo.

However, at present there is not enough information to establish a scale of efficacy for these drugs. Some comparative studies did not find

differences in efficacy between antiandrogen drugs, whereas in other studies flutamide appeared to have the greatest efficacy, and finasteride the lowest, of antiandrogens. Furthermore, these drugs do not appear to exert dose-dependent effects against hirsutism. Among approaches combining several antiandrogens, the combination of spironolactone with finasteride was more effective than spironolactone alone in two small 6-month studies carried out in women with PCOS or idiopathic hirsutism (Escobar-Morreale et al. 2012).

It must be stressed that antiandrogens cannot be given to pregnant women for the risk of feminization of male fetuses and should only be prescribed to women using secure contraception. Unless oral or transdermal contraceptives are contraindicated, antiandrogens should be given in combination with these drugs, especially cyproterone acetate and spironolactone. These medications may cause menstrual disturbances or even amenorrhea when given alone because of their strong progestin effects. If hormonal contraception is contraindicated, for instance, in women at risk for thrombophilia or in heavy smokers older than 35 years, contraception must be assured by the use of an intrauterine device or by surgical sterilization before using antiandrogens.

Another consideration for antiandrogens is the potential for significant side effects. In particular, flutamide is associated with an increased risk for severe or even fatal liver toxicity. In hirsute women, severe liver toxicity is anecdotic but has been reported to occur with low doses. Finally, with the exception of cyproterone acetate and spironolactone in some countries, antiandrogens are not approved for the treatment of hirsutism and are used off-label after adequate informed consent.

In summary, antiandrogen should be prescribed combined with OC in women presenting with moderate or severe hirsutism or in those with a milder hirsutism who do not reach a satisfactory control of hair growth using OC alone after 1 year of treatment or as single drugs in women in whom OC are contraindicated, warranted that a reliable contraceptive method is used.

Considering their similar efficacy and potential for side effects, we suggest prescribing finasteride, cyproterone acetate, or spironolactone instead of flutamide when an antiandrogen is needed, although the latter is apparently safe at doses below 250 mg/day.

Insulin Sensitizers

Insulin sensitizers are widely used for PCOS because insulin resistance contributes to the pathogenesis of this disorder. Insulin sensitizers improve insulin resistance and menstrual dysfunction and may decrease serum androgen concentrations; their effects on hirsutism are much less clear. Compared with OC and antiandrogens, metformin does not appear to be more effective for the treatment of hirsutism. Mixed results were observed when comparing metformin with OC. Most studies used a combination of ethinyl estradiol and low-dose cyproterone acetate, and in approximately half of them, the OC was more effective compared with the insulin sensitizer. However, the short length of these studies precludes reaching any definite conclusion on the possible long-term effects of both families of drugs.

A few trials compared antiandrogens with metformin for hirsutism. Overall, metformin was less effective compared with flutamide and spironolactone. Also, compared with antiandrogens, the effect of metformin on hirsutism may require longer periods of therapy to be noticeable. Very few studies compared the effects on hirsutism of the different insulin sensitizers that are available. Therefore, we recommend against the use of metformin or other insulin sensitizers as therapy for hirsutism as its possible effects are unconvincing and possibly not superior to placebo.

Other Drugs

There are inconsistent reports regarding the role of glucocorticoids in the treatment of hirsutism and concerns about their safety. In addition, there is considerable controversy about the

regimen and the most appropriate dosage. The studies currently available in patients with adrenal or unselected hyperandrogenism and in women with idiopathic hirsutism suggest that glucocorticoids are less effective on hirsutism compared with OC or antiandrogens. However, in women with nonclassic adrenal hyperplasia, prolonged remission after withdrawal of antiandrogen therapy may be obtained by the addition of glucocorticoids.

The adrenal enzyme inhibitor ketoconazole ameliorates hirsutism, but its frequent side effects limit its use to subjects with Cushing's syndrome while waiting for definite therapy.

GnRH analogues are potent inhibitors of ovarian steroidogenesis, but experience with these drugs in the management of hirsutism is quite limited.

So far, recommendation is against the use of glucocorticoids, ketoconazole, and GnRH analogues for first-line therapy of hirsutism because their effects are generally limited. In addition, other drugs are safer and/or more cost-effective.

Hormonal Therapy of Acne

Antiandrogens are usually used to block the effect of androgens on the sebaceous gland and the infundibulum of the hair follicle. In fact, androgen receptors are present on sebocytes and sweat gland cells along with epidermal and follicular keratinocytes, dermal papilla and fibroblasts, endothelial cells, and melanocytes.

Spironolactone may be more effective in adult women with acne as compared to OC. It competitively inhibits the androgen receptor at higher doses and inhibits 5α-reductase activity to a lesser extent. In a Cochrane review, spironolactone 100 mg/day was found to be superior to finasteride 5 mg/day and low-dose CPA 12.5 mg/day (first 10 days of cycle). Oral contraceptives and spironolactone are synergistic, and response rates can increase by 75 % with the use of this combination. Orally, the recommended dose is 50–100 mg after food, but many patients show the response with a lower dose of 25 mg once or twice daily. It inhibits type 2 17-β HSD and also reduces sebum secretion. It is contraindicated in pregnancy since it has been reported to cause hypospadias in the male fetus. Topical 5 % spironolactone has been used in Europe in acne and seborrhea.

Cyproterone acetate is reported to be effective as monotherapy in more than 75 % of women. It is commonly combined with estrogens in the OC. It is very effective in recalcitrant acne associated with PCOS. Topical CPA in a novel vehicle (solid lipid nanoparticles) having enhanced follicular penetration may be useful when systemic medication is unacceptable and can be used in both men and women. Drospirenone, in combination with lower doses of estrogen (drospirenone 3 mg/ethinyl estradiol 20, 30 μg), is reported to have a beneficial effect in acne vulgaris, hirsutism, and the OC-induced fluid retention caused by the estrogen component.

Hormonal Therapy of Hair Loss in Women and Men

Female Pattern Hair Loss (FPHL)

Spironolactone and cyproterone acetate are the most commonly used oral antiandrogens in the treatment of FPHL. The effects of these agents are comparable, with 44 % of patients with FPHL experiencing regrowth.

Topical spironolactone 2 % solution exists and has been used in combination with minoxidil with variable success. Spironolactone alone in pregnancy should be avoided.

Treatment with cyproterone can improve hair growth in patients with FPHL, alone or in combination with ethinyl estradiol or spironolactone. Cyproterone has shown efficacy in treating patients with FPHL with both increased and normal androgen levels. It is approved for use in Europe and Canada to treat hirsutism, acne, and female alopecia, while it is not available in the United States.

5-α reductase inhibitors work by inhibiting the conversion of testosterone to DHT and result in increased hair growth and halt progression of hair loss. Their use in women is limited because they

are contraindicated in women of childbearing age. Finasteride has not shown the same efficacy in FPHL as seen in male AGA. In postmenopausal women, a 1-year course of finasteride 1 mg daily failed to improve hair loss over placebo. In premenopausal women, finasteride has shown benefit in treating FPHL associated with hyperandrogenism. In normoandrogenic women, it seems to be efficacious when used in higher doses (5 mg) or in combination with drospirenone and ethinyl estradiol OC. The specific subset of women who respond well to finasteride may have an excessive activity of the 5-α reductase enzyme. Topical preparations of finasteride 0.05 % have a potential role in the treatment of FPHL. Finasteride is metabolized in the liver, and it should be used with caution in patients with liver abnormalities. It is a pregnancy category X medication, associated with feminization of a male fetus. Women of childbearing age should use strict birth control and should not handle crushed or broken pills.

Dutasteride is a 5-α reductase inhibitor with superior antiandrogenic effects to finasteride. It can decrease serum DHT levels by more than 90 %. Dutasteride is not currently approved by the FDA for the treatment of hair loss. The off-label use of dutasteride (0.25–0.5 mg/day) has led to resolution of FPHL in postmenopausal women. This medication should not be administered to women of reproductive age. Liver function needs to be monitored in all patients.

Fulvestrant is a pure estrogen receptor antagonist that was developed as a treatment of estrogen-sensitive breast cancer. In vitro studies have shown that fulvestrant can increase hair growth in mice, by stimulating telogen hair follicles to reenter anagen. In human studies, topical fulvestrant preparations have not been shown to be superior over control vehicle in the treatment of FPHL.

Ketoconazole is an antifungal used in the treatment of seborrheic dermatitis. The use of ketoconazole shampoo, especially in combination with finasteride, results in increased hair growth in FPHL. The mechanism by which it can improve hair growth is unclear. It has anti-inflammatory properties, and it reduces colonization of the skin by *Malassezia*. Ketoconazole also affects steroidogenesis locally, and it decreases DHT levels at the hair follicle. It should be part of the treatment regimen in women with FPHL who have accompanying inflammatory seborrheic dermatitis or sebopsoriasis. Hyperandrogenic women with FPHL can benefit from the antiandrogenic mechanism of ketoconazole.

Male Pattern Hair Loss (MPHL)

At present, minoxidil and oral finasteride are the only treatments approved by the FDA for MPHL. Both these drugs stimulate hair regrowth in some men and are more effective in preventing progression of hair loss. Minoxidil monotherapy in MPHL may not halt the process of miniaturization under the influence of androgens. Finasteride is a potent and highly selective inhibitor of 5α-reductase type 2. Taken orally it reduces DHT levels in serum and in scalp by up to 70 %. In 1993 it was registered in the United States for the treatment of mild to moderate MPHL.

Finasteride is quickly absorbed after oral intake, with peak plasma level occurring 1–2 h after drug intake. The serum half-life is about 6 h; the biological effect persists much longer. Recommended dosage is 1 mg once daily taken with or without food. If a patient forgets a tablet, taking the double dosage the next day is not recommended. Dosage need not be adjusted in the case of renal insufficiency. Finasteride has been shown to increase both total and anagen hair counts. Finasteride prevents or slows the progression of MPHL, and about two-thirds experience some improvement. The improvement peaks at around 12 months. Finasteride has been shown to produce significant and durable increase in hair growth in men with pattern hair loss. The previously miniaturized hair becomes longer and thicker. Finasteride is more effective over the vertex and superior frontal region of the scalp, compared with a minimal response over the temporal and anterior hairline region. Treatment should be continued because the benefits will not be maintained after ceasing

therapy. Baseline photographs of the vertex and frontal hairline are helpful and are repeated at six monthly to yearly intervals to monitor treatment response. Patients are able to observe their regrowth, which serves as a motivating factor in improving long-term compliance to medical treatment.

Patients should be made aware of the pros and cons prior to treatment. Finasteride can cause loss of libido, ejaculatory dysfunction, gynecomastia, and potential depression in a small number of individuals. In a small number of patients, adverse sexual effects have been reported to be persistent. Finasteride reduces the level of prostate-specific antigen (PSA). If treatment is started after age 45 years, monitoring of the PSA level should be considered. The PSA level should be doubled to compensate the reduction caused by finasteride, resulting in an interpretation of the test remaining accurate.

The level of finasteride in the semen of treated men is very low even with regular intake of finasteride 5 mg/day, and there is no risk in the case of sexual relations with pregnant women. Use of a condom is not necessary for this reason. Finasteride-treated men should avoid donating blood. Women who are or potentially may be pregnant should not handle crushed or broken tablets. Finasteride tablets are coated to prevent contact with the active ingredients during manipulation.

Dutasteride has similar characteristics to finasteride but is a more potent, selective inhibitor of the enzyme 5α-reductase types I and II. Dutasteride has been shown to significantly increase hair counts and hair weight, improve the ratio of anagen and telogen hairs, and improve scalp coverage based on assessment of global photography. Oral dutasteride 0.5 mg/day can be considered to improve or prevent progression of MPHL in male patients older than 18 years with mild to moderate pattern hair loss. Dutasteride significantly reduces the progression of hair loss in men with pattern hair loss. Adverse effects of dutasteride are impotence, decreased libido, breast tenderness and enlargement, and ejaculation disorders. These side effects are more common with dutasteride than with finasteride. Dutasteride is not FDA approved for MPHL. However, it is approved for men in Korea. More studies are needed comparing the efficacy of dutasteride, 0.5 mg, with finasteride, 1 mg.

Conclusions

Hormonal treatments are effective in reducing the clinical expression of skin androgen-related disorders. Hormonal therapy of hirsutism and acne is mainly based on the use of oral contraceptives (OC) and associated antiandrogens. Hormonal therapy of androgenetic alopecia mainly relies on the use of antiandrogens. Indications and adverse effects of both OC and antiandrogens should be well known and explained to the patient.

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Imiquimod

143

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Key Points

- Imiquimod has revolutionized not only the therapeutic protocols but also our understanding of the immunogenetic properties of some of the most frequent dermatovenereological disorders.
- Imiquimod's first official approval was for use in external genital and perianal warts.
- Meanwhile, imiquimod 5 % cream has been also officially approved for treatment of superficial small (<2 cm) non-facial basal cell cancer (BCC) and actinic keratoses on the face and scalp.
- However, the list of off-label indications continues to expand offering potential cost-effective and more elegant treatment options, including anal and vulvar intraepithelial neoplasias (AIN/VIN), common warts, mollusca contagiosa, Bowen's disease, etc.
- Imiquimod is available as a 2.5 %, 3.75 % (Zyclara™) and 5 % (Aldara™) cream.
- Future perspective lies upon further investigations of imiquimod and newer generation of imidazoquinolines such as resiquimod, an imiquimod analogue and agonist of toll-like receptors (TLR) 7 and 8. This will hopefully contribute to the extension of (often somewhat narrowed) therapeutic modalities in dermatovenereology.

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General Principles

Imiquimod (1-[2 methylpropyl]-1 H-imidazo [4, 5c] quinolin-4 amine), a non-nucleoside heterocyclic amine of the imidazoquinoline family, is a synthetic compound known as the first member of a new class of immune response modifiers (Sheth et al. 2013; Schön and Schön 2007; Garland 2003). It enhances innate and acquired immune pathways resulting in antitumourous, antiviral and immunoregulatory activities (Schön and Schön 2007; Garland 2003). Since its first official approval for use in external genital and perianal warts 16 years ago, it has revolutionized not only the therapeutic protocols but also our

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_143, © Springer-Verlag Berlin Heidelberg 2015

understanding of the immunogenetic properties of some of the most frequent dermatovenereological diseases (Sheth et al. 2013; Garland 2003; Gaspari et al. 2009). Besides the aforementioned external genital and perianal warts, imiquimod 5 % cream is officially approved for treatment of superficial small (<2 cm) non-facial basocellular carcinoma (BCC) and actinic keratoses on the face and scalp (Sheth et al. 2013; Jackson et al. 2012). However, the list of off-label indications continues to expand offering potential cost-effective treatment options (Sheth et al. 2013; Gaspari et al. 2009; Jackson et al. 2012).

Mechanisms of Action

Although the exact mechanism of action against HPV infection has not been fully explained so far, imiquimod is generally recognized to operate on several levels which interact synergistically/mutually with the resultant antitumourous activity (Sheth et al. 2013; Schön and Schön 2007). Imiquimod displays effects on both innate and acquired immune response (Garland 2003; Gaspari et al. 2009; Jackson et al. 2012). Innate immune response enhancement by imiquimod is manifested by the increased production of cytokines, such as IFN-α, IL-6 and TNF-α, secretion of nitric oxide from macrophages and upregulation of natural killer (NK) cell activity (Schön and Schön 2007; Miller et al. 1999). Its stimulation of acquired immune pathways is documented by increased production of Th1 cytokine IFN-γ together with the ability to activate and enhance the migration of Langerhans cells (antigen-presenting cells) to regional lymph nodes (Schön and Schön 2007; Garland 2003; Suzuki et al. 2000; Prins et al. 2006). Imiquimod is also well known as the agonist of toll-like receptor (TLR) 7 since some of its major biologic effects are explained through this particular activity (Sheth et al. 2013; Schön and Schön 2007; Garland 2003; Gaspari et al. 2009; Jackson et al. 2012). TLR 7 is localized on the intracellular endosomal membranes of cells involved in both innate and acquired immune responses such as Langerhans cells, other dendritic cells, and macrophages (Schön and Schön 2007; Gaspari et al. 2009; Jackson et al. 2012). Imiquimod acts by reprogramming of gene expression mediated by the TLR 7 signalling pathways, resulting in movement of the transcription nuclear factor kappa B (NF-κB) to the nucleus (Schön and Schön 2007; Gaspari et al. 2009). Activation of the NF-κB induces the production of proinflammatory cytokines, chemokines and other mediators, especially IFN-α, IL-12 and IL-18, which in turn induce CD4+ T cells to produce IL-12 β2 receptor and IFN-γ, thus enhancing the cell-mediated immunity (Schön and Schön 2007; Jackson et al. 2012). It has also been proposed that imiquimod interferes with adenosine receptor signalling pathways and receptor-independent reduction of adenylyl cyclase activity which may amplify its proinflammatory activity (Schön and Schön 2007). Several studies have demonstrated increased apoptosis through decreased Bcl-2 expression after imiquimod treatment of basocellular carcinoma (Schön and Schön 2006; Vidal et al. 2004).

Pharmacokinetics

Imiquimod is applied topically, and its percutaneous absorption is minimal with very small amounts found in urine and faeces (Jackson et al. 2012; Zyclara 2012). The potential site of its metabolism as well as protein binding is unknown (Jackson et al. 2012). Some observations regarding its apparent half-life after topical and subcutaneous application led to conclusion that it has prolonged retention in the skin (Zyclara 2012).

Indications for Use of Imiquimod in Dermatovenereology

Imiquimod is available as a 2.5 %, 3.75 % (Zyclara™) and 5 % (Aldara™) cream (Imiquimod; Aldara, Zyclara; Zyclara 2012). As a topical preparation for external use on the skin, it is officially approved for the following indications with certain modifications in therapeutic schemes depending on the formulation type:

external genital and perianal warts, actinic non-hypertrophic keratoses on the face and/or balding scalp and superficial small (<2 cm) non-facial basal cell carcinoma (Sheth et al. 2013; Jackson et al. 2012; Imiquimod; Aldara, Zyclara; Zyclara 2012) (Table 143.1). Its use on ocular, nasal, oral, intravaginal and intra-anal areas has not been comprehensively evaluated and is therefore not officially recommended, so far (Zyclara 2012). However, the authors' personal, off-label experience is rather encouraging. Regardless the formulation and indication, the cream should be applied in a thin layer over the skin lesion, left on for 6–10 hours and washed off with water and mild soap after each application, especially in the case of genital warts in penile region (Imiquimod; Aldara, Zyclara; Zyclara 2012; Aldara 2013). Occlusive dressing should be avoided since it may cause irritation (Sheth et al. 2013). Hands should be washed before and after application of the cream (Imiquimod; Aldara, Zyclara; Zyclara 2012; Aldara 2013). Imiquimod 5 % cream (Aldara™) is packed in packets containing 250 mg of cream or 12.5 mg of imiquimod (100 mg of cream contains 5 mg of imiquimod) (Aldara 2013). Packets are designed for single use and should be disposed after use. Imiquimod 3.75 % and 2.5 % creams (Zyclara™) are packed in packets and pumps with the recommended dosage of 250 mg of cream (one packet) at each application or one full actuation of the pump (Zyclara 2012).

For the treatment of *external genital warts*, imiquimod 5 % cream is used topically three times per week until complete clearance of clinically visible lesions or for a maximum of 16 weeks (Imiquimod; Aldara, Zyclara; Zyclara 2012). The cream should be applied on three nonconsecutive days, e.g. Monday, Wednesday and Friday or Tuesday, Thursday and Saturday with the days of drug application preferably determined by the patient herself/himself at the beginning of therapy for better compliance and avoidance of confusion (Aldara 2013). Another formulation of imiquimod, the 3.75 % cream, is also approved for this indication and applied once daily for up to 8 weeks (Imiquimod; Aldara, Zyclara; Zyclara 2012). Special care should be applied in uncircumcised males with genital warts under the foreskin; to avoid irritations, the foreskin should be pulled back and cleaned daily (Imiquimod; Aldara, Zyclara; Aldara 2013).

Therapeutic modalities for treatment of non-hyperkeratotic *actinic keratoses* of the face and/or balding scalp include all three formulations of imiquimod. Imiquimod 5 % cream is applied three times weekly on nonconsecutive days (e.g. Monday, Wednesday, Friday) for 4 weeks (Aldara 2013). After that period, decision about prolonged therapy for 4 weeks more is brought based on thorough clinical inspection and evaluation by the dermatologist (Aldara 2013). Imiquimod 3.75 % and 2.5 % creams for this indication should be applied once daily for two 2-week cycles separated by 2 weeks without therapy (Jackson et al. 2012; Imiquimod; Aldara, Zyclara; Zyclara 2012).

Imiquimod is relatively novel therapeutic option for treatment of *small* (*<2 cm*) *superficial non-facial basal cell carcinomas*. Efficacy of imiquimod in the treatment of other types of basal cell carcinomas has not been completely

Table 143.1 Schematic overview of dermatovenereological treatment with imiquimod

	External genital and perianal warts	Actinic keratoses	Basal cell carcinoma
Imiquimod 5 % cream (Aldara™)	3 times weekly for up to 16 weeks	3 times weekly for 4 weeks (+/– 4 weeks more)	5 times weekly for 6 weeks
Imiquimod 3.75 % cream		2 cycles once daily for 2 weeks separated by 2 weeks with no treatment	
Imiquimod 2.5 % cream (Zyclara™)	Once daily for 8 weeks		

evaluated and is therefore not officially recommended, so far (Imiquimod; Aldara, Zyclara). Before beginning of therapy, the diagnosis should be confirmed histopathologically. For this indication, imiquimod is used in the formulation of 5 % cream which is applied five times per week (e.g. Monday–Friday) for up to 6 weeks. Cream should be applied across the lesion and within 1 cm diameter around the lesion in a thin layer avoiding the periorificial areas (Imiquimod; Aldara, Zyclara; Aldara 2013). Patients should be re-examined 12 weeks after treatment at which point clinical inspection is made with, preferably, biopsy as the only reliable method to ensure the complete clearance of tumour (Sheth et al. 2013; Imiquimod; Aldara, Zyclara).

Off-Label Usage of Imiquimod and Future Perspectives

Owing to the better understanding of diverse potentials of TLR 7 and more precise insight into molecular biomechanisms that have been accumulated in recent years, several new potential approaches for imiquimod have been suggested and investigated. Since this issue still awaits clinical and scientific approval for use, these alternative treatment options remain classified as "open-label" or "off-label".

Reports of successful treatment of common warts, periungual and plantar as well as flat facial warts have been submitted although the efficacy of imiquimod 5 % cream in these cases is inferior to its efficacy in genital warts (Gaspari et al. 2009; Jackson et al. 2012; Grussendorf-Conen et al. 2002; Micali et al. 2003).

Mollusca contagiosa are another open-label indication for the use of imiquimod 5 % cream confirmed by several studies and clinical trials. Frequency and duration of application of imiquimod varied between the reports (Sheth et al. 2013; Gaspari et al. 2009; Jackson et al. 2012; Imiquimod; Aldara, Zyclara; Myhre et al. 2008; Syed et al. 1998; Theos et al. 2004; Skerlev and Husar 2011; Husar and Skerlev 2002).

Acyclovir-resistant herpes simplex virus (HSV) infections can be managed with topical application of imiquimod according to some reports (Imiquimod; Aldara, Zyclara; Centers for Disease Control and Prevention (CDC) 2010; Bernstein et al. 2005). Still, one double-blind placebo-controlled study questioned these results (Schacker et al. 2002).

Efficacy of imiquimod 5 % cream in the treatment of keloids following surgical excision has been reported as well (Berman and Kaufman 2002). However, results of some later reported studies failed to confirm it (Cação et al. 2009; Berman et al. 2009).

Imiquimod 5 % cream has also been proven efficient against lentigo maligna (melanoma in situ) (Sheth et al. 2013; Gaspari et al. 2009; Jackson et al. 2012; Imiquimod; Aldara, Zyclara; Naylor et al. 2003; Powell et al. 2004; Ahmed and Berth-Jones 2000; Erickson and Miller 2010; Rajpar and Marsden 2006). Regardless the clinical studies confirming success of such treatment, it remains experimental and is generally regarded with great caution. Good therapeutic results with topical imiquimod were achieved for cutaneous melanoma metastases (Jackson et al. 2012; Florin et al. 2012; Wolf et al. 2003).

Bowen's disease (cutaneous squamous cell carcinoma in situ) is another potential indication for use of imiquimod which lacks solid evidence so far (Gaspari et al. 2009; Jackson et al. 2012; Patel et al. 2006; Rosen et al. 2007). Reports concerning its use in invasive squamous cell carcinoma also exist (Peris et al. 2006; Huang et al. 2009; Ahn et al. 2012).

Imiquimod has been used successfully also against anal and vulvar intraepithelial neoplasias (AIN/VIN) in both immunocompetent and immunodeficient (HIV/AIDS) patients (Imiquimod; Aldara, Zyclara; van Seters et al. 2008). In this context, imiquimod has also been used with success in combination with HPV vaccination (Daayana et al. 2010).

Other indications for off-label use of topical imiquimod include extramammary Paget's disease (Gaspari et al. 2009; Jackson et al. 2012; Cohen et al. 2006; Badgewell and Rosen 2006), mycosis fungoides (Deeths et al. 2005; Suchin et al. 2002; Martínez-González et al. 2008), Kaposi sarcoma (Gaspari et al. 2009; Celestin

Schartz et al. 2008; Babel et al. 2008), infantile superficial haemangioma (Ho et al. 2007) and cutaneous leishmaniasis (Jackson et al. 2012; Arevalo et al. 2007).

Future perspective lies upon further investigations of imiquimod and newer generation of imidazoquinolines such as resiquimod, an imiquimod analogue and agonist of TLR 7 and 8. This will hopefully contribute to the extension of (often somewhat narrowed) therapeutic modalities in dermatovenereology. Aiming for the better compliance, newer formulations of imiquimod and/or its analogues adjusted for daily application instead of three or five times per week is another potential direction on which future development would rely on (Gaspari et al. 2009).

Adverse Effects and Contraindications

Imiquimod is generally considered a safe drug. Contraindications for its use include hypersensitivity to its components, but absolute contraindications are not known (Sheth et al. 2013; Jackson et al. 2012; Imiquimod; Aldara, Zyclara). The most common adverse effects are restricted to the application site and include erythema, oedema, desquamation and ulceration, often accompanied by pruritus, burning, tenderness or scabbing (Sheth et al. 2013; Jackson et al. 2012). Their frequency is related to the frequency of application of the drug. However, they tend to subside once the use of drug is stopped. In cases of intense local reaction, application of imiquimod should be temporarily aborted and continued once the skin has recovered (Imiquimod; Aldara, Zyclara). Some unusual adverse effects of imiquimod have also been described such as psoriasis induced de novo or exacerbation of psoriasis (El Malki et al. 2013; Shibata et al. 2013; Gilliet et al. 2004), lichen planus and lichen sclerosus (O'Mahony et al. 2010), lupus-like skin reactions (Barr et al. 2011; Chan and Zimarowski 2011) and/or subacute lupus erythematosus (Burnett et al. 2010), erosive pustular scalp dermatosis (Vacarro et al. 2009), erosive cheilitis (Campanelli and Lubbe 2007) and aphthous ulcers (Chakrabarty et al. 2005). Systemic adverse effects are reported in 1–2 % of cases and include flu-like symptoms such as fatigue, fever, headache, diarrhoea and myalgia (Jackson et al. 2012). Serious systemic adverse effects have not been reported. Laboratory monitoring is not necessary (or cost-effective) during treatment with imiquimod (Imiquimod; Aldara, Zyclara).

Safety and efficacy of imiquimod has not been evaluated neither for children <12 years nor for immunosuppressed patients (Imiquimod; Aldara, Zyclara). During application of imiquimod on sun-exposed areas, sun-protective measures primarily sun avoidance and protective clothing (as well as avoidance of artificial UV sources) should be encouraged (Imiquimod; Aldara, Zyclara). Also, it is advised that any kind of skin disease or condition is healed before beginning of treatment with topical imiquimod (Imiquimod; Aldara, Zyclara; Aldara 2013).

Imiquimod is classified as pregnancy category C, and the data regarding its excretion in breast milk is limited (Jackson et al. 2012; Imiquimod; Aldara, Zyclara). Thus, its use in pregnant and lactating women should be carefully considered.

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Insect Repellents

144

Stefania Motta and Marcello Monti

Key Points

- Insect repellents are chemical substances that, when applied to the skin, are able to repel insects and block their attack on man.
- These compounds can block the insect's approach phase to the host by deviating the flight and hence taking the insect far from the target. Insect repellents exploit their action on many insects such as mosquitoes, flies, sandflies, horseflies, fleas, mites and ticks.
- There are three categories of insect repellents: physical repellents, synthetic repellents and natural-origin repellents.
- The insect repellents marketed in Europe possess a high level of safety due to especially low concentrations of the active ingredient. However, to increase the safety profile, dermatologists should suggest to their patients the following guidelines.
- The use of insect repellents is to be reserved to adults who, for professional or recreational activities, are at risk of contracting diseases transmitted by insect bites. Other forms of protection (e.g. the mosquito net) are recommended in common situations and for children.

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General Principles and Classification

Insect repellents are chemical substances that, when applied on the skin, are able to repel insects and block their attack on man. These compounds can block the insect's approach phase to the host by deviating the flight and hence taking the insect far from the target. Insect repellents exploit their action on many insects such as mosquitoes, flies, sandflies, horseflies, fleas, mites and ticks. There are three categories of insect repellents:

- Physical repellents
- Synthetic repellents
- Natural-origin repellents

Physical repellents are instruments, usually employing ultrasound and claiming to modify insect flight and host identification. High-frequency sounds are used also in many smartphone applications. Their efficacy is questionable, so they will not be considered in this chapter.

Synthetic and natural repellents are particularly effective when directly applied onto the skin. Therefore there is an interaction between human skin and the repellent substance that may

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_144, © Springer-Verlag Berlin Heidelberg 2015

cause cutaneous and/or systemic toxicity by absorption. From the dermatotoxicological point of view, insect repellents have to be considered as 'leave on products', though they can be absorbed if applied frequently for a long period. These products, which are available over the counter, are indiscriminately used nowadays, so it is necessary to consider them with particular concern for the possible risks of their use, misuse or abuse.

The substance most used as an insect repellent since World War II is a synthetic molecule called N,N[1]-diethyl-m-toluamide (DEET), chemically belonging to the diethylamide family.

Natural-origin repellents are essential oils derived from different plants. These products, unlike the synthetic insect repellents, have been relatively poorly investigated.

In this chapter, insect repellent compounds and their mechanism of action and toxicity will be considered.

The Ideal Insect Repellent

The perfect topical repellent would repel multiple species of biting arthropods, remain effective for at least 8 h, cause no irritation to mucous membranes, possess no systemic toxicity, be resistant to washing off and be greaseless and odourless. No available insect repellent meets all of these criteria.

Mechanism of Action of Repellents

The relationship between chemical structure and repellent effectiveness has not been completely clarified, thus insect repellents cannot be classified on the basis of their mechanism of action. However, the most active repellents belong to the following chemical moieties: amides, imides, alcohols and phenols. There is also a kind of relationship between vapour-producing property and the level of repellency. The repellency activity is somehow related to the olfactory receptors of insects via:

- A block of neurons which sense attractive chemical stimuli
- Activation of receptors which promote inappropriate behaviour
- Activation of receptors for noxious odours
- Activation of too many receptors and loss of attractive messengers

Factors Affecting Effectiveness of Repellency

Multiple factors play a role in how effective a repellent is; these factors are product dependent, product independent and user dependent as listed in Table 144.1.

Repellents form a barrier between the skin and mosquito receptors, and this barrier extends to 4 cm from the skin when the repellent is freshly applied. Apart from some individual host characteristics, repellents are inactive due to excessive evaporation when the temperature exceeds 30 °C. In sweaty areas such as the forehead, the duration of protection is significantly decreased. Moreover, for unknown reasons some insect species are more sensitive to repellents than other related species, which remain unaffected. Among mosquito species, *Aedes taeniorhynchus* and *Culex pipiens* are more sensitive than *Aedes aegypti* and *Anopheles albimanus*.

Table 144.1 Factors affecting repellent effectiveness

Product-dependent factors	Product-independent factors	User-dependent factors
Evaporation rate from skin surface	Species of the biting insect	Activity level of the host
Absorption rate	Density of the biting insect	User attractiveness
Resistance to abrasion	Wind velocity	Frequency of application
Resistance to wash off	Air temperature	Uniformity of application
	Wet environment	Anatomical site

Factors Attracting Insects

Mosquitoes use visual, thermal and olfactory stimuli to locate a host. Visual stimuli are important for in-flight orientation, whereas olfactory stimuli are more important as a mosquito nears its host. Even host movement and wearing of dark-coloured clothing may promote orientation. Investigations about host-attracting factors have pointed out that some body odours may attract insects. These are eccrine sweat because of the presence of amino acids, urea and ammonia and apocrine sweat and sebum secretion due to the presence of cholesterol. Urine, carbon dioxide and sexual hormones are considered as attractants. In particular carbon dioxide is a long-range attractant, whereas at close range skin moisture and warmth are attractants. Body temperature is a discriminating factor: mosquitoes choose hosts with higher body temperatures. Body humidity is also a discriminating factor due to mosquitoes having hygrometric sensors (see Table 144.1).

Types of Insect Repellents

Synthetic Insect Repellents

Thousands of chemical compounds have been demonstrated to have repellence activity. However, only few of these are considered suitable for human use. These are:

- Dimethyl phthalate (DMP)
- Ethylhexanediol
- Diethyltoluamide (DEET)
- Ethyl butylacetylaminopropionate
- Picaridin

The discrepancy between the number of active substances and the registered ones is mainly due to skin absorption toxicity.

Dimethyl Phthalate (DMP)

This compound, registered in 1929, has been the reference repellent for many years. It is an oily, colourless, water-insoluble liquid with an aromatic odour. DMP has a mean protective duration of 80 min, and its effectiveness is variable among different insect species. It is used at 40 % preparation. The minimum amount of DMP necessary to inhibit mosquito biting has been determined to be 8–8.15 mg/square inch. The toxicological data available indicate that over a 40 % concentration, DMP exerts eye, mucous and skin irritation; by ingestion it is a central nervous system and respiratory depressant. Nowadays DMP is used exclusively in association with other repellents. Recently DMP was mentioned for its efficacy against ixodid ticks and advocated for the prevention of Lyme disease.

Ethylhexanediol

This compound was patented in 1935. It is an oily, colourless, water-insoluble, chemically stable liquid. It has a protective duration ranging from 1 to 8 h depending on the different insect species. Its repellency decreases as the temperature increases due to rapid evaporation. It is used from 30 to 50 % and at these concentrations is a mild skin irritant. The only data available on the toxicity of ethylhexanediol cites suspected teratogenicity via skin absorption.

Diethyltoluamide (DEET)

This compound was patented in 1943 and marketed since 1956. It is considered the reference repellent since it still remains the best one in thousands of comparative tests with other compounds. Today DEET is distributed worldwide, and it is estimated that 200 million people use DEET each year. The repellency of this compound covers a wide range of insect species: mosquitoes, biting fleas, gnats, chiggers, ticks and others. It is oily, colourless, odourless, water and glycerin insoluble, and soluble in alcohol, ether and polyethylene glycols. It has a protective duration of about 4 h. The protectiveness

decreases to 24 min at 40 °C. Of the marketed products, DEET concentration has a wide range (from 7 to 100 %). As opposed to the previously cited repellents, a great bulk of literature on DEET toxicology is available. DEET toxicology may be subdivided into: general, systemic and skin toxicology.

Pharmacology

Human studies show variable penetration of DEET ranging from 9 to 56 % of topically applied dose. Absorbed DEET is metabolized completely within 12 h with 99 % urinary elimination. Hepatic microsomal cytochrome P450 enzymes are involved in DEET metabolism. There is no evidence of stratum corneum or systemic accumulation.

General Toxicology

DEET applied to skin is absorbed in about 20 min. The systemic LD_{50} is 2 mL/kg in rats and 10 mT Ikg in rabbits. The poisoned animals manifested laboured respiration, ataxia and convulsions.

Human Systemic Toxicity

Some cases of encephalopathy in children after the application of DEET were reported in 1961. After this, several reports on systemic toxicity after DEET application were published. Among these, the most frequently described symptoms were encephalopathy ataxia, seizures, bradycardia and hypotension. Severe toxic reactions and death after the ingestion of repellents containing DEET were also reported. In 1988, an editorial in the *Lancet* suggested that products containing less than 50 % DEET were safe; however, in children even preparations containing 20 % DEET, applied to large areas repeatedly, caused slurred speech, agitations, tremors and convulsions.

A comprehensive review of side effects due to DEET was published in 1994 (Veltri et al. 1994).

Skin Toxicology

There are several reports on specific skin sensitivity to DEET, while some reports refer to skin irritation, contact urticaria, generalized urticaria and vesiculobullous reactions (Amichai et al. 1994; Von Mayenburg and Rakoski 1994; Wantke et al. 1996).

No photosensitivity has been reported. DEET is considered a substance with a high profile of safety.

Ethyl Butylacetylaminopropionate

Ethyl butylacetylaminopropionate was synthesized by Merck and was registered as IR3535 compound.

The structure of ethyl butylacetylaminopropionate is based on alanine and beta-alanine, and the *Environmental Protection Agency* (EPA) has classified it as a biochemical substance based on the fact that it is 'functionally identical' to beta-alanine: both repel insects and the end groups are not likely to contribute to toxicity.

Picaridin (1-Piperidinecarboxylic Acid 2-(2-Hydroxyethyl)-1-methylpropyl Ester)

Picaridin, synthesized by Bayer, is an insect and acarid repellent in the piperidine chemical family. The chemical name is 1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropyl ester.

Mode of Action

Picaridin both repels and deters insects, so that insects move away from the chemical and do not feed if they encounter skin or clothing that has been treated. Insects appear to detect the chemical through olfactory sensing.

Toxicity

Picaridin is not considered a skin irritant and is not a sensitizer, but it can cause slight to moderate eye irritation and is considered to be slightly toxic for acute dermal and ocular exposure.

Insect Repellents of Natural Origin

All substances with repellent activity not produced by chemical synthesis are considered natural-origin insect repellents. Among these, some are of historical value such as smoke, plant

derivates, tars and animal urine. Plants whose essential oils have been identified as having repellent activity include cedar, citronella, clove, coconut, eucalyptus, geranium, lavender, menthe, onion, rosemary and thyme. Plant-derived insect repellents have been poorly studied, and when tested most of these tend to give short-lasting protection.

Oil of Citronella

Oil of citronella is the most studied and utilized essential oil as a repellent. Oil of citronella is extracted from *Cymbopogon nardus*, a Gramineae native to tropical Asia (Sri Lanka and Java). The active component is the aldehyde citronellal, present in the plant from 20 to 60 %, which gives the characteristic scent. The protective duration is variable from 40 to 90 min. Citronella at 10 % has been proved to repel flies but not mosquitoes.

Skin Toxicity

There are no scientifically trusted data on systemic toxicity due to absorption of essential oils. Citronella as with other essential oils is a mild irritant or rubefacient over 20 % concentration. Some reports indicate that essential oils are sensitizers and photosensitizers. Contact urticaria has also been reported.

Pyrethrum

Pyrethrum is derived from *Chrysanthemum cinerariaefolium* and the terms pyrethrum powder and extract are used to describe the crude products obtained from the crushed dried flowers. The pyrethrins are the active components. These substances are valid insecticides but weak insect repellents and thus no longer used in commercial repellents.

Permethrin

Permethrin, a pyrethroid synthesized in 1973, is mainly an insecticide four times as effective as natural pyrethrins. It also possesses some repellent activity, and for this reason it is included in many textbooks among insect repellents. Permethrin is considered a valid tick repellent. Systemic and skin toxicity of this compound is minimal. Permethrin should be applied directly to clothing or to tent and mosquito net fabrics. Permethrin is nonstaining, odourless and resistant to degradation by heat or sun and maintains its potency for at least 2 weeks.

The best barrier against biting insects is considered the combination of permethrin-treated clothing and skin application of DEET.

Indications for Safe Use of Insect Repellents

The insect repellents marketed in Europe possess a high level of safety due to especially low concentrations of the active ingredient. However, to increase the safety profile, dermatologists should suggest to their patients the following guidelines:

- Verify that the product has been registered.
- Read the label information.
- Use the repellent only as suggested by the manufacturer.
- Use the repellent only for the insects it claims to be effective against.
- Keep repellents out of the reach of children.
- Apply repellents only to body parts suggested by the manufacturer.
- Avoid use of repellents on or near wounds or on inflamed skin.
- Avoid use around the eyes and mouth.
- Wash repellent off skin with soapy water when protection is no longer needed.
- Contact the local poison control centre if repellent-induced toxicity is suspected.

Insect repellents are useful compounds to avoid the annoyance of many insects or to prevent the transmission of some infectious diseases. In Table 144.2 insect repellent sensitivity and infectious diseases transmitted by principal arthropods are summarized. However, the insect repellents are far from being the ideal product from a pharmacological point of view. The correct use of these products is fundamental to their safety (see Table 144.2).

Table 144.2 Insect repellent sensitivity and infectious diseases of principal arthropods

Class	Common names	Species	Blood sucking	Repellent sensitivity	Vectors for
Acars	Ticks	*Ixodes*	+	+	Borrelia, rickettsiae, arbovirus
	Trombidium larvae	*Trombidium*	+	+	Rickettsiae
Insects	Lice	*Pediculus*	+	+	Rickettsiae, borrelia
	Human fleas	*Pulex*	+	+	Yersinia, rickettsiae
	Bedbugs	*Cimex*	+	–	Nothing
	Deerflies	*Chrysops*	+	+	Filaria
	Tsetse flies	*Gliossina*	+	+	*Trypanosoma*
	Houseflies	*Musca*	–	+	
	Black or buffalo flies	*Simulium*	+	+	*Onchocerca*
	Biting midges or sandflies	*Phlebotomus*	+	+	Leishmania
	Mosquitoes	*Anopheles*	+	+	*Plasmodia*
		Aedes	+	+	Arbovirus, yellow fever virus
		Culex	+	+	Arbovirus
		Mansonia	+	+	Filaria
	Ants	*Formica*	–	+	Nothing
	Bees	*Apis*	–	–	Nothing
	Wasps and hornets	*Vespula*	–	–	Nothing
		Vespa	–	–	Nothing

Relief from Arthropod Bites

Skin responses to arthropod bites range from wheal-and-flare reactions to delayed papules to rare systemic Arthus reactions and anaphylaxis. Several strategies may be considered for the relief of the itch of insect bites. Topical corticosteroids may reduce erythema, induration and itching, but the time of effectiveness after skin application is considered too long (about 20 min) for relief of wheal-and-flare reaction that usually lasts 20 min.

Diphenhydramine and benzocaine should be avoided due to allergic contact sensitivity. Oral antihistamines are effective in reducing the symptoms of insect bites, but they are poorly employed due to the delay in reducing symptoms.

Ammonium solution 3.6 % is used after bite treatment to relieve symptoms, but caution should be adopted due to causticity of the product.

Aluminium chloride hexahydrate hydroalcoholic gel 5 % (see Chap. 152) is effective in suppressing itching and burning and possesses a good safety profile.

Aluminium chloride 5 % gel is at the same time astringent and antiseptic.

Controversies in Insect Repellents

Risk Assessment

One of the main problems in the use of insect repellent is the risk of toxicity via transcutaneous absorption. Regarding this topic, toxicological studies have been performed only for the DEET molecule, while for the other insect repellents, present studies about absorption must be considered insufficient. For this reason we can say prudentially that insect repellents are not suitable for their use in children, although they are the main victims of insect bites.

Application on Clothes

Efficacy studies of insect repellents are performed on forearm bare skin placed in cages containing insects; on the other hand there are no conclusive studies on the application of the same insect repellent on clothes in the same conditions and the relationship between application on clothes and its effectiveness.

Long-Lasting Protection

Some studies have related the long-lasting protection with the repellent concentration as Fradin and Mittal. This relationship, however, is not supported by conclusive studies. Moreover no studies can confirm a night-lasting protection.

For the above considerations, we believe that the use of insect repellents is to be reserved to adults who, for professional or recreational activities, are at risk of contracting diseases transmitted by insect bites. Other forms of protection (e.g. the mosquito net) are recommended in common situations and for children.

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Phytotherapeutic Approaches

145

Corrado Giua Marassi and Annalisa Rossi

Key Points

- Ever since, a large number of plants are used for their therapeutic properties within the healthcare.
- The set of substances that have physiological action and with determined pharmacological effect is defined as phytocomplex.
- Natural remedies and herbal preparations, such as tea tree oil, borage oil and aloe vera gel, are found to be useful in the treatment of dermatologic disorders; these products can be administered orally, externally or by inhalation and can be used alone or in combination with classical dermatological preparations.

Phytotherapy: From Tradition to Evidence-Based Medicine

Ever since, a large number of plants are used for their therapeutic properties. The use in all cultures throughout history of these compounds has been one of the first concrete forms of healthcare known to humanity.

Over the years we have witnessed a change in the usage of medicinal plants handed down from ancient uses to named extracts of active ingredients supported by scientific evidences.

In order to be considered effective, any remedy, medicinal plant or traditional therapeutic practice should fulfil the basic requirements of being safe and effective and it should be determined whether they have any therapeutic effect.

Phytotherapy (from the Greek *python* or plant and *therapeia* or cure) is a discipline that involves the use of medicinal plants and their derivatives for the prevention and treatment of diseases, with regard to the pharmacological properties of the chemical constituents present in the plant. As a matter of fact, products can offer efficacy, safety and repeatability of results only through the use of selected and calibrated extracts in active molecules. We would like to stress out that phytotherapy does not follow particular philosophies or religious beliefs as well as diagnostic or therapeutic methods other than those of scientific medicine.

Phytotherapy uses vegetable drugs from the plant that has therapeutic or preventive activities taking advantage of their active ingredients. Vegetable drugs can present different types of active compounds that may perform several functions and others that modulate the effect. The set of substances that have physiological action and with determined pharmacological effect is defined as phytocomplex.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_145, © Springer-Verlag Berlin Heidelberg 2015

The phytocomplex distinguishes the herbal compound from the synthetic drug, providing a multiplicity of pharmacological actions and lower toxicity. The phytocomplex has two main advantages compared to synthetic drugs: a pharmacological activity obtained through the interaction of different receptors with a lower risk of adverse events and a better tolerability. This means that a phytocomplex can be used alone or in combination with other phytocomplexes to treat different diseases and can be extracted from one or more vegetable drugs. The phytocomplex represents the core of the clinical phytotherapy.

Modern methods of extraction and analysis of medicinal plants are effective in advancing the development of traditional herbal remedies allowing to obtain a formulation that has an accurate and standard quantity of constituents with a real therapeutic value. One of the most important prerequisites for the production of a quality preparation is a well-defined and constant composition of the drug.

The processes of standardisation include a physical, chemical and biological evaluation to ensure herbal quality. Moreover preclinical and clinical studies confirmed, explained and clarified many pharmacological properties often acquired in a non-scientific way or, on the other hand, to show an incorrect use, highlighting the risks and adverse effects of herbal products.

One of the most representative examples is the study conducted on St. John's wort (*Hypericum perforatum*), the only herbal alternative to classic synthetic antidepressants in the therapy of mild to moderate depression, which has been considered a placebo for a long time. Similarly, a meta-analysis conducted on extracts of peppermint oil (*Oleum menthae piperitae*), garlic (*Allium sativum*) and *Serenoa repens* (saw palmetto) confirmed the pharmacological properties of these herbal products.

Thanks to a more rigorous scientific approach in the use of herbal plants, phytotherapy has become a medical discipline that evaluates the biological properties of vegetable drugs. But always bear in mind that although it is generally believed that most herbal preparations are safe, some herbs like most biologically active substances could be toxic with undesirable side effects.

Some herbal remedies are used in combination with synthetic drugs for the treatment of diseases like menopausal syndrome, sleep disorders, benign prostatic hyperplasia and many others. In any case the prescribing doctor will recommend the right therapeutic regimen according to the patient's pathology and its clinical history.

Phytotherapy in Dermatology

Natural remedies and herbal preparations are found to be useful in the treatment of dermatologic disorders; these products can be administered orally, externally or by inhalation and can be used alone or in combination with classical dermatological preparations. Obviously, the most serious skin conditions cannot be treated with herbal preparations while others may find a benefit from a correct phytotherapeutic approach. Learning all the information regarding the safety of each herb is very important for physicians because this will enable them to decide which herbal therapies they may want to use in practice. In this brief report, we would like to introduce some herbal medications that show clinical efficacy and that are used for the treatment of the most common dermatologic disorders.

Tea Tree Oil

The tea tree oil (TTO) is a volatile essential oil, extracted from the leaves and branches of *Melaleuca alternifolia*, a small tree indigenous to Australia. The primary uses of tea tree oil have historically capitalised on the antiseptic and anti-inflammatory actions of the oil. This oil contains about 100 chemical compounds, mainly terpene hydrocarbons, monoterpenes, sesquiterpenes and their corresponding alcohols. The use of tea tree oil is mainly topical and is indicated for the treatment of different dermatological problems.

Tinea Pedis

In a double-blind, placebo-controlled trial (Satchell et al. 2002a, b), 158 patients with tinea pedis were randomised to receive either placebo (20 % ethanol, 80 % polyethylene glycol) or 25 % or 50 % tea

tree oil mixed in ethanol and polyethylene glycol solution and were instructed to apply the solution to the affected areas twice daily for 4 weeks.

The results obtained showed that the two tea tree oil solutions (both 25 and 50 %) were found to be significantly more effective than placebo at eradicating the infection and that 25 % tea tree oil is associated with fewer complications than 50 % tea tree oil solution.

Few people developed dermatitis in response to the tea tree oil and had to drop out of the study, but most people did not experience any significant side effects.

Another double-blind, placebo-controlled trial (Tong et al. 1992) followed 104 people with athlete's foot who were given either a 10 % tea tree oil cream, the standard drug tolnaftate or placebo. The results showed that tea tree oil reduced the symptoms of athlete's foot more effectively than placebo but less effectively than tolnaftate. Neither treatment cured the infection in 100 % of the cases, but each treatment cured many cases. Other recent studies have demonstrated significant advances in the treatment of tinea pedis with TTO.

Dandruff

One placebo-controlled study has examined 126 people with mild to moderate dandruff. Patients were treated daily for 4 weeks with placebo or with a shampoo containing 5 % tea tree oil. The use of the shampoo has significantly reduced the symptoms of dandruff.

The dandruff was scored on a quadrant-area-severity scale and by patient self-assessment scores of scaliness, itchiness and greasiness. The 5 % tea tree oil shampoo group showed a 41 % improvement in the quadrant-area-severity score compared with 11 % in the placebo group ($P<0.001$). Unfortunately, this study (Satchell et al. 2002b) was not double blind, and for this reason, the results cannot be taken as completely reliable.

Head Lice

Head lice represent a very common problem, affecting millions of people each year, especially preschool and elementary school-aged children. Usually therapy is initiated with products that contain permethrin (1 %) or pyrethrins plus piperonyl butoxide when resistance to these products is not suspected. Plant-based compounds have been taken into account for their activity against both insects and their eggs and could represent an interesting approach to limit the emergence and the spread of the parasitic infestation.

The TTO activity against these insects has been evaluated in a randomised, assessor-blind, comparative, parallel study of 123 children with live head lice.

Children were divided into three groups: the first used a product containing tea tree oil and lavender oil 1 % (TTO/LO), the second a product that caused lice asphyxiation and the last one a product containing pyrethrins and piperonyl butoxide (P/PB); these products were applied two or three times at weekly intervals according to manufacturer instructions. The results showed that TTO/LO product and head lice "suffocation" products were both >97 % effective and were almost four times as effective as the P/PB product.

Acne

One of the first clinical trials of TTO evaluated the efficacy and skin tolerance of 5 % tea tree oil gel in the treatment of mild to moderate acne when compared with 5 % benzoyl peroxide lotion. Both treatments had reduced the number of comedones, although the onset of action in the case of tea tree oil was slower, but encouragingly, fewer side effects were experienced by patients treated with tea tree oil.

A randomised double-blind study (Enshaieh et al. 2007) has examined 60 patients with mild to moderate symptoms of acne. In this study, the participants were divided into two groups and treated with placebo or with 5 % tea tree oil gel. During the period of the study (45 days), the researchers assessed the seriousness of acne in two ways: by counting the total number of acne lesions and by looking at the acne severity on a standardised index (ASI). The results showed that the tea tree oil gel was significantly more

effective than placebo in reducing both, the number of acne lesions and even their gravity. This effect was possibly due to the anti-inflammatory and antibacterial effects of the tea tree oil.

Moreover the low and minimal side effects of this treatment render it as a suitable treatment option for mild to moderate acne vulgaris.

Other Pharmacological Properties

Tea tree oil has antimicrobial and anti-inflammatory properties, but there is still a lack of clinical evidence demonstrating efficacy against bacterial, fungal or viral infections. Some studies have demonstrated that tea tree preparations were effective, safe and well tolerated and could be considered in regimens for eradication of MRSA (methicillin-resistant *Staphylococcus aureus*) carriage (Flaxman and Griffiths 2005).

Borage Seed Oil

Borage oil is a light yellow liquid extracted from the seeds of *Borago officinalis*. Purified borage oil is rich in polyunsaturated fatty acids (PUFAs) like a minimum of 23 % γ-linolenic acid (GLA), known to be essential for normal skin function. Borage seed oil is used both as skin treatment and a dietary supplement, especially to fortify infant foodstuffs with essential fatty acid.

Chronic Dermatitis and Atopic Eczema

The GLA is necessary for proper growth and development of the epidermis. It is also required for synthesis of the important long-chain ceramides necessary to protect against dry skin and has anti-inflammatory effects. This oil finds many applications in dermatology, especially when there is alteration of the epidermal barrier and reduced water content in the epidermis like atopic dermatitis, seborrheic dermatitis, contact dermatitis, psoriasis, hives, etc.

Some clinical studies have shown that γ-linolenic acid contained in borage oil is effective against seborrheic and atopic dermatitis, in children.

Aloe Vera Gel

Aloe vera gel is the colourless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of *Aloe vera* (L) Burm. The main chemical components of aloe gel are water and polysaccharides (pectin, hemicellulose, glucomannan, acemannan and mannose derivatives). It also contains amino acids, lipids, sterols, tannins and enzymes.

Aloe vera gel is widely used for the external treatment of minor wounds and inflammatory skin disorders. Aloe gel is also indicated as a topical herbal remedy in dermatology. It is used for treatments of small wounds, irritations, first and second degree burns and abrasions.

Fresh aloe gel has been used for the treatment of radiation ulcers. Burns treated with the aloe vera gel healed faster (11.8 days) than the burns treated with petroleum jelly gauze (18.2 days).

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Prodrugs

146

Andy Goren, John McCoy, and Torello M. Lotti

Key Points

- Prodrugs are a class of inactive drugs that require a physical or chemical transformation in order to provide a therapeutic benefit.
- Prodrugs may render certain compounds safer or more effective.
- Endogenously activated prodrugs present novel opportunities for the development of predictive response testing.
- Exogenously activated prodrugs in dermatology can be activated by a wide spectrum of natural or artificial agents.
- Prodrugs should always be considered as a first-line therapy in complex and chronic dermatological diseases requiring systemic therapy.
- Side effects from the prodrug or the activator need to be considered carefully prior to starting a prodrug regimen.
- Prodrug development is one of the most promising fields in medical research due to the targeted delivery and lower systemic adverse events associated with prodrug regimens.

General Principles

Prodrug Definition

Prodrugs are a unique class of inactive or weakly active drugs that require a physical or chemical transformation in order to exert a therapeutic benefit.

History

The earliest documented use of a prodrug dates to the nineteenth century. A white crystallized powder, hexamine, demonstrated antibacterial activity against urinary tract infections. While initially believed to have direct antibacterial effect, careful examination determined that hexamine exerted its antibacterial activity after hydrolysis to formaldehyde in the acidic environment of urine. Similarly, the mechanisms of action of many drugs were shown to require activation by chemical or enzymatic processes. The twenty-first century experienced the largest expansion

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_146, © Springer-Verlag Berlin Heidelberg 2015

in the development of prodrugs, as directed drug design encountered the challenges of drug absorption, distribution, metabolism, and excretion toxicity (ADMET). In fact, it is estimated that approximately 10 % of all medicines can be classified as prodrugs and over 30 % of approved small molecule drugs are prodrugs.

Prodrug Design

Overcoming the challenges of ADMET is perhaps the most difficult problem encountered in drug design. Many candidate drug compounds exhibit promising safety and effectiveness in in vitro and in animal models but fail human studies largely due to pharmacokinetics, limited bioavailability at the site of therapy, and toxicity. Thus, during the early stages of drug development, prodrugs that can be activated on demand at a focal site of therapy by an endogenous or exogenous agent should always be considered as the preferred choice. Dermatological drugs present unique challenges and opportunities: while the skin allows for focal delivery, there remain the obstacles of barrier penetration, systemic side effects, and rapid metabolism. For this reason, dermatological prodrug design should take advantage of exogenous activation and skin permeability as well as the unique environment presented by the sebaceous glands and hair follicles.

Classification and Mechanisms of Action

There are several methods to classify prodrugs. Traditionally, prodrugs have been classified based on the location of their activation (e.g., intracellular vs. extracellular). Here, we suggest an alternative classification (Goren-McCoy-Lotti prodrug classification) for dermatological prodrugs. Due to the fact that cutaneous application provides for easy focal delivery, the classification of dermatological prodrugs is more appropriately based on whether the prodrug is activated by an endogenous (Class I) or exogenous (Class II) agent.

Class I. Endogenous Prodrug Activation

Endogenously activated prodrugs are converted to their active form by enzymatic catalysis or chemical degradation. The human hair follicle serves as a good model to illustrate prodrug activation in dermatology. Minoxidil, an oral drug originally developed to treat hypertension, was found to elicit hair growth as a side effect. The Upjohn Corporation exploited this property and subsequently developed a topical prodrug for the treatment of androgenetic alopecia (AGA). The mechanism of action by which minoxidil promotes hair growth is not known, but it was discovered that sulfation of minoxidil to its bioactive form, minoxidil sulfate, is required to exert its therapeutic effect. Minoxidil sulfate cannot be readily administered, as it is unstable. An interesting corollary to the use of endogenously activated prodrugs is that pretreatment testing of the endogenous activator can serve as a treatment response predictor. In the case of minoxidil, the follicular activity of the sulfotransferase enzyme (SULT1A1) that is required to convert minoxidil to its bioactive form, minoxidil sulfate, serves as a biomarker for treatment response.

Predicting minoxidil treatment response for androgenetic alopecia is an important clinical tool due to the long treatment duration (a minimum of 6 months) and low therapeutic efficacy (approximately 30–40 % of patients regrow hair) of the drug. To demonstrate the clinical utility and validity of such a prodrug response biomarker, a colorimetric enzymatic assay for SULT1A1 in plucked hair follicles was developed (Frame et al. 2000). The assay couples minoxidil sulfation and the conversion of p-nitrophenyl sulfate to p-nitrophenol (Fig. 146.1). Each molecule of minoxidil that is sulfated results in the production of p-nitrophenol, which is optically visible at 405 nm (i.e., appears yellow). In a clinical study that was subsequently conducted, the assay demonstrated 95 % sensitivity and 73 % specificity in predicting minoxidil treatment response for AGA (Goren et al. 2014a, b). Thus, when considering the use of an endogenously activated prodrug, it is important to evaluate the bioavailability of the

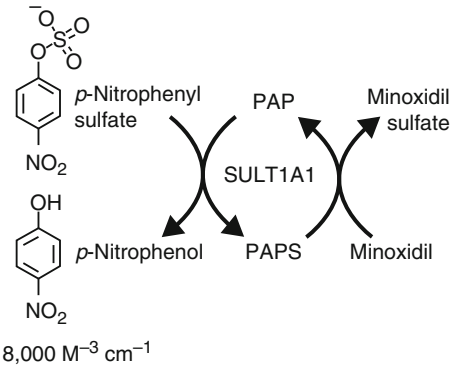

Fig. 146.1 Assay for predicting minoxidil response based on SULT1A1 enzymatic activity

activator and (if possible) administer a predicative response test.

Class II. Exogenous Prodrug Activation

The skin, being an external organ, presents a unique opportunity to combine topical or systemic prodrugs with a broad array of exogenous agents to deliver targeted therapy with minimal side effects. A further subclassification into artificial and naturally occurring prodrug activators is useful for determining applicability in dermatology practice. Artificial prodrug activators, such as artificial ultraviolet light therapy, require numerous visits to a light therapy clinic. The applicability of such a therapy may be limited by lack of equipment at the dermatological practice or poor patient compliance due to the demanding regimen (2–3 times a week for an average of 12 weeks). Naturally occurring prodrug activators, such as sunlight or resident bacterial flora, may provide an alternative to artificial activators when their use is feasible and results in improved patients' compliance.

Class II. a. Artificial Exogenous Activation

Artificial light and chemical agents are routinely used with prodrugs in dermatological practices. Some regimens require multiple sessions, such as psoralen plus ultraviolet A (PUVA), while others, such as photodynamic therapy (PDT), require a single session. PDT, a common treatment for actinic keratosis, basal cell carcinoma, Bowen's disease, and mycosis fungoides, is a prodrug-mediated therapy activated by artificial light. PDT is administered in two steps: (1) a photosensitive porphyrin-based prodrug is applied topically, orally, or interlesionally; (2) after sufficient absorption, the lesion is exposed to a suitable light source (typically blue light). The porphyrin, once excited with a specific wavelength of light, interacts with endogenous molecular oxygen to produce reactive singlet oxygen, which is cytotoxic to the targeted tissue and results in tissue destruction.

Class II. b. Natural Exogenous Activation

Natural exogenous activation of prodrugs holds the promise of higher patients' compliance in chronic disease management. Sunlight provides one such example as it is abundant. The sun at sea level provides minimal ultraviolet phototherapy benefit due to the development of erythema prior to achieving therapeutic dosage. The sun produces a wide spectrum of UVB and UVA radiation. Natural UVB radiation below 300 nm is harmful radiation leading to erythema with no therapeutic benefit. An optimal psoriasis action spectrum was determined to be radiation between 300 and 320 nm in the ultraviolet B (UVB) spectrum. A novel prodrug, Photocil (US FDA), recently introduced by Applied Biology, Inc., acts as selective filter for natural sunlight (McCoy et al. 2014). When applied to psoriasis lesions, Photocil attenuates a large percent of the sun's radiation below 300 nm and above 320 nm while allowing therapeutically beneficial radiation to reach the lesion. Several clinical studies have demonstrated that Photocil and other natural means (such as locals below sea level) of attenuating sunlight radiation below 300 nm clear psoriatic skin lesions on par with artificial light sources (Goren et al. 2014a, b; Harari et al. 2007). Since compliance is a major obstacle in artificial UVB

light therapy due to the numerous visits required to a specialized photo clinic, the sun as a natural exogenous activator of the prodrug Photocil can significantly improve patients' compliance.

Perhaps the most promising area of research in prodrug development is the use of microorganisms for exogenous prodrug activation. The recent breakthroughs unraveling the vast human microbiome and virome open the door to potential therapeutic applications utilizing these organisms. Among many projects utilizing symbiotic microorganism for prodrug activation, Goren and McCoy (subject of multiple US PTO patents) are currently exploring the use of microbial species residing in the hair follicle to sulfate minoxidil in patients deficient in SULT1A1. The future will undoubtedly bring many novel approaches to exploiting our symbiotic residents.

Indications and Other Uses

Prodrugs should always be considered as a first-line therapy in complex and chronic dermatological diseases requiring systemic therapy. The delivery, toxicity, and pharmacokinetics of traditional systemic drugs pose safety and efficacy concerns in long-term therapy often leading to lower compliance, lower response, and lower patient satisfaction.

While a prodrug regimen may address the delivery, toxicity, and pharmacokinetics issues associated with traditional drugs, the majority of prodrugs in dermatology require a more complicated treatment regimen. Typically, two steps are required: application of the prodrug followed by the activator agent. As such, it is important to assess the possibility of reduced compliance and hence ineffectiveness of the prodrug therapy. Each patient's lifestyle must be weighed carefully prior to selecting a treatment regimen. Keep in mind that in some cases of Class II. b. activators, such as natural light therapy with the novel prodrug Photocil, the more complicated prodrug regimen may yield higher compliance due to the convenience of at-home therapy.

Side Effects

Side effects of prodrugs regimens require careful evaluation of the patient to exclude contraindications related to (1) the inactive prodrug, (2) the activator, and (3) the activated prodrug. An activator, such as Class II. a. or Class II. b light therapy, may elicit an adverse event in patients prone to polymorphic light eruptions or those who have previously experienced an HSV outbreak. Keep in mind that the activated prodrug may elicit an adverse event as well. One example is the case when an endogenous enzyme that is deficient is required for the degradation of the activated prodrug.

Prodrug Regulation

When prescribing prodrugs, it is important to note that prodrugs are legally treated as drugs. Hence, the same limitations of off-label prescription and reimbursement should be taken into consideration. In addition, the activation mechanism of externally activated prodrugs may also be regulated as a drug or medical device in case of Class II. a. activators.

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Retinoids

147

Jean-Hilaire Saurat and Olivier Sorg

Key Points

Retinoids are analogues of vitamin A:

- They exert multiple effects on cellular differentiation and proliferation, the skin, the immune system, embryonic development, and several other organs.
- They regulate gene transcription via nuclear receptors – retinoic acid receptors (RARs) and retinoid X receptors (RXRs).
- Topical retinoids are used to treat photoaging, moderate acne, and a number of other conditions; the limiting factor is skin irritation, but teratogenicity risk is very low to nonexistent.
- Systemic retinoids are used only orally:
  - Oral isotretinoin is still the single most effective drug for severe acne; other retinoids do not have such effects.
  - Other retinoids are used orally in many disorders of cornification (isotretinoin, acitretin) and in psoriasis, especially pustular forms (acitretin), pityriasis rubra pilaris (acitretin), cutaneous T-cell lymphoma (acitretin, bexarotene), and chronic hand eczema (alitretinoin).
  - Teratogenicity is the most important systemic toxicity.

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General Principles

Vitamin A (retinol) and related compounds with either structural (retinol derivative) or functional (vitamin A activity) analogy are known as retinoids (Sorg et al. 2006).

Natural Retinoids (Fig. 147.1)

They include retin*o*l, retinaldehyde (retin*a*l), and all the metabolites resulting from normal metabolism in humans. All-*trans*-retinoic acid (tretinoin, a*t*-RA) is the natural ligand of the nuclear receptors RARs. 13-*cis*-retinoic acid, a *cis*/*trans* isomer (isotretinoin, 13-*cis*-RA), is a naturally occurring metabolite retinoic acid. 9-*cis*-retinoic acid is another isomer of retinoic acid (alitretinoin, 9-*cis*-RA) and a ligand of RXR, thus also a natural metabolite of a*t*-RA.

Synthetic Retinoids (Fig. 147.1)

Looking for retinoids with better therapeutic focused activity, synthetic molecules with "vitamin A activity" were developed: etretinate, acitretin, adapalene, tazarotene, and bexarotene already reached the market. Historically, therapeutic retinoids were classified as first (tretinoin, isotretinoin), second (alitretinoin, acitretin, etretinate), and third generation (adapalene, tazarotene, bexarotene) (Orfanos et al. 1997).

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_147, © Springer-Verlag Berlin Heidelberg 2015

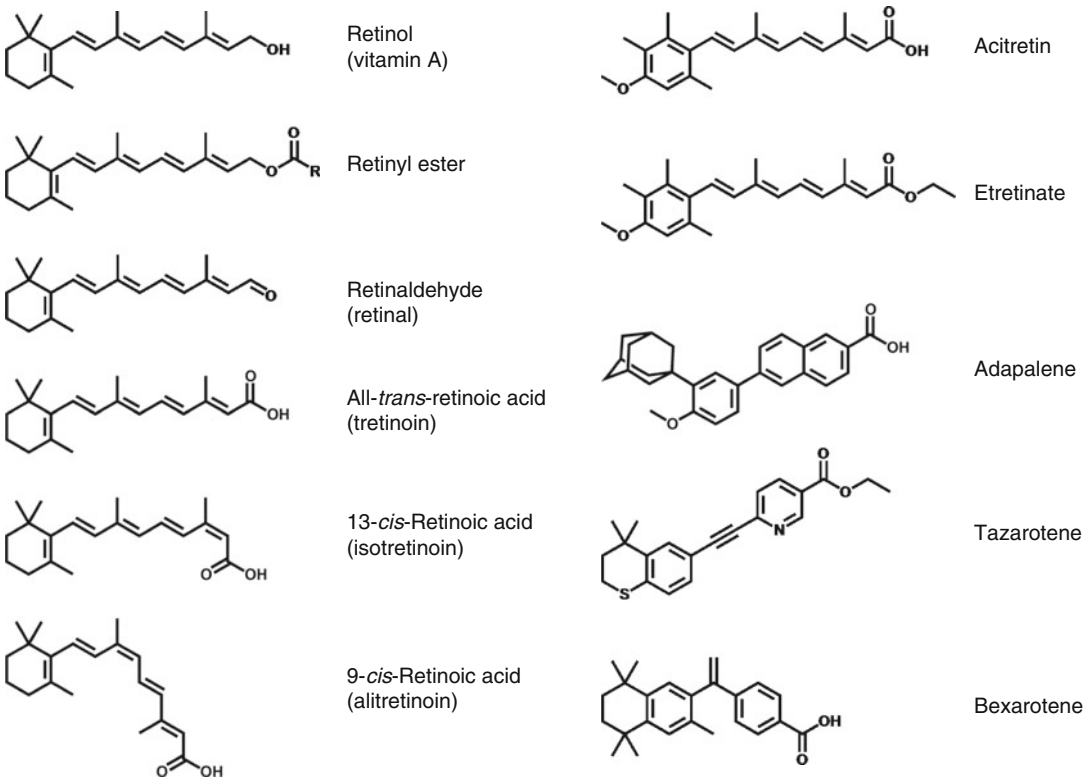

Fig. 147.1 Molecular structure of retinoids

Mechanisms of Action

Retinoids are involved in the regulation of diverse biologic functions. They affect cellular growth, differentiation, and morphogenesis; inhibit tumor promotion and malignant cell growth; exert immunomodulatory actions; and alter cellular cohesiveness.

Vitamin A Metabolism

Vitamin A is ingested as retinyl esters and as provitamin A carotenoids such as beta-carotene. Within the intestinal lumen, retinyl esters are hydrolyzed to retinol, which is then absorbed and stored in the liver in the ester form (especially retinol palmitate; Fig. 147.2). In the blood retinol is bound to a complex of retinol-binding protein (RBP) and transthyretin and delivered to organs including the skin (Blomhoff and Blomhoff 2006) (Table 147.1 and Fig. 147.3).

The biologically active ligands are thought to be generated within the target cell, a process designated as an "intracrine" system. In a reversible process, retinol (vitamin A alcohol) is oxidized to retinaldehyde (vitamin A aldehyde), which is then irreversibly converted to retinoic acid (vitamin A acid); subsequently, isomerization to 13-*cis* and 9-*cis* may occur. It is likely that, when given for therapeutic purpose, precursors such as retinol and retinaldehyde, which do not bind to receptors, exert part of their effects because they are transformed into retinoic acid within the target cell (Saurat et al. 1994).

Retinoid Receptors

Retinoids modulate DNA transcription through the binding to two distinct families of nuclear receptors: RAR (retinoic acid receptors) and RXR (retinoid X receptors). RAR and RXR belong to a superfamily of nuclear receptors that

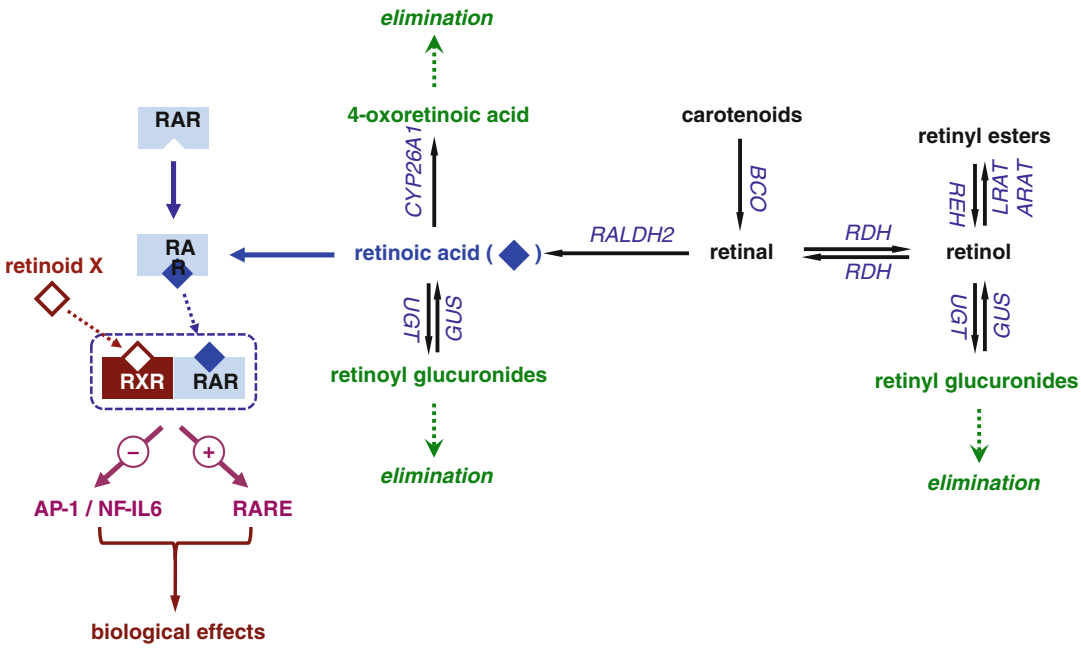

Fig. 147.2 Biology and metabolism of retinoids. Carotenoids, retinol, and retinyl esters come from the diet. In mucosal cells of the small intestine, retinyl esters are hydrolyzed to retinol, and some carotenoids may be converted to retinal. There is a reversible conversion between retinyl esters, retinol, and retinal, whereas retinal is oxidized irreversibly to retinoic acid, which binds to the nuclear receptors RAR. An unidentified retinoid X then binds to the RXR receptors, and the RAR/RXR heterocomplex binds to retinoic acid-response elements (RARE) in the promoter region of various genes, which induces their expression. On the other hand, the RAR/RXR complex inhibits the transcription factors AP-1 and NF-IL6

Table 147.1 Endogenous retinoid concentrations in the blood and the skin

	Retinoic acid	Retinaldehyde	Retinol	Retinyl esters
Blood	10	<5	2,500	400
Dermis	<5	<5	700	600
Epidermis	<5	<5	200	1,200

Values in (pmol/g ww)

act as ligand-activated transcription factors. The RAR receptor family contains three receptor isotypes (α, β, and γ) encoded by different genes. a*t*-RA binds only to RAR, whereas 9-*cis*-RA binds both to RAR and RXR. RAR functions as a heterodimer with RXR, whereas RXR may act as a homodimer or participate in the formation of heterodimers with a variety of other nuclear receptors, including vitamin D3, thyroid hormone, and peroxisome proliferator-activated receptors. Such heterodimers can provide a mechanism for cross talk between nuclear hormone signaling pathways.

Retinoid action is mediated via multiple pathways and results in the complex activation or inhibition of a large set of coordinately regulated genes. Retinoids can induce both direct and indirect effects on gene transcription as well as nongenomic effects (Dawson and Zhang 2002).

Classification

Natural Versus Synthetic

Natural retinoids are those that, besides their therapeutic or cosmeceutic use, are also constituents of the diet (e.g., retinol, retinaldehyde, and retinyl esters) and are transformed in the body into active molecules such as retinoic acid and its *cis*/*trans*

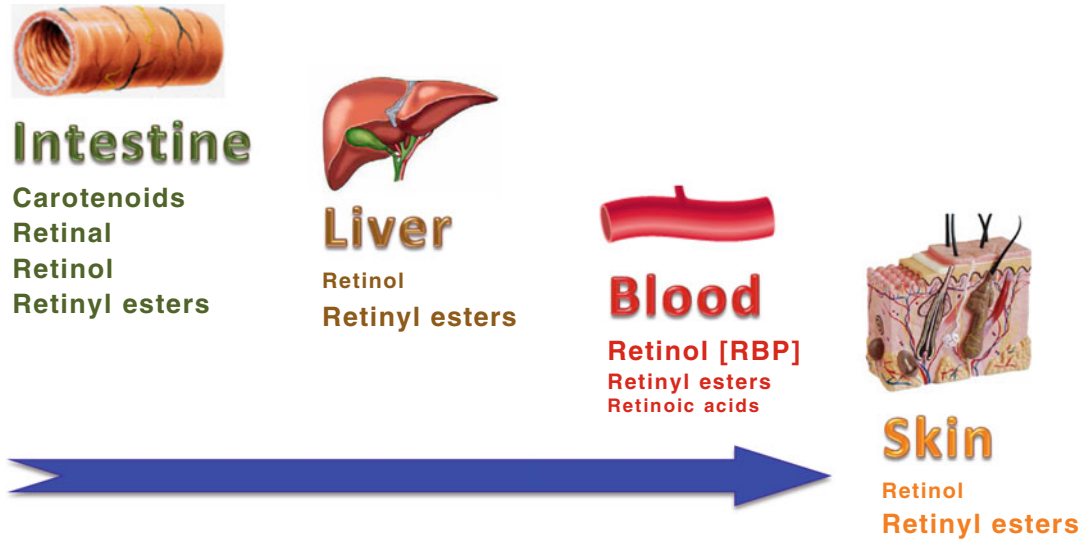

Fig. 147.3 Transport of retinoids in the body. Vitamin A precursors from the diet are converted to retinol and retinal in the small intestine and transported to the liver where there are stores mostly as retinyl esters. Endogenous retinoids circulate in the blood mostly as retinol bound to retinol-binding protein (RBP). In the skin, a part of retinol is esterified to fatty acids

isomers. These retinoids are thus inactive precursors of biologically active RAR/RXR agonists.

Synthetic *nonnatural* retinoids are analogues that have been synthetized for specific therapeutic purpose, with the aim of minimizing unwanted effects and optimalizing efficacy. This growing group includes etretinate, acitretin, adapalene, tazarotene, and bexarotene (Fig. 147.1).

Topical Versus Systemic

Retinoids can be given orally for the treatment of skin diseases that cover large surface areas and/or are not responsive to topical retinoid treatment. Four are currently available for oral use: isotretinoin, alitretinoin, acitretin, and bexarotene.

Eight are currently available for topical use: retinyl esters, retinol, retinaldehyde, tretinoin, isotretinoin, adapalene, tazarotene, and bexarotene.

Retinoids Currently Used in Humans as Drugs or Cosmeceutics

Natural retinoids and some retinoate esters are currently used in humans as drugs or cosmeceutics (Sorg et al. 2006).

Retinyl Esters

Retinyl esters are the main storage form of vitamin A in the body. The liver and the skin may esterify retinol to fatty acids and may release retinol from its esters. Retinyl esters also have the best tolerance profile among topical retinoids. For these reasons, many cosmetic products claim containing retinyl esters. The concentration is not always indicated. The claimed specificity of a given RE, based on the type constitutive fatty acid, is seldom based on sound scientific evidence.

Retinol

Topical retinol is more easily converted to retinoic acid and shows better antiaging activity than retinyl esters. It is usually available in Europe at the concentration of 0.1 % or more for the cosmeceutic treatment of skin aging. So far no controlled studies have compared its activity, which appears as inferior, to that of retinoic acid (Kang et al. 1995). It is likely that much higher concentrations should have a better activity profile; however, concentrations as high as 1 % may lead to side effects such as skin irritation without providing better antiaging activity. The best compromise between a good activity and minimal side effects seems to be 0.1 % (Bellemère et al. 2009).

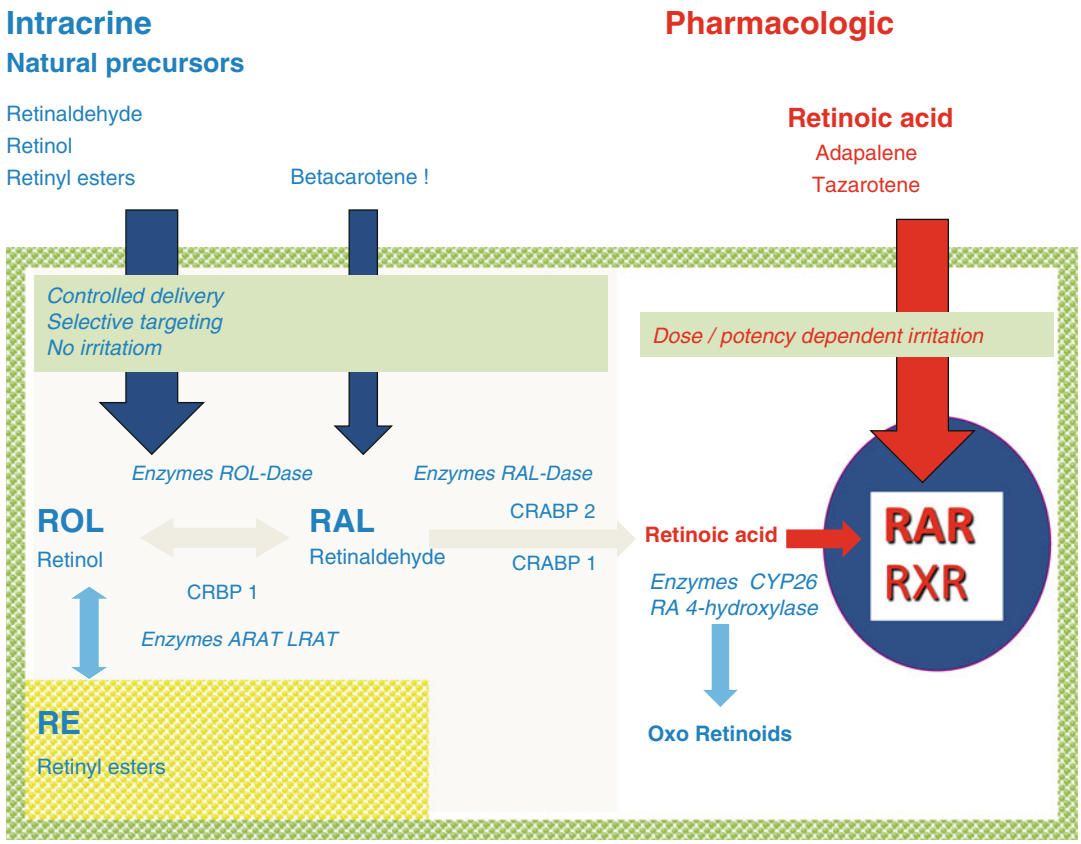

Fig. 147.4 Intracrine mechanism of endogenous retinoids. Retinoic acid precursors such as retinyl esters, retinol, and retinal are converted in the keratinocytes to retinoic acid, which exert its biological action via its binding to nuclear receptors, which are expressed in keratinocytes too

Retinaldehyde

Retinaldehyde, with retinol and retinyl esters, belongs to the natural retinoic acid precursors (Sorg and Saurat 2014). In the skin topical retinoids exert their biological activity via an intracrine mechanism: they are converted to the biologically active retinoic acids in keratinocytes, the cells that respond to retinoic acid activity by expressing RAR and RXR receptors (Fig. 147.4). Retinaldehyde requires only one step to be converted to retinoic acid, compared to retinol and retinyl esters, which required two and three steps, respectively (Fig. 147.2). In vivo animal and ex vivo human studies show that retinaldehyde is the natural retinoid with the best penetration profile through the skin (Antille et al. 2004; Tran et al. 2001), a property that makes topical retinaldehyde a good candidate to reverse UV-induced cutaneous vitamin A deficiency (Tran et al. 2001; Sorg et al. 2001, 2005). Its aldehyde functional group gives it a unique reactivity among retinoids; for instance, retinaldehyde exerts antibacterial activity against *P. acnes*, a property not shared with other retinoids (Péchère et al. 1999, 2002), which explains its use as adjuvant therapy of mild acne in association with glycolic acid (Kasraee et al. 2005; Tran et al. 2005). All these properties make retinaldehyde a good topical retinoid. Indeed, retinaldehyde was shown to exert retinoid biological activity in human skin in vivo (Saurat et al. 1994). It is available in concentrations between 0.015 and 0.1 %.

Retinaldehyde was demonstrated to be as effective as tretinoin in treating photodamage in less extensive trials but has a better tolerance profile (Creidi et al. 1998). It has been hypothesized that the reduction in side effects seen with retinaldehyde (compared with retinoic acid) may be

due to a more controlled delivery of retinoic acid to target cells via the "intracrine pathway" (Fig. 147.4), thus limiting an "overload" of retinoic acid in the skin, which may be responsible, in part, for producing the cutaneous irritation.

Based on CYP26 enzymatic activity, the biological activity of topical retinoids is as follows: Retinoic acid > retinaldehyde > retinol >> > retinyl esters. Their tolerance profile, however, is almost the reverse ranking order: retinyl esters > retinol = retinaldehyde > > retinoic acid.

Another use of topical retinaldehyde, based on its specific activity, is its high potential in inducing hyaluronate production by keratinocytes: this explains its use in association with defined hyaluronate fragments of intermediate size (HAFi) in dermatoporosis (i.e., chronic skin insufficiency; Kaya and Saurat 2007) and the prevention of topical steroid-induced skin atrophy (Kaya et al. 2006a, b)

Retinoic Acid

Topical retinoic acid has a long history of clinical and cosmeceutical use due to its high biological activity (Craven and Griffiths 1996; Kligman et al. 1986). It is available in the concentration of 0.025, 0.05, and 0.1 % for the treatment acne and photoaging (0.05 %). Other uses include a large number of skin conditions.

Acute promyelocytic leukemia, characterized by a chromosomal translocation involving the retinoic acid receptor alpha gene, is treated by oral retinoic acid in combination with an anthracycline chemotherapeutic agent (daunorubicin or idarubicin) or arsenic trioxide (Douer 2000).

Isotretinoin (13-*cis*-Retinoic Acid)

Isotretinoin is a naturally occurring physiologic compound resulting from the metabolism of vitamin A. 13-*cis*-RA and a*t*-RA are two interconvertible isomers that differ in their elimination half-lives: approximately 20 h for isotretinoin and 1 h for retinoic acid. Isotretinoin undergoes first-pass metabolism in the liver and subsequent enterohepatic recycling. In plasma, isotretinoin is greater than 99 % bound to plasma proteins, mainly albumin. There is neither liver storage nor adipose tissue storage, in sharp contrast to vitamin A. The major metabolite of isotretinoin (4-oxo-isotretinoin) is produced by oxidation. Isotretinoin and its major metabolites are excreted in the urine and feces.

After discontinuation of isotretinoin, natural concentrations of 13-*cis*-RA and its major metabolites are reached within 2 weeks, ranging from 2 days for a*t*-RA to 10 days for 4-oxo-isotretinoin. Therefore, 1 month of post-therapy contraception provides an adequate safety margin.

Among natural and synthetic retinoids, only oral isotretinoin significantly suppresses sebum production and considerably improves acne. Since no clear affinity with isotretinoin has been identified for any retinoid receptor, other mechanisms of action must be considered (Torma 2001). It may even be that isotretinoin is a prodrug that targets the sebaceous gland with sebosuppressive metabolites. Isotretinoin has a specific antiproliferative effect on human sebocytes due to cell cycle arrest and sebocyte apoptosis, which was not recapitulated by alitretinoin or tretinoin. Isotretinoin-induced apoptosis was shown to be an RAR-independent mechanism. Transcriptional profiling of patient skin and cultured human sebaceous gland cells indicated that lipocalin 2 was among the genes most highly upregulated by 13-*cis*-RA (Nelson et al. 2008).

Alitretinoin (9-*cis*-Retinoic Acid)

Alitretinoin is an endogenous pan-agonist retinoid that binds to both RAR and RXR retinoid receptors (Molin and Ruzicka 2008); likewise, it is considered as the natural endogenous ligand for RXRs. Topical alitretinoin gel (0.1 %) is indicated for cutaneous Kaposi's sarcoma, whereas systemic alitretinoin is a newly launched therapy for refractory chronic hand eczema (CHE) in adult patients. The absorption of alitretinoin from the gastrointestinal tract is variable and dose proportional over the therapeutic range from 10 to 30 mg. The absolute bioavailability of alitretinoin has not been determined. Alitretinoin is metabolized by oxidation by CYP3A4 isoenzymes of the liver into 4-oxo-alitretinoin. Both compounds undergo isomerization into all-t*rans*-retinoic acid and 4-oxo-all-*trans*-retinoic acid. The major metabolite 4-oxo-alitretinoin is further glucuronidated and eliminated in the urine.

Alitretinoin concentrations return to normal range within 1–3 days after treatment cessation and elimination is mainly in the urine. Elimination half-life of unchanged alitretinoin ranges between 2 and 10 h. The mechanism of action of alitretinoin in chronic hand eczema is unknown. Alitretinoin has demonstrated immunomodulatory and anti-inflammatory effects that are relevant to skin inflammation. Alitretinoin suppresses the expansion of cytokine-activated leukocyte subsets and antigen-presenting cells.

Acitretin

Acitretin is the major metabolite and the pharmacologically active compound of etretinate. Although acitretin and etretinate are equally effective, acitretin has a profound pharmacokinetic advantage because of its more rapid elimination compared with etretinate. The major serious adverse effect of synthetic retinoids is teratogenicity, and, therefore, the length of time that these drugs are present in the body is of great importance. Acitretin has an elimination half-life of 2 days. Paradoxically, acitretin activates all three RAR subtypes but binds poorly to them.

Re-esterification of acitretin to etretinate may occur when acitretin is taken simultaneously with alcohol. This finding prompted the manufacturer to extend the time of contraception in patients taking acitretin to 2 years after discontinuation, as it is for etretinate. The FDA advises a contraceptive period of at least 3 years for acitretin, based on the pharmacokinetics of acitretin and etretinate observed in clinical trials and on previous safety experience with etretinate. The pharmacokinetic advantage of acitretin over etretinate still holds true for all women who strictly avoid alcohol during treatment and for 2 months thereafter (Wiegand and Chou 1998).

The mechanism of action is still not clearly understood. Evidence supports a normalization of differentiation and proliferation as well as a modification of inflammatory responses and neutrophil function.

Adapalene

Adapalene is a light-stable, rigid, synthetic retinoid with higher affinity for RAR-β/RAR-γ than for RAR-α. Since RAR-β is not expressed in keratinocytes, RAR-γ is the primary retinoid target receptor for adapalene in the epidermis, provided the effects are receptor mediated.

Tazarotene

Tazarotene is a prodrug that is rapidly converted by skin esterases to its free carboxylic acid (tazarotenic acid), which is the active metabolite. It has a higher affinity for RAR-β/RAR-γ than for RAR-α and no affinity for RXR. Because of its rapid metabolism, systemic exposure is low. Tazarotenic acid upregulates tazarotene-inducible genes (TIG-1,2,3) and has antiproliferative properties.

Bexarotene

Bexarotene, a specific RXR-selective retinoid (rexinoid), was approved in 1999 in the USA for treatment of cutaneous T-cell lymphoma (CTCL) refractory to at least one systemic therapy. This compound is about 100-fold more potent at binding to RXR than to RAR. Bexarotene probably has a clearance profile similar to that of isotretinoin, with a terminal half-life between 7 and 9 h (Ethan-Quan and Wolverton 2001). The exact mechanism of action of bexarotene in CTCL is still unknown, but bexarotene probably acts through regulation of cellular differentiation and proliferation and induction of apoptosis. Clinical and biochemical central hypothyroidism frequently occur with bexarotene and is probably mediated through suppression of thyrotropin β-subunit (TSH-β) secretion by the thyrotrope cells of the anterior pituitary, which express RXR-γ.

Indications and Other Uses

Topical Retinoids

The most important element in topical therapy with retinoids is education of the patient. Local skin irritation can be expected with some but not all compositions, and noticeable beneficial effects may take weeks or months to appear. Administration of topical retinoids should be titrated depending on cutaneous irritant reactions, which may mean decreasing the concentration

or the frequency of application. It is generally wise to begin with the lowest strength formulation and then increase the concentration as tolerance builds. Another tactic is to start by applying a given concentration every other day. Daytime moisturizers with sunscreen are important components of any topical retinoid regimen. Of interest is the fact that irritation was initially considered, as a sine-qua-non condition for efficacy. Recent molecular and kinetic data indicate that retinoic acid-induced irritation is rather the mere indication of a toxic overload, whereas optimal gene regulation and therefore adequate response may be reached with either lower concentrations or ligands with controlled delivery to the receptors through the intracrine pathway (see Figs. 147.2 and 147.4).

Acne

Topical retinoids, of which tretinoin (a*t*-RA) is the prototype, are mainstays in the treatment of comedonal acne, even if their effect is slow and almost never reaches complete clearance. The primary mode of action is believed to be normalization of abnormal differentiation and proliferation of the follicular epithelium, which leads to the loosening and unseating of microcomedones. In addition, topical retinoids may have anti-inflammatory activity. The mechanism of action of topical isotretinoin is similar to that of topical tretinoin because of intraepithelial isomerization of isotretinoin to tretinoin. In contrast to oral isotretinoin, topical isotretinoin (as well as all topical retinoids) fails to suppress sebum production to the same extent. Isotretinoin is less irritating, but it is probably somewhat less effective than tretinoin. Because of the birth defects induced by the oral formulation, topical isotretinoin has not received FDA approval in the USA.

The newer synthetic derivatives, adapalene and tazarotene, are intended to improve tolerability while maintaining similar efficacy when compared to topical tretinoin. In company-sponsored studies of patients with acne, adapalene 0.1 % gel was as effective as tretinoin 0.025 % gel against open and closed comedones and more effective against inflammatory lesions and with less irritation (Cunliffe et al. 1997a). Tazarotene 0.05 and 0.1 % topical gels significantly decreased acne lesions compared with control patients, with tolerability clinically comparable to tretinoin.

Topical retinoids should be applied to the entire face, once a day (if tolerated) and in the evening to minimize inactivation by UV. The medication should be applied on dry skin to minimize dermal absorption correlating with skin irritation. Patients should be advised that the therapeutic response is slow, and beneficial effects do not become evident for weeks to months. An apparent exacerbation may occur during the first month of therapy, representing the externalization of deeper-seated acne lesions as the follicular epithelium is loosening. Topical retinoids, except in very mild acne, should be used concomitantly with antibiotics (oral or topical) or benzoyl peroxide, which have different modes of action and which target primarily inflammatory lesions

Psoriasis

Topical application of tretinoin or isotretinoin has limited efficacy in psoriasis. Tazarotene has been the first topical retinoid proven effective in treating mild to moderate plaque-type psoriasis not exceeding 10–20 % of the body surface area. When compared with twice-daily fluocinonide cream, tazarotene 0.05 and 0.1 % gels applied once daily were shown to produce similar reductions in plaque elevation. Nevertheless, tazarotene 0.1 % gel carries a significantly lower risk of relapse than does fluocinonide cream after 12 weeks off therapy (Lebwohl et al. 1998). A combination of tazarotene and a mid-potency corticosteroid improved efficacy and reduced the incidence of local adverse effects; this combination may also reduce the risk of corticosteroid-induced atrophy.

Photoaging

Photoaging is the consequence of UV-induced damage to the skin characterized by decreased expression of RXR-α and RAR-γ in the acute setting, by upregulation of AP1-driven matrix

metalloproteinases, as well as severe depletion of the vitamin A content of the epidermis (since retinoids are destroyed by the UV) (Wang et al. 1999). Topical retinoids promote cellular dedifferentiation and extracellular matrix synthesis, including an increase in hyaluronic acid via a CD44-mediated mechanism (Calikoglu et al. 2006). Histologic findings after repeated topical application of tretinoin include: compaction of the stratum corneum, epidermal hyperplasia (acanthosis), correction of atypia (e.g., actinic keratoses), dispersion of melanin granules, increased dermal collagen synthesis, and angiogenesis. These findings explain the reported smoother skin, rosy glow, decrease in blotchy pigmentation, and diminished fine lines and wrinkles.

Several controlled studies have clearly demonstrated that topical retinoids, particularly tretinoin and more recently tazarotene cream, improve fine wrinkling and lighten uneven pigmentation. It generally takes 3–6 months of daily applications to see significant clinical improvement. Cutaneous irritation is usually the limiting factor. It is not clear if the observed effects on parameters of skin aging with these retinoids are associated with a beneficial long-term effect. It has been reported that long-term use of retinoic acid for the prevention of actinic keratosis in fact resulted in a trend to increased incidence of actinic keratosis and squamous cell carcinoma. One hypothesis was that retinoic acid does not reverse the UV-induced vitamin A epidermal depletion due to the irreversible bioconversion of retinaldehyde to retinoic acid. This suggests that cosmeceutical retinoids such as retinaldehyde, which do restore epidermal vitamin A pool, warrant consideration (see section "Retinaldehyde").

Other Indications

Other approved indications include topical treatment of cutaneous Kaposi's sarcoma by alitretinoin (9-*cis*-RA) 0.1 % gel and topical treatment of CTCL by bexarotene (Breneman et al. 2002). Non-approved indications of topical retinoids are numerous.

Retinoids in Cosmeceutic Ranking and Issues

As mentioned in section "Retinaldehyde", the tolerance profile and the clinical efficacy are inversely correlated:

- Tolerance profile: retinyl esters > retinol = retinaldehyde > > retinoic acid
- Clinical efficacy: retinoic acid > retinaldehyde > retinol >> > retinyl esters

There is a need to determine the best dose of each retinoid, specifically natural retinoids such in consideration of the above.

Topical Retinoids and the Sun

Retinoids strongly absorb light in the UVA-UVB range (260–380 nm), which means that cutaneous retinoids are photosensitive. Indeed, in vitro and animal and human in vivo studies demonstrated a dose-dependent decrease of epidermal retinoids, leading to epidermal vitamin A deficiency (Sorg and Saurat 2014). Given that cutaneous vitamin A deficiency is a risk factor for skin cancer development (Fields et al. 2007), those topical retinoids that replenish endogenous levels of epidermal vitamin A might exert a preventive effect against sun-induced skin cancers (Carr et al. 2011).

The use of topical retinoids, which are photosensitive, raises the question of the possible phototoxic reactions. Although no photoallergic or phototoxic reactions have been proven for topical retinoids, many patients note a decreased tolerance to UV radiation shortly after sun exposure (Sachs and Voorhees 2011). This reaction is often accentuated by a sensation of heat, raising the question of involvement of infrared irradiation. For this reason, it is recommended to avoid sun exposure after the application of topical retinoids.

Systemic Retinoids

Psoriasis/Acitretin

Pustular Psoriasis

The efficacy of acitretin in plaque-type (Arechalde and Saurat 2000a) and pustular psoriasis has been established on several randomized

multicenter trials. The best results have been obtained in acral or generalized (von Zumbusch) pustular psoriasis, in which acitretin is considered to be first-line therapies. The lesions of both localized and generalized pustular psoriasis, as well as those of erythrodermic psoriasis, cleared more rapidly with etretinate or acitretin monotherapy than with most other therapies (White et al. 1985). Rebound does not usually occur after stopping treatment, and reintroduction produces a beneficial response.

Plaque-Type Psoriasis

Plaque-type psoriasis responds variably to acitretin. The decrease in the Psoriasis Area and Severity Index (PASI) score is approximately 60–70 %, depending on the dosage and duration of treatment. Many of the plaques may remain, but they are thinner with less scale and erythema. Approximately 20 % of patients may be considered treatment failures (Lowe 1991).

An initial worsening of the disease with an increase in erythema and/or extent of the involvement may occur within a few days of starting therapy at a dosage of 0.5–1 mg/kg/day (i.e., 30–70 mg/day in adults). A therapeutic dosage scheme utilizing a low-dosage (10 mg/day) acitretin initially, followed by progressively increasing the dosage, seems preferable. Different dosages (10–75 mg/day) were compared with placebo in a double-blind fashion. At the end of an 8-week treatment period in two studies, acitretin at doses of 25 and 50 mg/day (Lassus et al. 1987) or 50 and 75 mg/day (Goldfarb et al. 1988) was superior to placebo.

Total clearance of psoriatic lesions usually requires a combination of therapies, such as topical corticosteroids, topical vitamin D derivatives, anthralin (dithranol) or photochemotherapy (PUVA), bath PUVA, and NB-UVB phototherapy (Lebwohl 1999; Saurat et al. 1988).

Isotretinoin is less effective on psoriasis than acitretin although some efficacy has been shown in combination with PUVA (Saurat 1998). Nevertheless, isotretinoin is still used in women of childbearing age with psoriasis who need systemic retinoids to avoid the long post-acitretin contraception period.

Acne/Isotretinoin

Isotretinoin is still the only compound that has been shown to induce long-term remissions and even "cure" acne, because it is the only one that affects, albeit not to the same degree or permanently, all the etiologic factors implicated in acne: sebum production, comedogenesis, and colonization with *Propionibacterium acnes*.

Only oral isotretinoin, among all natural and synthetic retinoids tried in humans, was found to suppress sebum excretion and to significantly improve acne. The "sebo-specificity" of oral isotretinoin still remains unexplained in 2014.

In the early 1980s, isotretinoin use was restricted to patients suffering from severe nodulocystic acne. Its use has been extended to (i) patients with less severe disease who have responded unsatisfactorily to conventional therapies such as long-term antibiotics, (ii) patients with moderate acne that may induce scars, and (iii) patients with significant psychosocial consequences of acne in interpersonal and work-related difficulties. Studies with quality-of-life instruments have shown that isotretinoin treatment significantly improves sociability and self-esteem.

It was initially considered that optimal benefit would be achieved with a high daily dose of approximately 1 mg/kg/day (Layton et al. 1993). However, this high dose can induce undesirable effects, and similar short-term therapeutic results were obtained with doses below 0.5 mg/kg/day. In order to avoid the higher incidence of relapses associated with low-dose isotretinoin, the latter approach required that the treatment be maintained over a longer period of time in order to reach a critical cumulative dose threshold. The concept of cumulative dose (mg/kg body weight), introduced by Harms in 1989 (Harms et al. 1989), is the total amount of oral isotretinoin taken by the patient over the entire duration, divided by the body weight. A patient weighing 50 kg and receiving 25 mg/day of isotretinoin for 100 days would have received a cumulative dose of 50 mg/kg (25 mg × 100 = 2,500 mg, divided by 50 kg = 50 mg/kg). Data from several centers indicated that post-therapy relapse was minimized by a treatment course amounting to a total of at least 120 mg/kg (Lehucher-Ceyrac and

Weber-Buisset 1993), with no further therapeutic gain beyond about 150 mg/kg (Cunliffe et al. 1997b). Low dose (20 mg/daily) was also found to be effective in the treatment of moderate acne with a low incidence of severe side effects and at a lower cost than higher doses (Amichai et al. 2006).

A lag period of 1–3 months may exist before the onset of the therapeutic effect. Continued healing after the discontinuation of therapy is regularly observed. Approximately one-third of patients with acne require a second course of therapy, either for persistent disease or for relapse. The only predictive factor of resistance to isotretinoin treatment is closed comedonal acne and microcystic acne (Lehucher-Ceyrac et al. 1999).

A flare of disease during the first few weeks of treatment, and subsequent evolution of acne cysts into lesions resembling pyogenic granulomas, may be observed with isotretinoin treatment. The incidence of this side effect may be reduced by using lower doses of isotretinoin during the first 3–4 weeks of therapy.

Women of childbearing potential must have a (in the USA, two) negative pregnancy test(s) and practice effective contraception for 1 month prior to therapy, during therapy, and for 1 month after completing therapy. To afford a sufficient safety margin, a 1-month post-therapy contraceptive period is mandatory because plasma concentrations of isotretinoin return to physiologic levels within 10 days of completing therapy.

Isotretinoin has a more limited effect on hidradenitis suppurativa and dissecting cellulitis of the scalp. These disorders may occur together as part of the follicular occlusion tetrad. Some investigators recommend oral isotretinoin during the weeks or months preceding surgery for hidradenitis suppurativa and sometimes also during the postoperative period.

Cutaneous T-Cell Lymphoma/ Bexarotene

The FDA approved bexarotene as oral therapy for the treatment of CTCL that is refractory to at least one systemic therapy and as a gel formulation for cutaneous manifestations of early-stage refractory or persistent CTCL (Duvic et al. 2001a). Toxicity including hypothyroidism was a significant problem at the high oral doses. Response rates are approximately 50 % for the patients with advanced CTCL (Duvic et al. 2001b). Bexarotene combination therapies with PUVA/NB-UVB, IFN-α, denileukin diftitox, and methotrexate have also been evaluated by various clinical trials and case reports (Gniadecki et al. 2007).

Isotretinoin and acitretin are somewhat effective and are considered to be of equal potency in the treatment of mycosis fungoides (MF). They can be used in combination with PUVA, interferon, or systemic chemotherapy. Despite initial improvement of the various stages of MF, it is often impossible to maintain remissions with these retinoids as monotherapy.

Chronic Hand Eczema/Alitretinoin

A multicenter study of 6-month duration in adults with severe chronic hand eczema has shown responses to oral alitretinoin of this complex and difficult-to-define condition. Responses defined as “clear or almost clear hands” were seen in up to 47 % of patients treated with 30 mg, 27.5 % with 10 mg, and 16.6 % with placebo. Treatment was well tolerated, with dose-dependent adverse events including headache, mucocutaneous events, hyperlipidemia, and decreased free thyroxine and thyroid-stimulating hormone. The median time to relapse, defined as recurrence of 75 % of initial signs and symptoms, was 5.5–6.2 months in the absence of anti-eczema medication (Ruzicka et al. 2008).

Alitretinoin is indicated in adults who have severe chronic hand eczema that is unresponsive to potent topical corticosteroids (Ruzicka et al. 2008; Bollag and Ott 1999). Treatment should be initiated at 30 mg daily and duration should not exceed 12–24 weeks. Low dosage of 10 mg is indicated in patients experiencing adverse events at high dosage. High dosage induces a more rapid improvement and has a higher response rate. Clinical signs of improvement appear after only 4 weeks of treatment. Patients with a marked hyperkeratosis are best responders to treatment. Therapy should be interrupted in case of a nonresponse after 12 weeks. Eighty percent of the

patients who previously achieved "clear" or "almost clear" hands following treatment with alitretinoin 30 mg per day also respond to a second course of treatment, making intermittent therapy suitable for the long-term management of CHE.

A head-to-head comparison of alitretinoin (high-cost therapy) with acitretin (lower-cost therapy) would be interesting, since it is not unlikely that revisiting acitretin in this indication with an adequate RCT may help some patients.

Other "Off-Label" Clinical Uses

The pleomorphic effects of retinoids explain the broad potential benefit they could provide to patients with skin disease. Many other skin disorders respond to retinoids, but the benefit has been established in controlled studies for only a few of them (Arechalde and Saurat 2000b).

Ichthyosis/Acitretin

The best results can be obtained by using acitretin for non-bullous congenital ichthyosiform erythroderma and lamellar ichthyosis. Good results have also been observed in patients with recessive X-linked ichthyosis and ichthyosis vulgaris; however, the more limited severity of these diseases does not usually require systemic retinoid therapy. Given the lifelong duration of these disorders, intermittent courses are sometimes prescribed.

Darier's Disease/Acitretin

Severe forms of Darier's disease are often treated with systemic retinoids, but therapy should be initiated with a very low dose (e.g., acitretin 10 mg/day) in order to prevent an initial exacerbation of the disease; usually 20 mg/day is sufficient for significant improvement.

Pityriasis Rubra Pilaris/Acitretin

Early treatment with retinoids appears to offer the best chance for clearing pityriasis rubra pilaris (PRP). In extensive cases, concomitant use of methotrexate may be advantageous. Etretinate (now acitretin) has been considered to be superior to isotretinoin for the treatment of adult-onset PRP (Clayton et al. 1997).

Rosacea/Isotretinoin

In severe forms or treatment-resistant rosacea, isotretinoin often has a greater effect on inflammatory lesions than on vascular lesions (Erdogan et al. 1998). A low daily dose (10 mg) is often sufficient, although acne vulgaris regimens are sometimes used in severe disease.

Premalignant and Malignant Skin Lesions/Acitretin

Acitretin were both shown to be effective in the treatment of premalignant skin lesions, including HPV-induced tumors and actinic keratoses. In the nevoid basal cell carcinoma syndrome and in xeroderma pigmentosum, these drugs are able to dramatically reduce the incidence of malignant evolution of cutaneous lesions. A double-blind study demonstrated that acitretin (30 mg/day for 6 months) prevented the development of premalignant and malignant cutaneous neoplasms in renal transplant recipients (Bavinck et al. 1995).

Graft-Versus-Host Disease

In an open study, 3 months of etretinate therapy produced encouraging responses among patients with refractory sclerodermatous chronic GVHD resulting from allogeneic bone marrow transplantation (Marcellus et al. 1999).

Lichen Sclerosus

The use of acitretin is an effective treatment for patients with severe vulvar (and, occasionally, nongenital) lichen sclerosus. It may be used intermittently in patients who are intolerant of or resistant to topical therapies.

Lupus Erythematosus

Both isotretinoin and acitretin have been used successfully in patients with various forms of lupus erythematosus (LE). Recurrence of the lesions after completion of the treatment is a limiting factor. Comparable therapeutic efficacy has been observed for acitretin and hydroxychloroquine in chronic cutaneous LE and in subacute cutaneous LE (Ruzicka et al. 1992).

Side Effects

Topical Retinoids

By far the most common side effect of topical retinoids is skin irritation. This "retinoid dermatitis" occurs within the first month of treatment and tends to recede thereafter. It responds to a temporary reduction in the frequency or amount of retinoid application and to application of moisturizers. Desquamation and peeling correspond to the hyperproliferative response of the epidermis to tretinoin mediated by RARs, but the erythema does not seem to be receptor mediated (Kang et al. 1995). The perioral area of the face is most sensitive to peeling and use in this area can be limited or avoided.

Although no photoallergic or phototoxic reactions have been proven for topical retinoids (Sachs and Voorhees 2011), many patients note a decreased tolerance to UV radiation shortly after sun exposure. This reaction is often accentuated by a sensation of heat, raising the question of involvement of infrared irradiation.

Potential teratogenicity from long-term use of topical retinoids is very low: systemic absorption of topically applied retinoids is inconsequential in both animal and human studies (Jick 1998), and there is no evidence that application of tretinoin causes congenital disorders. Temporary worsening of acne may occur within the first weeks of therapy. Uncommon side effects include transitory hypo- or hyperpigmentation, koebnerization of psoriasis (especially tazarotene), allergic contact dermatitis, and ectropion.

Systemic Retinoids

Teratogenicity is the most troublesome adverse effect of oral retinoids. The side-effect profile of systemic retinoids qualitatively resembles the toxic effects of vitamin A or hypervitaminosis A syndrome.

Teratogenicity

Systemic retinoids are potent teratogens, and this is the major concern in treating fertile women with oral retinoids. With regard to teratogenicity, no safe minimal dose during pregnancy has been established. The range of defects seen in retinoid embryopathy includes multiple abnormalities (Lammer et al. 1985). The abnormalities may lead to premature birth, spontaneous abortion, or fetal death. The putative mechanism involves toxic effects on neural crest cells, particularly in the case of exposure during the fourth week of gestation.

No typical retinoid embryopathy malformations have been reported in pregnancies where the male partner had been the one taking acitretin or isotretinoin at the time of conception. However, it is usually recommended that men who are actively trying to father children avoid systemic retinoid therapy.

Skin and Mucous Membrane Adverse Effects

Dose-dependent mucocutaneous toxicity is the most commonly observed side effect with oral retinoids, and it mainly reflects a decreased production of sebum, reduced stratum corneum thickness, and altered skin barrier function. Dry lips or cheilitis is the earliest and the most frequent sign that appears after starting therapy. Dryness of the mouth accompanied by thirst and dryness and fragility of the nasal mucosa leading to epistaxis are also frequently observed.

Systemic retinoids do have different mucocutaneous side-effect profiles. Isotretinoin causes more mucosal dryness, and acitretin has been associated with higher incidences of alopecia and palmoplantar peeling, whereas bexarotene induces milder mucocutaneous and ocular side effects than do other classes of retinoids.

Dyslipidemia

Hypertriglyceridemia is the most frequently observed systemic effect of retinoid therapy. Isotretinoin and etretinate/acitretin elevate triglycerides in 50 % and cholesterol in 30 % of

treated patients (Koo et al. 1997; Pilkington and Brogden 1992; Tangrea et al. 1993), whereas bexarotene induces elevated triglycerides and cholesterol in approximately 79 and 48 % of patients, respectively (Duvic et al. 2001a).

Baseline serum lipids should be obtained before initiating bexarotene therapy, as well as every 1–2 weeks during therapy until levels become stable (generally in 4–8 weeks). For other oral retinoids, monitoring levels monthly for the first 2 months and then at 2- to 3-month intervals (if there are no increases in dosage) is adequate in cases of normal baseline lipid levels and an absence of risk factors (obesity, high alcohol intake, diabetes). Discontinuation of therapy is suggested if fasting triglycerides reach 800 mg/dl (8 g/l). Less severe increases may be treated by dose reduction, withdrawing therapy until normalization of serum lipids occurs, and dietary or physical management. In some instances, lipid-lowering agents may be indicated (Vahlquist et al. 1995). Coadministration of statins, including atorvastatin, in case of hypercholesterolemia, or fenofibrate for hypertriglyceridemia (or both) with bexarotene, is recommended to treat the retinoid-induced hyperlipidemia and to lower the risk of pancreatitis (Wiegand and Chou 1998; Talpur et al. 2002). Some authors even recommend to start in all patients a fibrate (ex fenofibrate) on day 7 before bexarotene treatment initiation (Gniadecki et al. 2007).

The effect of retinoid-induced hyperlipidemia, and its management during long-term therapy, on the development of atherosclerotic cardiovascular disease is unknown. Retinoids probably cause hyperlipidemia by interfering with lipid clearance. Bexarotene increases the expression of apolipoprotein C-III, which prevents the uptake of lipids from very-low-density lipoproteins (VLDL) into cells (Vu-Dac et al. 1998).

Liver Toxicity

Transitory abnormal elevations in serum transaminases have been reported in approximately 20 % of patients treated with either etretinate or acitretin, occurring much less frequently with isotretinoin or bexarotene therapy. Circulating levels of alkaline phosphatase, lactic dehydrogenase, and bilirubin may also become elevated during retinoid therapy. Liver function abnormalities, mostly mild, usually occur between 2 and 8 weeks of starting therapy, and they return to normal within another 2–4 weeks, despite continued therapy. Severe or persistent hepatotoxic reactions have been seen in less than 1 % of patients. Acitretin therapy elicited no biopsy-proven hepatotoxicity in a 2-year prospective study, thus suggesting that periodic liver biopsy is not necessary (Roenigk et al. 1999). No specific studies have evaluated the use of retinoids in patients with hepatic insufficiency. However, since retinoids are metabolized by hepatic cytochrome P450 isoenzymes (CYP3A4) and undergo partial biliary elimination, significant hepatic insufficiency may be expected to interfere with drug elimination. Transaminase elevations to greater than three times the upper limit of normal should lead to discontinuation of retinoid therapy. With two- to threefold transaminase elevations, therapy should be withdrawn until normalization of tests of liver function occurs (Wiegand and Chou 1998). Other causes should simultaneously be excluded.

Ophthalmologic Side Effects

The most common ocular retinoid effects are dryness and irritation. Alterations in visual function, mainly nyctalopia, excessive glare sensitivity, and changes in color perception, have also been reported (Safran et al. 1991). Competitive inhibition of ocular retinol dehydrogenase by retinoids, resulting in decreased rhodopsin formation, may be the cause of hemeralopia.

Central Nervous System and Psychiatric Effects

CNS side effects are rare. Although individual signs of increased intracranial pressure, such as headache, nausea, and vomiting, are occasionally observed, the complete syndrome with papilledema (pseudotumor cerebri) and blurred vision is considered very rare (Bonnetblanc et al. 1983). Concomitant use of other drugs associated with intracranial hypertension (e.g., cyclines) is considered a major risk factor for developing pseudotumor cerebri and should therefore be avoided

(Lee 1995). Examination for papilledema should be performed immediately when a patient receiving retinoid therapy complains of persistent headache, especially if it is accompanied by visual changes, nausea, or vomiting, or when pseudotumor cerebri is otherwise suspected.

There have been anecdotal reports suggesting a causal association between isotretinoin therapy in acne patients and severe depression, psychosis, and suicide attempts. That isotretinoin increases the risk of depression has actually not been proven (Bigby 2008). Patients with depressive symptoms or suicidal ideation should be carefully monitored and advised before treatment initiation (Bigby 2008).

Hypothyroidism

Clinical and biochemical central hypothyroidism occurred in 40 % of patients in the CTCL trials with bexarotene, and it was rapidly and completely reversible with cessation of therapy without any clinical sequelae (Duvic et al. 2001a; Sherman et al. 1999). This effect is probably mediated through suppression of thyrotropin β-subunit (TSH-β) secretion by the thyrotrope cells of the anterior pituitary, which express RXR-γ. Free T4 levels should therefore be monitored before and during bexarotene therapy and normalized with thyroid hormone replacement as necessary. Some authors recommend an initial dose of levothyroxine 0.05 mg daily, increased to 0.1–0.125 mg daily, depending on the bexarotene dose and the free T4 level which should be normal (Gniadecki et al. 2007).

Gastrointestinal Side Effects

Uncommon nonspecific gastrointestinal complaints have been reported in association with retinoid therapy. Synthetic retinoids have been temporally linked with other toxicities, such as inflammatory bowel disease; however, no cause-and-effect relationship has been established.

Bone Toxicity

Several reports have implicated synthetic retinoids, including acitretin and isotretinoin, after long term use, in the formation of diffuse hyperostosis of the spine (diffuse idiopathic skeletal hyperostosis [DISH]), as well as calcification of tendons and ligaments, particularly in the ankles (Carey et al. 1988). Prospective studies have shown that the effect of retinoids on bone, if present at all, is likely to involve worsening of preexisting skeletal overgrowth rather than induction of de novo changes. Even long-term use of isotretinoin in acne patients rarely causes clinically significant radiologic abnormalities, as most hyperostoses are asymptomatic and clinically insignificant (Ling et al. 2001).

Osteoporosis has been observed with hypervitaminosis A and after long-term therapy with etretinate but not with isotretinoin (DiGiovanna et al. 1995).

Muscle Effects

Muscular pain and cramps can be observed in patients taking acitretin; however, these symptoms are associated primarily with isotretinoin, especially in individuals involved in vigorous physical activity. Occasionally, elevated creatine kinase levels may be observed. Increased muscle tone and axial muscle rigidity and myopathy were reported to be related to etretinate and acitretin therapy, respectively (Lister et al. 1996).

Hematologic Toxicities

A high incidence (28 %) of dose-related leukopenia was reported in the studies of bexarotene in CTCL, occurring as early as 2–4 weeks, with a decrease in neutrophils rather than lymphocytes (Duvic et al. 2001a). Hematologic abnormalities are much less common with other retinoids, but careful hematologic monitoring in HIV-infected patients is warranted.

Contraindications

Topical Retinoids

Topical retinoids should be avoided during pregnancy and nursing, due primarily to medicolegal issues raised by the teratogenicity of oral isotretinoin. Concomitant use of irritating topical products should be avoided.

Systemic Retinoids

The absolute contraindications are pregnancy or women contemplating becoming pregnant, noncompliance with contraception, breastfeeding, and hypersensitivity to preservatives present in acitretin's capsule (parabens). Relative contraindications are leukopenia, moderate to severe hypercholesterolemia or hypertriglyceridemia, significant hepatic (especially bexarotene) or renal dysfunction, hypothyroidism (especially bexarotene), young children, and suicidal ideation (isotretinoin).

Drug Interactions

The following should be avoided or used with caution:

- *Cyclines* such as tetracycline, doxycycline, and minocycline may increase intracranial pressure. This side effect was in fact related to the very high doses of isotretinoin used in the early development of the drug (up to 2 mg/kg). Currently, the doses used are much lower, and patients given isotretinoin 0.25 mg/kg for severe rosacea may benefit of short periods of association with a cyclin.
- *Alcohol* may increase conversion of acitretin to etretinate (special problem in women; see above) and hepatotoxicity.
- *Methotrexate* may have synergistic liver toxicity with retinoids; however, combination used with caution in patients with PRP or severe psoriasis.
- *Vitamin A supplement* carries the risk of hypervitaminosis A.
- *Azoles and macrolides* are CYP3A4 inhibitors that may increase retinoid drug levels and resultant potential toxicity.
- In contrast, *antituberculosis drugs* (rifampin) *and anticonvulsants* (phenytoin and carbamazepine) may decrease the drug levels of retinoids via CYP 3A4 induction.
- Retinoids may also increase the drug levels of cyclosporine via competition for CYP3A4 metabolism (Wiegand and Chou 1998).

Use in Infant Children and Elderly

There are no significant age-related problems with prescribing retinoids, provided contraindications and drug interactions cited above are considered.

Pregnancy and Breastfeeding

Systemic Retinoids

All systemic retinoids are teratogenic and are absolutely contraindicated during pregnancy and lactation (FDA category X), which should be excluded by a pregnancy test before considering retinoid therapy and then at regular intervals (e.g., monthly in the case of isotretinoin) during its administration. Two pregnancy tests are recommended before instituting isotretinoin therapy. Pregnancy is not only an absolute contraindication to starting therapy; it must also be avoided throughout therapy and for an appropriate interval after completion of therapy. Adequate contraception for at least 1 month before therapy is required for all systemic retinoid therapy. Acitretin requires contraception for 3 years (USA) or 2 years (Europe) after cessation of therapy, whereas isotretinoin, bexarotene, and alitretinoin require contraception for just 1 month after cessation of therapy.

Topical Retinoids

Although no evidence exists for teratogenicity of topical retinoids in humans (Nohynek et al. 2006; Sorg et al. 2007), they are nevertheless not recommended for use during pregnancy. Since no dermatologic condition that is known to be responsive to topical retinoids, and which may be observed during pregnancy, is life threatening to the mother or fetus, it is wiser to postpone treatment until after delivery (primarily due to medicolegal rather than scientific data in the opinion of these authors). The same recommendations are also valid for lactating women, as it is not known whether topical retinoids pass into the breast

milk. Consequently, topical retinoid use is not recommended during breastfeeding; it may cause unwanted effects in the nursing baby.

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Scabicides and Pediculicides

148

Anna Górkiewicz-Petkow

Key Points

- Scabies and pediculosis are still very common and often underestimated ectoparasite infections.
- In new epidemiologic situations – prolonged life, various immunodeficiency syndromes and development of resistant strains – new challenging problems in the therapy are raised; therefore, new considerations should be made about the schedules for treating individuals and endemics in school, nursing homes, hospitals and underdeveloped communities. The use of medications is often influenced by economical circumstances.
- The treatment of scabies and pediculosis is mainly external, but it is possible to use orally administered drugs in difficult cases (ivermectin).
- Effectiveness of the various treatments depends not on the drug itself but on proper use and epidemiological approach to the treatment.

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General Principles

Scabies and pediculosis are still very common and often underestimated ectoparasite infections. Chronic, not recognized infestations complicated by local secondary bacterial infections can lead to superinfection with MRSA or nephritogenic strains of *Streptococcus* spp. in the population.

Infestations may result not only from human mites or insects but also from domestic animals, grain and dust mites. In the presence of unexplained, often puzzling, pruritic, papular eruption, the possibility of an ectoparasite infestation should always be considered. In new epidemiological situations – prolonged life, acquired immunodeficiency syndrome (AIDS) and other immunodeficiency syndromes and development of resistant strains – new challenging problems in therapy are raised. Laboratory studies indicate that acaricide resistance in scabies is likely mediated by P-glycoprotein (for ivermectin) and sodium channel blocker mutations (for permethrin). Addition of enzyme synergists can reverse resistance in vitro to permethrin, suggesting a possible improvement of local therapy. Therefore, new considerations should be made about the schedules for treating individuals and endemics in schools, nursing homes, hospitals and underdeveloped communities. It is important that treatment schedules with different medications should correlate with life cycle of the scabies mite or lice acting on living organisms and/or eggs. The frequency of use of different insecticides varies in

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_148, © Springer-Verlag Berlin Heidelberg 2015

different countries. Among well-known drugs, there are often locally produced herbal preparations recommended for the treatment. The use of different medications is also influenced by economic circumstances. Effectiveness depends not only on the drug itself but also on their proper use according to the instructions and epidemiological approach to the treatment. In ectoparasite infections it is necessary to treat not only the patient but also the contacts and often the environment to prevent the reinfection and spread of the disease.

An accurate and informative education programme is also very useful. The treatment of scabies and pediculosis is mainly external, but there are reports on possible use of orally administered drugs (co-trimoxazole, ivermectin, thiabendazole). The most effective insecticides originate from plants (pyrethrins) or from pesticides used in agriculture and for household purposes (lindane, malathion, carbaryl); therefore, the therapy has some potential toxicity.

Table 148.1 Efficacy of different scabicides

Drug	Treatment regimen	Day 28 (cure rate %)
Permethrin	5 % topical single dose	100
Benzyl benzoate	12.5 % topical single dose	70.5
	12.5 % topical two doses 1 day apart	95.8
Sulphur	8–10 % single dose	42.4
	8–10 % three consecutive nights	90.6
Ivermectin	200 mg/kg single dose	90.0
	200 mg/kg two doses 14 days apart	89.7
Ivermectin	1 % topical single dose only to affected sites	100.0
Lindane	1 % topical two applications 1 week apart (*withdrawn from treatment in many countries*)	69.1

Modification from Mounsey and McCarthy (2013)

Topical Treatments (Tables 148.1 and 148.2)

Pyrethrins and Pyrethroids

The insecticide properties of flowers in the genus *Chrysanthemum* have been known for centuries and originate from ancient Persia. Pyrethrum is the name of dried flowers; pyrethrins are the active component of pyrethrum. The first commercialized production started in Dalmatia in 1840; then by the year 1860 the Dalmatian powder was widely used as household insecticide. In 1948 the first synthetic pyrethroid (permethrin) was developed. Based on oral LD values in rats, permethrin is about 3 times less toxic than malathion, 15 times less than carbaryl and about 40 times less than lindane and DDT. In 1986, permethrin was introduced for the treatment of head lice and soon after for scabies. Percutaneous absorption in human studies is less than 2 %; permethrin is rapidly detoxified by esterase hydrolysis in the blood and most body tissues including the skin. Plasma levels of permethrin following topical application of 5 % cream formulation in human clinical trials were below detectable levels. In adverse reactions some irritation of the skin may occur at the time of treatment. Some concern has been expressed about possible allergic reactions, since some individuals are allergic to pyrethrum, but a sensitizing factor was removed from the final product. For topical treatment single dose or two doses 1 week apart is recommended. Permethrins have also been used for impregnation of beds, curtains and military clothes to prevent mosquito, ticks and tsetse fly bites.

Commercial Preparations

- Lyclear dermal cream (5 % permethrin), scabicide
- Lyclear cream rinse (1 % permethrin), pediculicide
- Nix (1 % permethrin), pediculicide

Acetylcholinesterase Inhibitors

Malathion, Carbaryl

From 1954, acetylcholinesterase inhibitors have been used as pesticides in agriculture and for household purposes. In 1971 malathion and in 1977 carbaryl were introduced as pediculicides and scabicides following evidence of the

Table 148.2 Pharmacologic treatment of pediculosis (head lice, pubic lice)

Treatment	Ovicidal	Directions
Permethrin 1 % lotion (Nix)	No	Apply to damp hair and leave on for 10 min; then rinse and repeat in 7 days
Pyrethrins 0.3 %/piperonyl butoxide 4 % shampoo or mousse	No	Apply to dry hair and leave on for 10 min, and then rinse
Malathion 0.5 % lotion	Partial	Apply to dry hair enough to sufficiently wet the hair and scalp; allow to dry naturally Shampoo 8–12 h later, rinse and use lice comb Repeat after 7–9 days if live lice still are present
Spinosad 0.9 % topical suspension (Natroba)	Yes	Apply to dry hair and leave on for 10 min; then rinse and repeat in 7 days only if live lice are seen
Ivermectin (Stromectol not approved for treatment of pediculosis)	Partial	200–400 mcg/kg, given on day 1 and day 8 (total of two doses) in refractory cases
Infection of eyelashes: physostigmine eye ointment, malathion and carbaryl aqueous sol. With caution. Petrolatum, mercuric oxide eye ointment, mechanical removal of lice		

Modification from Gunning et al. (2012)

emergence of the resistance of head lice to other drugs, mainly organochlorine insecticides. Malathion is rapidly broken down by hepatic enzymes in humans and warm-blooded animals, thus diminishing its cholinesterase inhibitory properties. In insects it is converted to the oxy-analogue, which is an active metabolite. Human studies with inhalation of malathion aerosols, the use of powder or dust on the skin, indicated no inhibition of cholinesterase activity. Possible poisoning manifestations include visual disturbances, respiratory difficulty and gastrointestinal hyperactivity. Malathion and carbaryl are also ovicides for head lice, although the ovicidal activity is not complete. Malathion is absorbed into keratin within 6 h and confers residual, protective effect against reinfection for about 6 weeks. The effectiveness of carbaryl is determined by the components of the bases used in preparations. Both insecticides are degraded by heat. Generally, the medications are well tolerated, safe and effective.

Commercial Preparations

- Carylderm lotion (carbaryl 0.5 % alcohol-based lotion), Carylderm shampoo (pediculicide)
- Derbac-C (carbaryl 1 % aqueous solution), Derbac-C shampoo (pediculicide)
- Derbac-M (malathion 0.5 % aqueous solution) (pediculicide/scabicide)
- Prioderm (malathion 0.5 % alcohol lotion), Prioderm shampoo (pediculicide)
- Malathion powder – disinfection of clothes

Chlorinated Insecticides

Gamma-Hexachlorocyclohexane (Lindane)

This drug has been known since 1940 to be both a potent pesticide and an effective topical scabicide/pediculicide. Until recently the use of lindane was limited only by the potential side effects which appear to have occurred almost entirely in children when it was not used properly or was accidentally ingested. Adverse effects are associated with central nervous system (CNS) effects (vertigo, seizures, convulsions) and the gastrointestinal tract (nausea, vomiting). Lindane binds to plasma proteins, epidermis, dermis and subcutaneous tissue and is readily dissolved in fat tissue. In animal studies (guinea pig), plasma and brain levels of lindane were significantly higher than permethrin. Lindane absorption through the skin was ten times greater as compared with permethrin. Within the past decade, there have been reports on drug resistance concerning both scabies and pediculosis treatment. The following recommendations have been proposed to minimize the potential risk of lindane, mainly in the treatment

of scabies: the drug should not be applied after a hot bath (enhancement of absorption); avoid or use with extreme caution in the treatment of children under 4 years of age and pregnant women (FDA pregnancy category C); time of skin exposure should be no longer than 8–12 h; use with caution in patients with epidermal barrier dysfunction and excoriations; use the lowest effective concentration; treatment should be reapplied only in proven reinfestation and no more than twice a month. Following all the instructions, lindane remains as a second-line treatment for scabies and head lice infestation. Recently, lindane has been withdrawn from many countries worldwide due to concern regarding neurotoxicity and evidence that it is less effective than other treatments.

Commercial Preparations

- Quellada lotion – 1 % lindane (scabicide)
- Quellada shampoo – 1 % lindane (pediculicide)
- Scabicide (cream), Aphtiria (cream, powder) and Jacutin (emulsion, gel, cream) – 1 % lindane (scabicide, pediculicide)

Other Medications Used for the Treatment of Scabies and Pediculosis

Benzyl Benzoate

Benzyl benzoate is known for over 60 years for the treatment of scabies. In the past it was used as a compound of Balsam of Peru and from 1937 manufactured synthetically. General toxicity occurs only if ingested orally in large amounts (convulsions). Locally, benzyl benzoate may be an irritant to the skin or give allergic reactions. Because of low toxicity, it is recommended in lower concentrations for children (exclusion of neonates [gasping syndrome] and up to 4 months of age) and pregnant women.

Commercial Preparations

- Ascabiol 10 % solution benzyl benzoate for children. Twenty-five percent benzyl benzoate solution for adults (mainly scabicide may be used as pediculicide). It is still very effective.

Sulphur

Sulphur remained in use from other old remedies for scabies (like hydrargyrum, creosote, resorcine, formalinum, chrysarobinum, lactic acid). Sulphur is a compound of ointments and lotions used for the treatment of scabies known as ung (Wilkinson ung). It was used in different concentrations from 6 % to 50 %. It acts through keratolytic properties. Sulphur still remains as a recommended treatment of scabies in children and pregnant women, but it is not pleasant and very messy to use. There are no toxicology or percutaneous absorption studies.

Commercial Preparations

- Six percent or ten percent ointments in petrolatum or 25 % ung. Wilkinson in zinc paste in equal dose

Crotamiton (*N*-Ethyl-*O*-Crotonotoluidide)

Very little is known about the toxicology of crotamiton. There are no studies on percutaneous absorption. The drug has a lower efficacy in the treatment of scabies but has been useful in the follow-up treatment of postscabietic pruritus or pruritus of other origin.

Commercial Preparations

- Eurax – lotion or ointment (10 % crotamiton)
- Euraxil – 5 % crotamiton gel (scabicide)

Spinosad

The 0.9 % solution available from 2011 (new compound) derived from fermented *Saccharopolyspora spinosa* is acting causing hyperexcitation, paralysis and death of lice. Spinosad is more effective than 1 % permethrin for treatment of head lice.

Commercial Preparations
- 0.9 % topical suspension, pediculicide

Monosulfiram

Introduced in 1940 for the treatment of scabies, monosulfiram is chemically similar to disulfiram (Antabuse). A disulfiram-like reaction occurs with flushing, sweating and tachycardia if alcohol is ingested during or soon after treatment. Monosulfiram is not an efficient scabicide, often needs several applications and may cause prolonged inhibition of aldehyde dehydrogenase enzyme which is needed for enzymatic breakdown of alcohol, thus making possible an accumulation of acetaldehyde. Such a reaction is potentially serious in children. A single report was published on TEN induced by monosulfiram, and local irritation of the skin is reported. Consequently, the drug is not recommended for use as a scabicide, since other more efficient drugs are available.

Commercial Preparations
- Tetmosol 25 % solution, Tetmosol soap (scabicide)

Copper II Oleate-Tetrahydronaphthalene

This mixture diluted in acetone and mineral oil is a pediculicide for head lice. It is very effective but readily combustible and an irritant, so it should not be applied to patients with eczema.

Commercial Preparation
- Cuprex (head lice)

Oral Treatment of Scabies and Pediculosis

Ivermectin

Ivermectin is an antiparasitic agent with a structure similar to the macrolide antibiotics but without antibacterial activity. It is a synthetic derivative of abamectin. The drug has an endectocidal effect causing paralysis by suppressing the conduction of the nervous impulses in the interneuronic synapses of parasites. Ivermectin is widely used for the treatment of onchocerciasis. During 15 years of this treatment, there have been few side effects described: macular eruption, headache, tachycardia and hypotension. Ivermectin is also used worldwide to control infestation with sarcoptic mites in domestic animals. Since 1992 there have been reports of the general administration of this drug for uncomplicated scabies infestations in humans (worldwide), scabies in HIV positive patients, crusted scabies and endemics in the nursing homes. There have been single reports on possible death in elderly patients treated with ivermectin for scabies.

Commercial Preparation
- Ivermectin (Stromectol) – not registered for the treatment of scabies and pediculosis in humans in all countries. The recommended dose is 200 μg/kg twice in week intervals (7 days apart) in scabies and head lice in children >15 kg. Use with caution only in cases of resistance to other treatments of scabies, and do not administer in pregnant or lactating women. There are reports on topical use of ivermectin 1 % lotion for scabies with effects comparable to 5 % permethrin cream.

Trimethoprim (Sulfamethoxazole TMP/SMX)

The efficacy of oral co-trimoxazole in the eradication of head lice was discovered incidentally in 1978 while treating a child for an upper respiratory tract infection. This effect is probably related to ingestion of the antibiotic by feeding lice and its subsequent effect on their symbiotic bacteria present in a midgut organelle. These bacteria are essential for the synthesis of B vitamins without which the lice cannot survive. Suggested duration of treatment is 4–7 days with adult or children dose of the antibiotic. Due to possible drug reaction (Stevens-Johnson syndrome, erythema

multiforme), TMP/SMX should be considered only in head lice infestation refractory to other treatment.

Possible New Therapeutics for Scabies and Pediculosis

To avoid resistance and improve topical efficacy, new combined formulations of pyrethroids with synergists (e.g. pyrethrins with piperonyl butoxide) or new synthetic pyrethroids or use of insect growth regulators in topical treatment is proposed. As for oral treatment, moxidectin is a new macrocyclic lactone closely related to ivermectin but with longer half-life activity.

Alternative Therapies

Several essential oils and herbal remedies show acaricidal activity in vitro, e.g. eugenol and derivatives, clove oil, neem oil, tea tree oil and aloe vera. Very few of these natural products have been assessed in clinical trials.

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Sunscreens

149

John L.M. Hawk

Key Points

- Sunscreens have effect through absorbing ultraviolet radiation into appropriately shaped molecules of organic chemical substances and re-emitting it as harmless quantities of heat (chemical sunscreens) or by reflecting (remitting) it through scattering by tiny particles of titanium dioxide or zinc oxide (physical sunscreens) or a combination of both.
- Sunscreens are effective if used properly against skin sunburning, skin photo-ageing, nonmelanoma and probably melanoma skin cancer and many photodermatoses, particularly polymorphic light eruption.
- Sunscreens are usually not used properly, so it should be used last in the hierarchy of sun-protective measures, namely, first, avoidance of exposure when sun high in sky; second, use of shade and third, use of clothing cover.
- Proper use of sunscreens means using high protection factor products (preferably 50 or more) offering good UVA protection (preferably at least a third of the sun protection factor), applying it liberally to all exposed areas, including the ears in males, about 15–30 min before exposure and again 15–30 min after and also again after perspiration or exercise and for greatest reliability, every 2–3 h as long as exposure continues.
- Adverse effects include not infrequent mild irritation at the time of exposure and rarely contact or photocontact dermatitis.
- Concerns have also been intermittently raised about the carcinogenic effects of sunscreens, either directly on DNA or through encouraging long sun exposure with poorly applied sunscreen, anti-inflammatory effects of sunscreens masking inefficacy and oestrogenic effects of sunscreen through skin absorption and impaired vitamin D production through sunscreen use, but except perhaps for encouraging excessive exposure, these possibilities have not come to pass in any important way.

General Principles

Sunscreens, also variously known as sun creams, sunblocks, suntan lotions or similar, are creams, lotions, sprays, gels or salves applied to the skin to attenuate the effects of ultraviolet radiation

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_149, © Springer-Verlag Berlin Heidelberg 2015

(UVR) emitted by the sun or other sources, thereby theoretically reducing the likelihood of its damaging effects.

The originator of sunscreens appears to have been Swiss chemistry student, Franz Greiter, who developed one with a sun protection factor (SPF) of two, as later measured, after suffering sunburn while climbing the mountain Piz Buin in the Swiss Alps. PIZ BUIN sunscreens, as he named them, still exist today. Shortly after, in 1944, Florida pharmacist Benjamin Green produced red veterinary petrolatum, a messy substance again with only moderate UVR-protective effect, for use on chronically sun-exposed soldiers' skin during World War II. It was then marketed in the USA under the Coppertone label in the 1950s, following which in 1962, Greiter introduced the concept of the SPF, now a worldwide standard of sunscreen efficacy. Sunscreen development has since proceeded steadily and modern sunscreens when used carefully are generally extremely effective against UVR-induced skin effects. They are also very cosmetically acceptable for the most part, and in spite of various intermittent claims to the contrary, largely free of adverse effects, as well as being able to withstand water and sweat wash-off and the effects of heat.

The damaging effects on the skin of sunlight which sunscreens are designed to avoid, much more likely in fair skins, are principally skin sunburning, ageing and cancer, although a significant minority of subjects also develop UVR-induced skin rashes, also known as photodermatoses. UVR (100–400 nanometres, nm) comprises only 5–10 % of terrestrial sunlight, of which the much more damaging UVB (280–315 nm) forms only about 5 % and UVA (315–400 nm) the remaining 95 %. Both UVB and UVA cause similar deleterious skin effects but much more so the more active UVB, even though reaching the earth only in relatively small amounts and when the sun is high in the sky. UVA though much less active is constantly present, so for optimal efficacy, sunscreens should offer high both UVB and UVA protection, and virtually all do nowadays.

The theoretical protection offered by sunscreens against UVR-induced skin damage has also been confirmed in practice by a series of studies, the efficacy against sunburning being definite in that the SPF is defined by its efficacy at reducing sunburn, as described below. In addition, they have been shown to be very effective against the development of actinic keratoses and squamous cell carcinoma, while studies on photo-ageing, basal cell carcinoma and melanoma prevention show less definitive efficacy, though good if not total protection is strongly suggested and would be expected if the sunscreens are used very carefully throughout life. Sunscreens may also be very effective in patients with photodermatoses such as polymorphic light eruption (PLE), actinic prurigo (AP), hydroa vacciniforme (HV) and chronic actinic dermatitis (CAD) and light-exacerbated dermatoses, particularly seborrhoeic eczema and xeroderma pigmentosum, though not usually in solar urticaria (SU) or the porphyrias. PLE is the commonest of these and sunscreens are usually effective for this and the other disorders mentioned except in more severe forms.

Classification and Structure

Sunscreens may be classified as:

1. Chemical sunscreens (organic chemical absorbers)
2. Physical sunscreens (metal oxide inorganic absorbers)
3. Combination sunscreens (combining both chemical and physical agents)

Chemical sunscreen agents are organic molecules capable because of their structure of absorbing UVR, then re-emitting it as harmless low energy longer wavelengths, mostly in the infrared region. Physical sunscreens scatter and reflect UVR, though modern nanoparticulate metal oxide products also absorb it.

Chemicals cannot absorb both UVB and UVA efficiently at concentrations suitable and permissible in commercial preparations, and thus sunscreens generally contain multiple ingredients so as to offer a broad spectrum of protection. Chemical absorbers in general are compounds with an aromatic ring structure conjugated with a

carbonyl group, with an electron-releasing amine or methoxyl group substituted in the *ortho* or *para* position of the ring. Derivatives of *para-aminobenzoic* acid (PABA), cinnamates, salicylates, camphor, anthranilates, benzophenones and dibenzoylmethanes are the seven major groups of these agents currently used in sunscreen formulations. Such agents with a high optical density or molar extinction coefficient at the wavelength of maximum UVR absorption, the so-called absorption maximum (λ_{max}), are likely to give maximum protection at the lowest concentrations.

The SPF is the most widely accepted way of measuring this protection and is the ratio calculated by dividing the UVR dose (as produced by artificially produced solar simulated sunlight) required to evoke minimal erythema on skin covered by 2 mg/cm^2 or 2 μl/cm^2 of sunscreen by that required on unprotected skin. Substantivity (water resistance) is a sunscreen's ability to remain on the skin when subjected to environmental conditions likely to remove it, such as swimming or sweating, as measured by determination of the SPF after one or more 20 min immersions of the sunscreen-applied test site in moving water.

More recently, effective methods of assessing UVA protection have also been sought, since UVA as stated above is also damaging to skin. It produces similar though in sunlight more slowly induced effects to UVB but particularly tends to induce photo-ageing and photodermatoses, as well as contributing somewhat to sunburning and cancer. Several assessment techniques have been considered.

Of the techniques used, the persistent pigment darkening (PPD) method is most widespread, being similar to the SPF method of measuring protection against erythema during SPF testing with a solar simulator. However, the PPD technique instead assesses persistent tanning (as distinct from the transient immediate pigment darkening) of the skin with and without sunscreen following just UVA irradiation, such tanning known to be reliably inducible by UVA. Following this, Colipa, the European Cosmetics Association, has also developed an in vitro technique claimed to provide the same result. Given the deleterious effects on the skin now known to be induced by UVA, the European Union now requires a minimum one-third level of UVA protection in relation to the SPF.

In the UK and Ireland, the Boots Company in Nottingham has developed a so-called star rating system, recently modified slightly following development of the Colipa UVA PF test mentioned above. This is a proprietary in vitro method of assessing the ratio of sunscreen UVA to UVB protection based on prior work by Diffey et al. The test logo and methodology are also licensed to any other sunscreen brand sold in Boots' shops, while those not offered by Boots are excluded. Five-star (5*) products are best, and three-star products least effective. The method uses a spectrophotometer to measure the sunscreen absorption of UVA and UVB after samples are pre-irradiated to ensure photostability of the product.

Finally, Asian brands, particularly Japanese, often use the Protection Grade of UVA (PA) system, again based on the PPD reaction, PA+ on sunscreen labels indicating a UVA PF of two to four, PA++ four to eight and PA+++ more than eight.

Chemical Sunscreens

The names of chemical sunscreen ingredients tend to be a confusing array of differing nomenclatures. The nature and UVR absorptivity of a selection of these are outlined below with a more detailed listing provided in Table 149.1.

PABA has a reactive carboxylic and an amino group substituted in a *para* orientation on the benzene nucleus. It has a λ_{max} at 296 nm and a molar extinction coefficient of 13,600 and is therefore a good UVB absorber. However it is easily oxidised and stains clothing, may crystallise and has a moderate contact sensitising potential. On the other hand, PABA derivatives such as the ethyl, butyl, amyl and octyl esters of *N,N-dimethyl-PABA* were designed to minimise the disadvantages of the parent molecule while retaining its UVB screening ability. Thus N,N-dimethyl-PABA octyl ether, also

Table 149.1 The following are US Food and Drug Administration (FDA)-allowable active sunscreen ingredients

UVR filter	Other names	Maximum concentration	Permitted countries	Safety testing results
p-Aminobenzoic acid	PABA	15 % (European Union-banned from sale to consumers from 8 October 2009)	USA, AUS	Protects against skin tumours in mice. Shown able to increase DNA defects and now less commonly used
Padimate O	OD-PABA, octyldimethyl-PABA, σ-PABA	8 % (EU, USA, AUS), 10 % (JP)	EU, USA, AUS, JP	Not tested
		Not currently supported in EU and may be delisted		
Phenylbenzimidazole sulphonic acid	Ensulizole, Eusolex 232, PBSA, PARSOL HS	4 % (US, AUS), 8 % (EU), 3 % (JP)	EU, USA, AUS, JP	Genotoxic in bacteria
Cinoxate	2-Ethoxyethyl-p-methoxycinnamate	3 % (US), 6 % (AUS)	USA, AUS	Not tested
Dioxybenzone	Benzophenone-8	3 %	USA, AUS	Not tested
Oxybenzone	Benzophenone-3, Eusolex 4360, Escalol 567	6 % (US), 10 % (AUS, EU), 5 % (JP)	EU, USA, AUS, JP	Not tested
Homosalate	Homomenthyl salicylate, HMS	10 % (EU, JP), 15 % (US, AUS)	EC, USA, AUS, JP	Not tested
Menthyl anthranilate	Meradimate	5 %	USA, AUS	Not tested
Octocrylene	Eusolex OCR, 2-cyano-3,3-diphenyl acrylic acid, 2-ethylhexylester	10 %	EU, USA, AUS, JP	Increases ROS
Octyl methoxycinnamate	Octinoxate, EMC, OMC, ethylhexyl methoxycinnamate, Escalol 557, 2-ethylhexyl-paramethoxycinnamate, PARSOL MCX	7.5 % (US), 10 % (EU, AUS), 20 % (JP)	EU, USA, AUS, JP	
Octyl salicylate	Octisalate, 2-ethylhexyl salicylate, Escalol 587	5 % (EU, USA, AUS), 10 % (JP)	EU, USA, AUS, JP	Not tested
Sulisobenzone	2-Hydroxy-4-methoxybenzophenone-5-sulphonic acid, 3-benzoyl-4-hydroxy-6-methoxybenzenesulphonic acid, Benzophenone-4, Escalol 577	5 % (EU), 10 % (US, AUS, JP)	EU, USA, AUS, JP	Not tested
Trolamine salicylate	Triethanolamine salicylate	12 %	USA, AUS	Not tested
Avobenzone	1-(4-Methoxyphenyl)-3-(4-tert-butyl phenyl) propane-1,3-dione, butyl methoxy dibenzoylmethane, BMDBM, PARSOL 1789, Eusolex 9020	3 % (US), 5 % (EU, AUS), 10 % (JP)	EU, USA, AUS, JP	No longer available

UVR filter	Other names	Maximum concentration	Permitted countries	Safety testing results
Ecamsule	Mexoryl SX, terephthalylidene dicamphor sulphonic acid	10 %	EU, AUS (US: approved in certain formulations up to 3 % via New Drug Application (NDA) route)	Protects against skin tumours in mice
Titanium dioxide	CI77891	25 % (no limit in JP)	EU, USA, AUS, JP	Not tested
Zinc oxide		25 % (US), 20 % (AUS) (EU, 25 % provided particle size >100 nm) (JP, no limit)	EU, USA, AUS, JP	Protects against skin tumours in mice

Other ingredients approved within the EU and other parts of the world, not included in FDA Monograph			
UVR filter	Other names	Maximum concentration	Permitted in
4-Methyl-benzylidene camphor	Enzacamene, PARSOL 5000, Eusolex 6300, MBC	4 %	EU, AUS
Tinosorb M	Bisoctrizole, methylene bis-benzotriazolyl tetramethylbutylphenol, MBBT	10 %	EU, AUS, JP
Tinosorb S	Bis-ethylhexyloxyphenol methoxyphenyl triazine, Bemotrizinol, BEMT, anisotriazine	10 % (EU, AUS), 3 % (JP)	EU, AUS, JP
Neo Heliopan AP	Bisdisulizole disodium, disodium phenyl dibenzimidazole tetrasulphonate, bisimidazylate, DPDT	10 %	EU, AUS
Mexoryl XL	Drometrizole trisiloxane	15 %	EU, AUS
Benzophenone-9	Uvinul DS 49, CAS 3121-60-6, sodium dihydroxy dimethoxy disulphobenzophenone	10 %	JP
Uvinul T 150	Octyl triazone, ethylhexyl triazone, EHT	5 % (EC, AUS), 3 % (JP)	EU, AUS
Uvinul A Plus	Diethylamino hydroxybenzoyl hexyl benzoate	10 % (EC, JP)	EU, JP
Uvasorb HEB	Iscotrizinol, diethylhexyl butamido triazone, DBT	10 % (EC), 5 % (JP)	EU, JP
PARSOL SLX	Dimethico-diethylbenzalmalonate, Polysilicone-15	10 %	EU, AUS, JP
Isopentenyl-4-methoxycinnamate	Isoamyl p-methoxycinnamate, IMC, Neo Heliopan E 1000, amiloxate	10 %	EU, AUS

Adapted from FDA Sunscreen Monograph 2012 (www.fda.gov)

EU European Union, *AUS* Australia, *JP* Japan

Table 149.2 Indications for sunscreen use (after the hierarchy of all other possible UVR avoidance measures has been used first, as outlined in the text)

1. To avoid sunburning
2. To avoid photo-ageing, actinic keratoses cell carcinoma, squamous cell carcinoma, basal cell carcinoma and malignant melanoma (though the evidence remains only moderate for photo-ageing, basal cell carcinoma and malignant melanoma)
3. To avoid photodermatoses, particularly polymorphic light eruption, mild actinic prurigo, mild hydroa vacciniforme (to a degree), mild chronic actinic dermatitis, light-exacerbated dermatoses and xeroderma pigmentosum (if used constantly and very carefully) but not usually solar urticaria to any extent or the porphyrias

known as padimate O, has overcome most of the undesirable effects of PABA, being a liquid with almost double the molar extinction coefficient of PABA and an efficient and popular UVB sunscreen (Tables 149.1 and 149.2).

Salicylates are *ortho*-disubstituted aromatic compounds with peak absorption around 300 nm and hence UVB absorbers. They are non-water-soluble, stable compounds easily incorporated into cosmetic formulations and excellent solubilisers of other nonsoluble ingredients such as benzophenones. They also have an excellent safety profile but are relatively weak UVR absorbers. The most widely used of the group is octyl salicylate, also known as 2-ethylhexyl salicylate.

Cinnamates are UVB absorbers with a λ_{max} around 310 nm. 2-Ethylhexyl p-methoxycinnamate or octyl *p-methoxycinnamate* is the most popular member of the group, while octocrylene is a more recent introduction.

Anthranilates, as with the salicylate group, are stable and safe compounds. Menthyl anthranilate is an *ortho*-disubstituted aminobenzoate with a λ_{max} at 336 nm.

Benzophenones are aromatic ketone derivatives of dibenzoylmethane capable of some absorption in the UVA range of the spectrum, some exhibiting a shift in λ_{max} in different solvents; for example, dioxybenzone has been shown to have a λ_{max} of 326 and 352 nm in polar and nonpolar solvents, respectively. These compounds however are relatively difficult to solubilise in cosmetic formulations and have a sensitising potential.

Dibenzoylmethanes are substituted diketones capable of undergoing keto-enol tautomerism. Compounds such as isopropyl dibenzoylmethane (Eusolex 8020) and butyl-dibenzoylmethanes (avobenzone, PARSOL 1789) absorb UVA relatively well but are not very photostable. Avobenzone has a λ_{max} of 355 nm and a very high extinction coefficient of greater than 30,000.

Camphor derivatives (bicyclic compounds), such as 3-benzylidene camphor and benzylidene camphor sulphonic acid, are UVB absorbers. This group of agents is currently not approved by the Federal Drug Administration for use in the USA. In particular, however, terephthalylidene dicamphor sulphonic acid (Mexoryl SX) is a newer derivative with a λ_{max} of 345 nm, with excellent photostability and UVA absorptivity.

Recently, concerns have been raised that many chemical sunscreen ingredients have an anti-inflammatory effect on the skin, thereby reducing the erythema of sunburn and also artificially raising the SPF as measured in vivo, as is usual, compared with that in vitro. As a result, it might be possible that sunburn is prevented while DNA damage continues unabated to long-term disadvantage. However, although such an anti-inflammatory effect does seem to occur, some of the in vitro SPFs were higher than the in vivo measurements, indicating some experimental uncertainty, while also many studies over the years have confirmed sunscreen efficacy in reducing DNA damage, as well as actinic keratosis and skin cancer incidence, as described earlier. Thus if there is any artificial anomalous raising of the SPF, the residual sunscreen efficacy is clearly still sufficient to maintain its substantial effect.

Physical Sunscreens

Titanium dioxide and zinc oxide are chemically inert particulate metal oxides which have a num-

ber of advantages in that they are photostable, not a cause of photoallergy or phototoxicity and protective against UVB, UVA and to some extent visible radiation. In the past such preparations have tended to be thick, opaque and cosmetically unacceptable to many people, but more recently, micronised or nanoparticulate formulations containing particles of less or much less than 100 nm diameter have ensured improved translucency and cosmetic acceptability. They are also often combined with organic chemical absorbers in order to achieve higher SPFs than when used alone.

Recently, concerns have been raised concerning nanotitanium dioxide-containing sunscreens, because they demonstrate unusual solar radiation responses as compared with the earlier thicker forms of the same material, in that their electrons are contained within each minute particle in a way which produces quantum molecular behaviour. As a result, ultraviolet radiation (UVR) attenuation is much higher than in continuous forms of the same material, but free radical formation may occur within them during UVR exposure and even sometimes without. This would be of concern if they were adjacent to or within living cells, but many in vitro studies, as well as many in vivo studies in animals and man, have shown their at most minimal penetration beneath the inert stratum corneum and also their lack of significant penetration into or persistence within hair follicles, where they are in any case still outside the stratum corneum. They are therefore unable to cause damage to living tissue, as further supported by their lack of adverse effects in the majority of the in vitro and in vivo studies undertaken and by clinical experience over the years, which has revealed no deleterious outcomes.

Another concern with respect to either chemical or physical sunscreen use has been that systemic vitamin D production, initiated in the skin by the UVB radiation in sunlight, might be prevented or seriously reduced as a result, with potentially serious consequences for normal bone metabolism and a host of other vitamin D-ASSOCIATED metabolic functions. However, careful studies have shown that even careful use of high-SPF sunscreens in areas of high UVR intensity at most mildly reduces systemic vitamin D levels, suggesting the substance is slowly created in the skin with even minimal exposure, a contention supported by the fact that average population summer and winter levels at all latitudes are the same.

Indications for Sunscreen Use

UVR exposure whether to UVB or UVA leads to acute inflammatory changes in the skin with vasodilatation, erythema, inflammatory cellular infiltration and release of pro-inflammatory mediators such as prostaglandins (PGD_2, PGE_2) and interleukins (IL_1, IL_6), along with keratinocyte apoptosis. Such effects are most pronounced in the sunburn reaction. UVR-mediated damage to DNA can be detected as early as 30 min after exposure, probably then leading causally to the subsequent inflammatory changes. Both epidermis and dermis are affected, principally by UVB, but UVA is known also to produce significant dermal damage, probably playing an important role in skin photo-ageing, the gradual deterioration of cutaneous structure and function from the cumulative imperfectly repaired damage of long-term recurrent UVR exposure. Manifestations of this include wrinkling, freckling, lentigines, telangiectasia, comedones, mottled pigmentation, coarseness and a yellowish discoloration of the skin. UVR has also been shown to be the most important cutaneous carcinogen, its role in the development of nonmelanoma skin cancers such as squamous and basal cell carcinomas having been clearly demonstrated. There is strong evidence also for the aetiological involvement of UVR in melanoma, although this has not yet been indisputably proven. An individual's inherent burning and tanning capacity along with associated behavioural and environmental factors greatly influences these events, those with fairer skins being more prone to damage. As mentioned previously, sunscreens are therefore strongly indicated as protective agents against the occurrence of skin sunburn, photo-ageing and cancers. Nevertheless some studies have shown a slightly increased incidence of melanoma in subjects who

claim to have used sunscreens, but this is thought likely to be due not to the sunscreen agents themselves but to other factors, particularly inadequate product use along with a possible tendency to stay outdoors for longer periods in the belief that protection is now adequate.

As also mentioned previously, sunscreens are routinely advised and can be very effective in patients with photodermatoses such as PLE, AP, HV, chronic actinic dermatitis (CAD), XP and the light-exacerbated dermatoses such as seborrhoeic eczema, but not usually SU. PLE is the commonest of these and usually affects young adults with an itchy erythematous papular eruption over some or all exposed areas within a few hours of sun exposure, thereafter subsiding within a few days; it may be induced by UVB, UVA or both, and broad-spectrum sunscreen use is advised, usually with very good effect except in very severe cases. AP is a more chronic condition of generally young girls characterised by an excoriated papular or nodular eruption of the exposed sites with a tendency to involve covered areas as well; as in PLE it may be induced by UVA or UVB. Sunscreen use is helpful only in milder instances. HV is a rare blistering and scarring photodermatosis otherwise closely resembling PLE; it responds moderately to sunscreen use, UVB and short wavelength UVA probably being causal. SU is an uncommon wealing condition induced by sunlight and only responding to sunscreen use in the rare mild cases induced by UVB. CAD is a relatively persistent eczematous condition of elderly males, the face, neck, upper chest and hands usually being involved with sparing of the eyelids, submental, retroauricular and other photo-protected areas. Most patients with CAD react abnormally to both UVA and UVB, so broad-spectrum sunscreens are advised, although again with only moderate effect.

Porphyrias are disorders of haem biosynthesis resulting in the excess production of porphyrin and its precursors; these compounds absorb radiation of wavelengths around 400 nm and then re-emit the energy leading to the production of free radicals destructive to cellular components. Patients with these disorders require protection particularly in the short visible light range of the spectrum, but this is not well provided by topical sunscreens, although inorganic chemical preparations such as titanium dioxide may help to a very small extent. Oral agents such as β-carotene 120–180 mg/day have long been tried in erythropoietic protoporphyria (EPP), but their benefit has never been proven. A newer agent is alpha-melanocyte–stimulating hormone given by injection, thereby stimulating a tan, but not theoretically enough to work: however, some patients are convinced of its efficacy.

Eczemas such as atopic and seborrhoeic dermatitis, not light-induced by themselves, can sometimes be worsened by sun exposure in some patients and sunscreens may be helpful in these, as mentioned above, as well as in other much rarer light-exacerbated dermatoses such as systemic lupus erythematosus.

Adverse Effects and Cross-Reactions

Sunscreen users may note an immediate burning or stinging sensation at sites of sunscreen application, more frequently with the benzophenones and PABA esters. Preparations containing physical agents may also cause on occasion miliaria due to occlusion. As with other topically applied agents, sunscreen preparations too may at times induce allergic contact dermatitis from preservatives, fragrances and other non-active constituents of the preparation, although the sunscreen chemicals themselves are also being increasingly reported as allergenic; sensitisation is higher in those with photodermatoses, especially CAD or PLE. In the early years of sunscreen use, PABA was the most frequent cause of this, but reactions over the last decade have been fewer because of its decreasing use. Glyceryl PABA was also reported as a potent sensitiser in several patients until the reaction was later shown to be due to impurities present in the preparation, the contaminant being either benzocaine (ethylaminobenzoic acid) or other unidentified agents. Procaine, benzocaine, *p*-phenylenediamine and sulphonamides can cross-react with PABA such that patients sensitised to any of these compounds

may also demonstrate an allergic reaction to sunscreens containing PABA or its esters. In recent years however the benzophenone (oxybenzone, mexenone) group has replaced PABA as the most frequent cause of sunscreen allergy, especially as these compounds are also widely used in non-sunscreen cosmetics and toiletries. Several allergic reactions have also been reported to isopropyl dibenzoylmethane, leading to its removal from several products; it can cross-react with the structurally related butyl methoxydibenzoylmethane. 3-4′-Methyl-benzylidene camphor was previously used in combination with isopropyl dibenzoylmethane and those sensitive to one agent often demonstrated a concomitant sensitisation to the other. Amongst the cinnamates, 2-ethoxyethyl-*p*-cinnamate (cinoxate) is the most frequent sensitiser; these compounds also cross-react with balsam of Peru, balsam of tolu, cinnamic aldehyde, cinnamic acid and cinnamon oil, all ingredients used in cosmetics, fragrances, toothpastes and flavourings.

Photoallergic reactions too have been reported to a variety of sunscreen chemicals, the photoallergen being apparently formed in some instances when a parent molecule undergoes chemical alteration following the absorption of radiation, usually UVA, thus resulting in the formation of an altered compound or hapten; this then presumably binds to carrier protein to form allergen. Alternatively, the photochemical alteration of an already formed protein-hapten complex by radiation absorption could probably make it allergenic. Photoallergy has been reported to 2-hydroxy-4-methoxy methylbenzophenone (Eusolex 4360, oxybenzone), benzophenone-4, isopropyl dibenzoylmethane (Eusolex 8020), butyl methoxydibenzoylmethane (PARSOL 1789) and isoamyl *p*-methoxycinnamate.

Potential absorption of sunscreen ingredients to cause carcinogenic or oestrogenic effects has also been of intermittent concern, but absorption is minimal and has not been shown to be of importance during everyday sunscreen usage.

However, despite this list of possible adverse effects from multiple ingredients, sunscreens generally are very effective without causing major problems.

Sunscreen Usage

The recommended thickness of application of a sunscreen for achievement of the quoted SPF and optimum benefit is 2 mg/cm^2 or 2 μl/cm^2, being a relatively liberal amount. However studies have shown that users generally apply much less than this recommended quantity in practical settings. Thus most have found the applied film thickness to range from 0.5 to 1 mg/cm^2, while a European study on 148 students found the median quantity to be 0.39 mg/cm^2. This leads to SPF values of around a third of the quoted value because of the reduced ingredient thickness through which the UVR passes to be attenuated. It has therefore been proposed that the methodology of testing and labelling of sunscreens might be altered to suit a more realistic consumer usage pattern; this approach has so far not been adopted however because of concerns that major consumer confusion might ensue. Further, SPF assessments for the same thickness of application may vary considerably in actual practice, and it has been suggested that the term SPF be abandoned in favour of a system referring to sunscreen protectivity as low, moderate, medium, high and very high or similar, but this has not been adopted either, given the consumer familiarity now with the SPF. In addition to inadequate application when sunscreen is applied, it is frequently not applied to all exposed areas or before sun exposure begins or reapplied after sweating or swimming, so the chances of effective use are hugely diminished. Further, sunscreen reapplication has been advised every 2–3 h, partially because of possible product photodegradation and partially the likelihood of removal in environmentally unsuitable conditions, and this still is the case for some products, but most modern sunscreens do not photodegrade and do persist for long periods on the skin, so though 2–3 hourly reapplication is still safest, more recent work by Diffey now suggests in addition that sunscreens are best first applied 15–30 min before exposure and then again 15–30 min after exposure has begun for maximal effect, in addition to the further applications thereafter mentioned above.

Clearly sunscreens are very effective if used carefully by users, but significant effort on their part is required to ensure that this is the case.

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Targeted Therapies for Melanoma 150

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Key Points

- Before the treatment of disseminated melanoma metastases, a mutational testing for BRAF and NRAS and in subgroups for c-Kit has to be performed.
- For patients with BRAF mutation, treatment with BRAF inhibitors and their combination with MEK inhibitors results in a high percentage of tumor remissions.
- New immunotherapies with blockade of the inhibiting receptors CTLA-4 and PD-1 on T lymphocytes lead to durable remissions in 15–50 % of patients with disseminated metastases of melanoma.
- In part of the patients, particularly with BRAF and probably with NRAS mutation, both therapeutic approaches can be applied.
- The best combined therapies and sequential schedules with all these new therapeutic approaches have to be investigated in the future.

General Principles

A new era of melanoma therapies began few years ago. In the past, chemotherapies and unspecific immunotherapy mainly with interferon alpha were available for metastatic melanoma and for adjuvant treatment. This situation changed, and new substances are now applied for systemic treatment of metastatic melanoma (Garbe et al. 2011). Targeted therapy with kinase inhibitors is particularly used for metastatic melanoma carrying the BRAF V600 mutation (Eigentler et al. 2013). Two specific BRAF inhibitors are currently on the market in the USA and in Europe: vemurafenib and dabrafenib. Additionally, a MEK inhibitor has been approved in the USA and will come onto the market in the near future in Europe: trametinib. Combination of specific BRAF and MEK inhibitors seems to improve the treatment outcome and seems even to decrease adverse events. Furthermore, MEK inhibitor are presently tested in patients with metastatic melanoma carrying an NRAS mutation. Several other MEK inhibitors are presently under clinical development: selumetinib, cobimetinib, binimetinib, etc. (Table 150.1).

Another important development is the targeting of lymphocytes for immunotherapy of metastatic melanoma. During the last decade, a number of activating co-stimulatory lymphocyte receptors and of inhibiting receptors have been detected and better understood in their function.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_150, © Springer-Verlag Berlin Heidelberg 2015

Table 150.1 Specific inhibitors of the MAP kinase signaling pathway, approved or in clinical trials for metastatic melanoma

Generic name	Brand name	Company	Specific inhibition	Indication	Dosage (mg/day)
Vemurafenib	Zelboraf	Roche Pharma	Mutated BRAF	Met. melanoma BRAF mutated	2×960
Dabrafenib	Tafinlar	GlaxoSmithKline	Mutated BRAF	Met. melanoma BRAF mutated	2×150
Encorafenib	–	Novartis	Mutated BRAF	Met. melanoma BRAF mutated	300–450
Trametinib	Mekinist	GlaxoSmithKline	MEK	Met. melanoma BRAF mutated; NRAS mutated?	2
Cobimetinib	–	Roche Pharma	MEK	Met. melanoma BRAF mutated; NRAS mutated?	60
Binimetinib	–	Novartis	MEK	Met. melanoma BRAF mutated; NRAS mutated?	2×45
Selumetinib (AZD6244)	–	AstraZeneca	MEK	Met. melanoma BRAF mutated; NRAS mutated?	2×75
Imatinib	Glivec	Novartis	c-Kit	Met. melanoma c-Kit mutated	1–2×400

Table 150.2 Monoclonal antibodies for immune checkpoint blockade of T lymphocytes for immunotherapy of metastatic melanoma

Generic name	Brand name	Company	Specific inhibition	Indication	Dosage, (infusions)
Ipilimumab	Yervoy	Bristol-Myers Squibb	CTLA-4	Met. melanoma	3 mg/kg, 4× every 3 weeks
Tremelimumab	–	Pfizer	CTLA-4	Met. melanoma	15 mg/kg, once every 90 days
Nivolumab (BMS-936558)	–	Bristol-Myers Squibb	PD-1	Met. melanoma	1 mg/kg, 4× every 3 weeks
Pembrolizumab	–	Merck	PD-1	Met. melanoma	10 mg/kg, every 3 weeks
BMS-936559	–	Bristol-Myers Squibb	PD-L1	Met. melanoma	10 mg/kg, every 2 weeks

Blocking the inhibiting receptors was found to be an effective and survival-prolonging strategy in melanoma treatment. An unexpected high percentage of melanoma patients seem to have developed functional immune responses to the tumor antigens which are blocked by inhibiting signals to the T lymphocytes. A blockade of the inhibiting receptors by monoclonal antibodies was suitable for releasing the functional immune responses of T cells to the tumor. This led to partial and complete responses which seemed to be durable. This strategy is not dependent on the mutational status of the melanoma patients. Currently, the most important targets are the CTLA-4 receptor and PD-1 receptor on T cells. The CTLA-4 blocking antibody ipilimumab is already on the market in Europe and in the USA, and several antibodies against PD-1 are presently tested in clinical trials (Table 150.2).

Both therapeutic approaches, blockade of the MAP kinase signaling pathway with selective kinase inhibitors and activating immunotherapies

with CTLA-4 and PD-1 blockade, will also be tested in the adjuvant setting. A large adjuvant trial with ipilimumab has already been completed in its recruitment, and trials with vemurafenib and a combination of dabrafenib and trametinib are presently ongoing.

With the introduction of kinase inhibitors into the treatment of metastatic melanoma, a substantial progress in comparison to former chemotherapeutic treatments has been achieved. However, the development of immunotherapy in metastatic melanoma is another simultaneous event which opens new treatment approaches by the use of immune checkpoint blockade (Ott et al. 2013). The combined treatment with the CTLA-4 blocking antibody ipilimumab and the PD-1 blocking antibody nivolumab resulted in more than 50 % objective responses, which seem to be durable. Therefore, immune checkpoint blockade may develop to first-line treatment in metastatic melanoma in the future, and kinase inhibitors may find its place in second- and x-line treatments.

Mutational Testing

There are several activating mutations in the mitogen-activated protein kinase (MAPK) pathway, which drive melanoma proliferation and inhibit programmed cell death.

The most commonly mutated oncogene identified to date in melanoma is BRAF (~50 %), an upstream mediator of the MAPK pathway (Davies et al. 2002; Flaherty 2006). In over 80 % of the patients, this activating mutation results from the substitution of valine by glutamic acid at amino acid 600 (V600E mutation) with most of the remainder consisting of an alternate substitution (lysine for valine) at the V600 locus (V–K) (Satyamoorthy et al. 2003). Increased activation of the MAPK pathway is implicated in melanoma tumor genesis and is enhanced in advanced-stage melanoma. Generally, BRAF-mutated melanomas occur in younger-aged patients, on skin without signs of solar damage, and affect less frequently the head and neck area. Therefore BRAF-mutated melanomas seem to arise early in life at low cumulative UV doses, whereas melanomas without

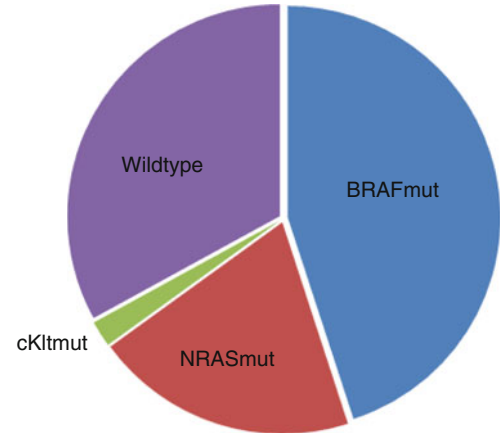

Fig. 150.1 Frequency of mutations in metastatic melanoma

BRAF mutations seem to require accumulation of high UV doses over time (Bauer et al. 2011).

Another 15–20 % of all melanomas harbor activating NRAS mutations. The most common oncogenic change with >80 % of all NRAS mutations is a point mutation leading to the substitution of glutamine by leucine at position 61. Mutations at positions 12 and 13 occur less frequently. NRAS mutations at position 61 are associated with impaired GTPase activity and the locking of the NRAS protein in its activated conformation (Bos 1989). Generally, BRAF and NRAS mutations are mutually exclusive.

Activating c-Kit (CD117) mutations are found in not more than 1–2 % of melanoma patients, mainly in acral and mucosal melanoma subtypes, with a frequency of 5–10 % in these subtypes. c-Kit is a receptor tyrosine kinase on the cell surface, which is naturally activated by binding of stem cell factor and then activates the MAPK and other pathways. Inhibiting molecules for c-Kit are available (Fig. 150.1).

BRAF Kinase Inhibitors

Vemurafenib

Vemurafenib is an inhibitor of the oncogenic V600E mutant BRAF kinase, which has been approved for unresectable advanced melanoma in

the USA and Europe. In a phase II trial (BRIM-2) evaluating 132 patients with metastatic melanoma carrying a BRAF V600 mutation, the confirmed overall response rate was 53 % (Sosman et al. 2012). Median duration of response was 6.7 months, the median progression-free survival was 6.8 months, and the median overall survival was 15.9 months. Results from the phase III registration trial (BRIM-3) were published in 2011 (Chapman et al. 2011). Six hundred seventy-five patients were randomly assigned to vemurafenib (960 mg p.o. bid) or dacarbazine (1,000/m^2 i.v. every 3 weeks). At 6 months, overall survival was superior in the vemurafenib group in contrast to the dacarbazine group (84 % vs. 64 %). The hazard ratio (HR) for death in the vemurafenib group was 0.37 ($p<0.001$). Response rates were 48 % for the vemurafenib and 5 % for the dacarbazine treatment arm. In an updated analysis, median overall survival rates for vemurafenib- and DTIC-treated patients were 13.2 and 9.6 months, respectively. In the BRIM-3 trial, a crossover from DTIC to vemurafenib was allowed after progression, and, therefore, the OS >9 months in the chemotherapy arm is rather high.

Vemurafenib has multiple adverse reactions. To the common adverse reactions, occurring in about 30 % of patients, belong skin rashes, photosensitivity reactions, joint pain, fatigue, nausea, alopecia, and pruritus. In addition, about one-fourth of patients develop cutaneous squamous cell carcinoma (SCC) mainly from the keratoacanthoma subtype, which can be successfully removed surgically. So far, no development of metastasis from this SCC has been described. Additionally, the development of second primary melanomas was observed in some patients. The toxicity is well manageable and less severe as compared to most chemotherapeutic treatments.

Dabrafenib

The BRAF inhibitor dabrafenib was likewise tested in clinical trials. For dabrafenib a clinical objective response rate of 66 % has been reported in V600-mutant melanoma patients treated with >150 mg two times daily (bid) (Ascierto et al. 2013a). Data from a registration phase III trial comparing dabrafenib and dacarbazine have led to its approval in the USA and in Europe (Hauschild et al. 2012). In this trial, 250 BRAF (V600E) patients were randomly assigned to receive either dabrafenib 150 mg twice daily p.o. (187 patients) or dacarbazine 1,000/m^2 i.v. every 3 weeks (63 patients). Median progression-free survival was 5.1 months for dabrafenib and 2.7 months for dacarbazine (HR, 0.30; $p<0.0001$).

In another multicenter, open-label, phase II trial for patients with V600E or V600K BRAF-mutant melanoma metastatic to the brain, 172 patients with at least one asymptomatic brain metastasis ($\geq$5 and $\leq$40 mm in diameter) were enrolled to receive 150 mg oral dabrafenib bid until disease progression, death, or unacceptable adverse events (Long et al. 2012). The primary end point was the proportion of patients with Val600Glu BRAF-mutant melanoma who achieved an overall intracranial response, which was defined as a complete response or partial response. An objective intracranial response was achieved in 29 (39.2 %) of 74 patients with V600E BRAF-mutant melanoma previously untreated, as was observed in 20 (30.8 %) of 65 of the pretreated patients. This opens a new perspective for the treatment of brain metastasis in advanced melanoma, where nearly no treatment options exist.

The spectrum of adverse reactions of dabrafenib is similar to that of vemurafenib. Common side effects include pyrexia, skin rashes, joint pain, fatigue, nausea, alopecia, and pruritus. Likewise, about 10 % of patients develop cutaneous squamous cell carcinoma (SCC) mainly from the keratoacanthoma subtype. A possible difference is a lower phototoxicity rate, which was ~3 % with dabrafenib versus ~30 % with vemurafenib according to the phase III trials.

Encorafenib

No clinical data have been published on encorafenib so far except initial results from a phase I, open-label, dose-escalation study reported at ASCO 2013. It is a potent and selective RAF

kinase inhibitor with little activity against wild-type BRAF (Huang et al. 2013). encorafenib did not suppress the growth of >400 cell lines expressing wild-type BRAF. Encorafenib treatment at oral doses as low as 6 mg/kg in human melanoma xenograft models resulted in strong MAPK pathway blockade.

MEK Kinase Inhibitors

Trametinib

The MEK inhibitor trametinib was approved in May 2013 for treatment of unresectable advanced melanoma in the USA, and approval in Europe is expected soon. First clinical results have been reported for trametinib in 20 patients with BRAF-mutant melanoma showing six partial responses and two complete responses (40 % OR) and were presented at the ASCO meeting 2010. Interestingly, two partial responses have likewise been observed in 22 BRAF wild-type melanoma patients (Infante et al. 2012). In 2012, data of the phase III registration study (METRIC) have been published (Flaherty et al. 2012a). In this trial 322 patients with a V600K/E BRAF mutation were randomly assigned to receive either trametinib (2 mg p.o. daily) or chemotherapy (dacarbazine 1,000/m^2 i.v. every 3 weeks or paclitaxel 175 mg/m^2 i.v. every 3 weeks) in a 2:1 ratio. A crossover to the trametinib arm was permitted for patients who were progressive in the chemotherapy arm. Median progression-free survival was 4.8 months in the trametinib arm versus 1.5 months for the chemotherapy arm (HR for disease progression or death, 0.45; $p<0.001$). The 6-month overall survival was 81 % in the trametinib group compared to 67 % in the chemotherapy group despite crossover (HR for death, 0.54; $p=0.01$). These data show the clear superiority of trametinib versus monochemotherapy; however, the efficacy of MEK inhibition seems to be below BRAF inhibition.

Trametinib has a broad spectrum of adverse reactions. Most commonly found (greater than or equal to 10 % of any grade) in patients receiving trametinib were rash, diarrhea, lymphedema (swelling of the face, arms, or legs), acne-like rash, stomatitis (mouth sores), hypertension (new or worsening high blood pressure), abdominal pain, hemorrhage (bleeding), dry skin, pruritis (itching), and paronychia (nail infection). A decreased ejection fraction or ventricular dysfunction was observed in 7 % of patients. Ocular events (mostly grade 1 or 2) occurred in 9 % of patients. No cutaneous squamous cell carcinomas were diagnosed under trametinib.

Selumetinib

Selumetinib (AZD6244, ARRY-142886) is a potent inhibitor of MEK1/2 kinase (Davies et al. 2007). First results of selumetinib antitumor activity were presented at the ASCO 2008 annual meeting, indicating partial responses in mainly BRAF-mutated patients (Kirkwood et al. 2012). Recently, data of a double-blind, randomized, placebo-controlled phase II study investigating selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment was published (Robert et al. 2013). Patients were randomly assigned 1:1 to take either oral selumetinib (75 mg bid in a 21-day cycle) or placebo; all patients received dacarbazine (1,000 mg/m^2 on day 1 of a 21-day cycle) intravenously. The primary end point was overall survival analyzed by intention to treat. Ninety-one patients were randomly assigned to receive dacarbazine in combination with selumetinib ($n=45$) or placebo ($n=46$). Overall survival did not differ significantly between groups (median, 13.9 months in the selumetinib plus dacarbazine group and 10.5 months in the placebo plus dacarbazine group; HR, 0.93). However, progression-free survival was significantly improved in the selumetinib plus dacarbazine group versus the placebo plus dacarbazine group (HR, 0.63, one sided; $p=0.021$), with a median of 5.6 months versus 3.0 months, respectively (Robert et al. 2013).

The spectrum of adverse reactions shows some differences in comparison to trametinib. Most frequently nausea was observed in 64 % of patients, followed by acneiform dermatitis in

52 %, diarrhea in 48 %, vomiting in 48 %, and peripheral edema in 43 %. The most common grade 3–4 adverse event was neutropenia in 14 % of patients. Dysgeusia, mucositis, and flatulence have likewise been observed less frequently.

Binimetinib

Data of a phase II clinical trial of binimetinib, a small-molecule MEK1/2 inhibitor, in patients with NRAS-mutated or V600 BRAF-mutated advanced melanoma were published in 2013 (Ascierto et al. 2013b). Three different arms were evaluated: binimetinib 45 mg bid for NRAS-mutated and BRAF-mutated melanoma and binimetinib 60 mg bid for BRAF-mutated melanoma. The primary end point was the proportion of patients who achieved an objective response (CR or PR). Unfortunately only data of the 45 mg groups were reported. Seventy-one patients who received at least one dose of binimetinib 45 mg were evaluated. Median follow-up was 3.3 months. Six of 30 patients with NRAS-mutated melanoma (20 %) achieved a partial response as did 8 (20 %) of 41 patients with BRAF-mutated melanoma. No complete response was detected.

In the trial reported above, at 45 mg bid, binimetinib showed a good safety profile with manageable toxicity. Acneiform dermatitis and diarrhea were the most frequent adverse events as grade 1–2. Ocular toxicity impacted in 18 %, as grade 1–2, and it was reversible without interruption of treatment in the majority of patients. No cardiac adverse event was observed in this study.

Combination of BRAF Kinase Inhibitors and MEK Kinase Inhibitors

Flaherty et al. reported about results from their phase I and phase II trials of a combined treatment with dabrafenib (BRAF kinase inhibitor) and trametinib (MEK kinase inhibitor) (Flaherty et al. 2012b). Two hundred forty-seven patients suffering from BRAF V600-mutant metastatic melanoma were included. Eighty-five patients received dabrafenib (75 or 150 mg bid) and trametinib (1, 1.5, or 2 mg daily). One hundred sixty-two patients were then randomly assigned to receive combination therapy with dabrafenib (150 mg) plus trametinib (1 or 2 mg) or dabrafenib monotherapy. Median progression-free survival for patients treated with the combination of 150 mg dabrafenib and 2 mg trametinib was 9.4 months, as compared with 5.8 months in patients treated with dabrafenib alone (HR, 0.39; $p<0.001$). The rate of complete or partial responses in the cohort treated with 150 mg dabrafenib and 2 mg trametinib was 76 %, as compared with 54 % in patients with dabrafenib alone ($p=0.03$).

Most frequent adverse reactions in the subgroup treated with highest dosages were pyrexia in 71 % and chills in 58 %. Other adverse reactions more common in the combination group than in the monotherapy group included fatigue in 53 % of patients, nausea in 44 %, vomiting in 40 %, and diarrhea in 36 %, in the broad majority of grade 1 or 2. Most frequently occurring grade 3 or 4 adverse reactions were neutropenia in 11 % of patients. The incidence of cutaneous squamous cell carcinoma (including keratoacanthomas) was clearly reduced in the combination arms with 2–7 % as compared to the monotherapy arm with 19 %. Also the rates of rash in the combination 150/1 and 150/2 groups were lower than the rate in the monotherapy group (20 % and 27 %, respectively, vs. 36 %).

Adjuvant Treatment with BRAF Kinase Inhibitors and MEK Kinase Inhibitors

It is an interesting question whether potential future uses of kinase inhibitors in an earlier phase of melanoma progression such as in the adjuvant setting will be more effective than therapy in unresectable advanced melanoma. There are presently no data in regard to this question, but there are already phase III clinical trials on the way. The BRIM-8 adjuvant vemurafenib study is ongoing, and patients with stage III disease and complete tumor resection are eligible. A phase III

adjuvant trial with the combination of dabrafenib and trametinib (COMBI-AD) has also recently started. Currently it remains a speculation as to whether the use of kinase inhibitors will improve overall survival for earlier-stage patients or only extend progression-free survival.

Mechanisms of Resistance to BRAF and MEK Inhibition

A major challenge for the clinician is the development of resistance to BRAF kinase and MEK kinase inhibitors. Numerous mechanisms have already been described. One major mechanism is the reactivation of the MAPK pathway through amplification of mutant BRAF or truncations in the BRAF protein through alternate splicing resulting in an increased dimerization and kinase activity (Poulikakos et al. 2011; Shi et al. 2012). Additionally, secondary mutations in NRAS and MEK have been described in patients with BRAF inhibitor treatment (Nazarian et al. 2010). Another reported mechanism is the overexpression of Cancer Osaka thyroid (COT) kinase, which activates ERK through MEK-dependent mechanisms not depending on RAF signaling. Even if BRAF kinase inhibitors sufficiently block the MAPK pathway, expression or activation of PDGFR-β or IGF1R can induce oncogenic signaling through the PI3K-AKT-mTOR pathway (Shi et al. 2012). One treatment strategy focuses on the combination of BRAF kinase inhibitors and MEK kinase inhibitors significantly prolonging the time period to the development of resistance and tumor progression (Flaherty et al. 2012b).

KIT Inhibitors

Imatinib

A minority of melanomas arising from acral, mucosal, and chronically sun-damaged locations harbor activating mutations and amplification of the type III transmembrane receptor tyrosine kinase KIT. The KIT inhibitor imatinib mesylate is approved and well established in other cancers such as gastrointestinal stromal tumors (GIST) and dermatofibrosarcoma protuberans. In a phase II trial by Carvajal and colleagues, 295 patients with melanoma were screened for the presence of KIT mutations and amplification (Carvajal et al. 2011). A total of 51 patients were identified, and 28 of these were treated with imatinib mesylate 400 mg orally bid. Two complete responses and two durable and two transient partial responses among 25 evaluable patients were observed. Overall durable response rate was 16 %, median time to progression 12 weeks, and median overall survival 46.3 weeks. Response rate was superior in cases with mutations affecting recurrent hot spots or with a mutant to wild-type allelic ratio of more than 1, indicating positive selection for the mutated allele. A recent study of Hodi et al. led to a clarification of the presence of mutations or amplifications only: objective responses were statistically significantly different by mutation status (7 of 13 or 54 % KIT mutated, 0 of 11 KIT amplified only) (Hodi et al. 2013).

In another phase II trial, 43 patients with metastatic melanoma harboring c-Kit mutations and amplification were enrolled (Guo et al. 2011). Patients received imatinib mesylate 400 mg daily unless intolerable toxicities or disease progression occurred. Fifteen patients who experienced progression of disease were allowed to escalate the dosage to 800 mg daily. Median progression-free survival was 3.5 months; the 6-month PFS rate was 36.6 %. Ten patients (23.3 %) and 13 patients (30.2 %) achieved partial response and stable disease, respectively. Nine of the ten patients with partial responses had mutations in exons 11 or 13. One-year overall survival rate was 51 %.

Most frequently, hematologic toxicities have been observed, anemia in 61 % of patients and leukopenia in 31 % (Carvajal et al. 2011). In ~50 % of patients, fatigue, nausea, periorbital edema, and cutaneous rashes have been reported. In more than 20 % of patients, edema of the lower extremities, diarrhea, vomiting, and pruritus occurred. As known from long-term treatments in chronic myeloid leukemia, the toxicity is on an average rather mild, and the drug is well tolerated also for years.

Antibody Blockade of Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4)

Full T-cell activation requires stimulation through the T-cell receptor as well as a co-stimulatory signal provided by the binding of B7 on the antigen-presenting cell (e.g., dendritic cell) to CD28 on the T cell. Cytotoxic T-lymphocyte-associated antigen-4 is a homologue of CD28 and is an inhibitory T-cell receptor that is upregulated following T-cell activation (Ascierto et al. 2011). The normal function of CTLA-4 is to compete with CD28 to bind B7 in order to downregulate T-cell activation, acting as a natural "brake" by removing the co-stimulatory signal. The CTLA-4-B7 interaction can be blocked with an anti-CTLA-4 monoclonal antibody (mAb), which has a higher affinity for CTLA-4 than B7. Thus, the inhibitory signal is prevented and the "brake" on T-cell activation released. Phase III trials have been completed with two fully human anti-CTLA-4 mAbs: ipilimumab (MDX-010, Bristol-Myers Squibb) and tremelimumab (CP-675,206, Pfizer).

Ipilimumab

Two phase III trials have been conducted with ipilimumab which led to the approval of this drug for unresectable metastatic melanoma in the USA and in Europe. In a first trial, ipilimumab was compared to a cancer vaccine based on HLA-A*0201-restricted peptides deriving from the melanosomal protein glycoprotein 100 (gp100). Altogether, 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma received ipilimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136) (3:1:1 ratio randomization) (Hodi et al. 2010). Ipilimumab was administered at a dose of 3 mg/kg of body weight with or without gp100 every 3 weeks for up to four treatments (induction phase). Some patients could receive a re-induction therapy. The median overall survival was 10.0 months for patients receiving ipilimumab plus gp100 and 10.1 months for patients receiving ipilimumab alone versus 6.4 months for patients receiving gp100 alone (hazard ratio for death, 0.68 and 0.66, respectively; $p < 0.003$). The overall response rate was 11 % in the ipilimumab alone arm and 1.5 % in the gp100 alone arm. Survival rates at 24 months were 23 % in the ipilimumab alone group and 13.7 % in the gp100 alone group. Grade 3 or 4 immune-related adverse events occurred in 10–15 % of patients treated with ipilimumab and in 3 % treated with gp100 alone.

A second phase III trial compared ipilimumab plus dacarbazine with dacarbazine alone. A total of 502 patients with unresectable metastatic melanoma were randomized in a 1:1 ratio, to ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m^2 of body surface area) or dacarbazine (850 mg/m^2) plus placebo (Robert et al. 2011). This was administered at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks until week 22. Patients with stable disease or an objective response and no dose-limiting toxic effects received ipilimumab or placebo every 12 weeks thereafter as maintenance therapy. Overall survival was 11 months in the group receiving ipilimumab plus dacarbazine and 9.1 months in the group receiving dacarbazine plus placebo (hazard ratio for death, 0.72; $p < 0.001$). Survival rates were higher in the ipilimumab-dacarbazine group at 1 year with 47.3 % versus 36.3 %, at 2 years with 28.5 % versus 17.9 %, and at 3 years with 20.8 % versus 12.2 %. Best overall response rate was 5.2 % in the ipilimumab plus dacarbazine arm and 10.3 % in the dacarbazine plus placebo arm. Grade 3 or 4 adverse events occurred in 56.3 % of patients treated with ipilimumab plus dacarbazine, as compared with 27.5 % treated with dacarbazine and placebo ($p < 0.001$). Taken together, both studies demonstrated an about 10 % survival advantage for patients treated with ipilimumab which was durable over several years (McDermott et al. 2013).

Drug-related adverse events were frequent and occurred in 80 % of patients treated with ipilimumab alone. Most frequent were fatigue, diarrhea, and nausea followed by vomiting, constipation, abdominal pain, pyrexia, headache, cough, dyspnea, and anemia. Pruritus and skin rashes occurred in more than 20 % of patients.

Diarrhea as immune-related event was observed in 27 % of patients and colitis in 8 % of patients. Furthermore, endocrine toxicity was observed in 8 % of patients comprising hypothyroidism, hypopituitarism, hypophysitis, and adrenal insufficiency.

Tremelimumab

Two phase II studies with tremelimumab have been conducted in unresectable metastatic melanoma (Camacho et al. 2009; Kirkwood et al. 2010). Based on these phase II studies, a treatment regimen with 15 mg/kg every 90 days was chosen for further evaluation. In a phase III trial, patients with treatment-naive unresectable stage III or IV melanoma were randomly assigned to treatment with tremelimumab (15 mg/kg once every 90 days) or physician's choice of standard-of-care chemotherapy (temozolomide or dacarbazine) (Ribas et al. 2013). A total of 655 patients were enrolled in this study. The trial was prematurely stopped because the prespecified futility boundary was crossed at second interim analysis after 340 deaths. At final analysis the median OS was 12.6 months for tremelimumab and 10.7 months for chemotherapy (hazard ratio, 0.88; $p=0.127$). Objective response rates were similar in both arms: 10.7 % in the tremelimumab arm and 9.8 % in the chemotherapy arm. However, the response duration was significantly longer after tremelimumab (35.8 vs. 13.7 months; $p=0.0011$). Diarrhea, pruritus, rash, and endocrine toxicities were the most common treatment-related adverse events in the tremelimumab arm. This phase III study failed to demonstrate a significant survival advantage for the treatment with tremelimumab in comparison to standard-of-care chemotherapy. A possible explanation may be the treatment schedule with administration of the drug only every 90 days. The elimination half-lives of tremelimumab and ipilimumab are 25.6 and 14.7 days, respectively (Wilson and Kotb 2013). Ipilimumab had been administered every 21 days.

Toxicities of tremelimumab are similar to those of ipilimumab. Most frequently observed were diarrhea and colitis (51 %), nausea (34 %), fatigue (33 %), cutaneous rash (33 %), pruritus (31 %), vomiting (23 %), and decreased appetite. Endocrine disorders have likewise been observed.

Antibody Blockade of Programmed Death-1 (PD-1)

The programmed death-1 receptor (PD-1) is similar to CTLA-4, an inhibitory T-cell receptor. It is activated by two known ligands, PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). Both ligands are predominately expressed on the tumor and the tumor microenvironment. As for PD-1 the immune suppressive signals are predominately delivered by the cancer; it is likely that PD-1 blockade will have greater antitumor activity and fewer side effects than CTLA-4 inhibition (Ribas 2012).

Nivolumab

Presently several phase III trials in unresectable malignant melanoma are conducted in order to evaluate the efficacy and safety of nivolumab. So far, results have been published from a phase II trial in advanced melanoma, non-small cell lung cancer, castration-resistant prostate cancer, renal cell cancer, and colorectal cancer. In this study, the anti-PD-1 antibody nivolumab (BMS-936558) was administered at the dose of 0.1–10.0 mg/kg of body weight every 2 weeks. Patients received up to 12 cycles until disease progression or a complete response occurred. A total of 296 patients were enrolled and response evaluation was possible for a total of 236 patients. The objective response rate in melanoma patients was 28 % (26 of 94 patients). Similar response rates have been observed in renal cell cancer and non-small cell lung cancer. Interestingly, in 17 patients with PD-L1 negative tumors, no objective responses were assessed, whereas 9 of 25 patients with PD-L1 positive tumors (36 %) showed an objective response.

Grade 3 or 4 drug-related adverse events were observed in 14 % of patients, and three deaths from pulmonary toxicity have been observed.

Toxicity under the highest dosage of 10.0 mg/kg was observed in 38 % of patients. Diarrhea was the most frequent adverse event (9 %) followed by rash (8 %) and pruritus (7 %). Four percent of patients developed a pneumonitis. Endocrine disorders were observed in 2 % of patients.

Pembrolizumab

Presently, several phase III trials with pembrolizumab are conducted in unresectable metastatic melanoma. So far, a phase II trial was reported with pembrolizumab. In this trial pembrolizumab was administered intravenously at a dose of 10 mg/kg of body weight over 2 or 3 weeks or 2 mg/kg every 3 weeks (Hamid et al. 2013). A part of these patients had received a prior treatment with ipilimumab; another part had not. A total of 135 patients with advanced melanoma were enrolled in the trial. The confirmed response rate was 38 %, with the highest confirmed response rate in the cohort that received 10 mg/kg every 2 weeks (ORR 52 %). There were no significant differences between patients who had received prior ipilimumab and those who had not. The median follow-up time was 11 months, and at this time point 81 % of patients who had a response were still stable and continued receiving treatment. These results show that the objective response rate is clearly higher as compared to ipilimumab and that most of these responses seem to be durable.

Common adverse events were fatigue (30 %), rash and pruritus (21 %), diarrhea (20 %), myalgia (12 %), headache (10 %), asthenia (10 %), hypothyroidism (8 %), pyrexia (7 %), and dyspnea and pneumonitis (4 %).

BMS-936559

BMS-936559 is an anti-PD-L1 antibody; this means it is directed to the ligand of PD-1. Only a phase I trial has been published so far in advanced metastatic melanoma with BMS-936559. In this multicenter phase I trial, anti-PD-L1 antibody was administered at escalating doses ranging from 0.3 to 10 mg/kg of body weight every 14 days in 6-week cycles for up to 16 cycles (Brahmer et al. 2012). A total of 207 patients have been enrolled in this trial with multiple solid cancers. Among them were 55 patients with metastatic melanoma. An objective response was observed in 9 of 52 patients with melanoma (18 %). The responses were durable.

Toxicity was mild and in infusion-related reactions was most frequently observed (10 %), followed by diarrhea (9 %), cutaneous rashes (7 %), pruritus (6 %), and hypothyroidism (3 %).

Combination of CTLA-4 Antibodies and PD-1 Antibodies

One phase I trial of nivolumab combined with ipilimumab in patients with advanced melanoma has been published to date. Intravenous doses of nivolumab and ipilimumab were administered in patients every 3 weeks for four doses, followed by nivolumab alone every 3 weeks for four doses (concurrent regimen). The combined treatment was subsequently administered every 12 weeks for up to eight doses. A total of 53 patients received concurrent therapy with nivolumab and ipilimumab. The objective response rate for all patients in the concurrent-regimen group was 40 %. Evidence of clinical activity (OR + SD) was observed in 65 % of patients. At the maximum doses (nivolumab at a dose of 1 mg/kg and ipilimumab at a dose of 3 mg/kg), 53 % of patients had an objective response, all with tumor reduction of 80 % or more.

Grade 3 or 4 adverse events related to therapy occurred in 53 % of patients in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible.

Prospects

Both the introduction of selective kinase inhibitors and the blockade of immune checkpoints on T cells in melanoma patients are major progresses in melanoma treatment. With the introduction of BRAF kinase inhibitors and MEK kinase inhibitors during the last years, treatment for advanced melanoma changed dramatically. For patients

with a BRAF mutation, the objective response rate increased to 50 % and more, and the progression-free survival and overall survival are significantly prolonged. A major problem is the development of resistance to the kinase inhibitors through multiple different mechanisms.

Dramatic progress developed in the immunotherapy of melanoma with the immune checkpoint blockade in T lymphocytes involving CTLA-4 and PD-1 receptor antibodies. Likewise response rates around 50 % were achieved with these new immunotherapies, which was quite unexpected for the immune approach. The blockade of inhibitory receptors on T cells showed that many patients have functional T-cell responses against tumor antigens but that these were inhibited by different mechanisms. Seemingly the tumor responses induced by immunotherapy are rather durable and are lasting with ipilimumab in some patients already 5 years and longer. Probably we will see cures in metastatic melanoma in an unknown percentage of patients in the future.

Combined therapies and sequential schedules are currently under evaluation. Several authors feel that beginning with immunotherapy would be the best option for melanoma patients (Ascierto et al. 2012). Antibodies for checkpoint blockade can be administered without consideration of the mutational status of the tumor and may also make kinase inhibitor therapies dispensable. The combined use of both or the administration of kinase inhibitors directly after the immune therapy may be associated with unexpected high toxicity (Harding et al. 2012). Combinations and sequences will be evaluated in many different clinical trials in the future.

In conclusion, selective kinase inhibitors and immune checkpoint blockade have completely changed the therapy of unresectable metastatic melanoma, and cures of patients with metastatic melanoma will come into reach in the near future.

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Topical Anaesthetics

151

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Key Points

- Topical anaesthetics are used to decrease the pain associated with superficial dermatological, aesthetic, and laser procedures.
- Topical anaesthetics act on sodium channels in the nerve membranes.
- EMLA is the only topical anaesthetic registered for use in children from the age of 3 months.
- It is important to take into account the maximum recommended dose, application area, and application time by age and weight, when using topical anaesthetics.
- Factors that should be considered to reduce the risk of adverse effects associated with the use of topical anaesthetics include the amount of product used, body location, size of the surface area, and duration of product application.

History

The Incas derived a substance from the plant *Erythroxylum coca*, 'coca', and discovered anaesthetic and stimulatory properties. In 1860, Niemann isolated cocaine, the plant's active ingredient. In 1884, Karl Koller demonstrated that general anaesthesia could be avoided for ophthalmic procedures by the application of cocaine to the conjunctiva. In the early twentieth century, ester anaesthetics, such as procaine and tetracaine, were created. These were noted to result in high rates of allergic contact dermatitis. In 1943, Löfgren synthesised the first amide anaesthetic, lidocaine. Subsequently, a large number of topical formulations of esters, amides, and adrenalines have been developed and used for dermatological procedures.

General Principles: Classification and Structure

A local anaesthetic cream consists of hydrophilic groups, usually a tertiary amine, and hydrophobic groups, generally an aromatic residue. These groups are separated by an alkyl chain. They may be separated into two groups: those containing an ester linkage (e.g. procaine, tetracaine, cocaine) and those containing an amide linkage (e.g. lidocaine and prilocaine). The linkage is responsible for the pathway by which the molecule is metabolised and excreted. Ester and amide anaesthetics

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_151, © Springer-Verlag Berlin Heidelberg 2015

differ in their chemical stability and metabolism. Esters are hydrolyzed by plasma cholinesterases and form para-aminobenzoic acid, a common allergen. Amides tend to be more stable and less allergenic and are metabolised in the liver by microsomal enzymes. Mucosal surfaces are penetrated more easily than a keratinised (skin) surface because of the absence of a stratum corneum.

Topical anaesthetics exist in many different preparations and vehicles for delivery. Only after traversing the superficial layers of the skin and affecting the nerve endings within the dermis the topical anaesthetics will be effective. For optimising the percutaneous absorption of topically applied drugs, different strategies are utilised in formulations. The first strategy is using a vehicle or device which maximises drug delivery into the skin without affecting the physiochemical properties of stratum corneum, and the second is using penetration enhancers. Occlusion is a physical method utilised to enhance the permeation of the anaesthetic through the skin.

Eutectic mixtures permit higher concentrations of anaesthetic to be used safely and facilitate application to the skin. Liposomal encapsulation is another vehicle that facilitates percutaneous drug delivery. Liposomes are microscopic, spherical, phospholipid-based carriers. These carriers deliver a greater concentration of local anaesthetic to sensory nerves than other conventional formulations with lower lipophilicity.

Mechanism of Action

Local anaesthetics act on sodium channels in the nerve membranes. The conduction is decreased via interaction with specific binding sites, and total inhibition of conduction is achieved with increasing concentration of the local anaesthetic.

Drugs

Local anaesthetics play a useful role in simple or superficial interventions.

Lesions can be frozen by refrigerants such as ethyl chloride spray. The same effect may be achieved with liquid nitrogen, but its lower temperature may cause greater post-operative discomfort. Local anaesthetics are generally ineffective when applied to intact human skin because they are poorly absorbed.

Lidocaine has a rapid onset and intermediate duration of action. Prilocaine has a slower onset of action but a longer duration of action than lidocaine.

EMLA is a topical anaesthetic cream developed by Broberg and Evers for use on intact skin. The acronym EMLA stands for Eutectic Mixture of Local Anaesthetics. EMLA is a mixture of lidocaine 25 mg/g and prilocaine 25 mg/g. EMLA is composed of the following ingredients: lidocaine 25 mg, prilocaine 25 mg, Arlatone 289 (emulgent), Carbopol 934 (thickener), and distilled water in 1 ml cream.

The lidocaine/tetracaine patch (lidocaine 70 mg/tetracaine 70 mg, Synera™, known in Europe as Rapydan™) is a novel drug delivery system designed to warm the skin and enhance the delivery of local anaesthetics through the skin. The patch contains a small amount of topical anaesthetic under a patented heating element that raises the temperature to 40 °C for longer than 14 h and enhances delivery of the anaesthetic. The heating system portion of the patch is activated through an exothermic reaction when oxygen interacts with the internal components of iron powder, activated carbon, wood flour, sodium chloride, and water. When the patch is applied to the skin, it increases the skin temperature by approximately 5 °C, but the maximum skin temperature produced by the patch at the site of application does not exceed 40 °C. The product manufacturer states that the patch should be placed on intact skin 30 min before superficial dermatological procedures such as a shave biopsy. The safety and effectiveness of this patch have been established in patients 3 years or older. In a double-blind study in 82 healthy adult volunteers, the lidocaine/tetracaine patch provided effective anaesthesia before a vascular access procedure, with an application time as short as 10 min, and was better than lidocaine/prilocaine cream at all application times shorter than 60 min, demonstrating a substantial improvement in time to onset of anaesthesia. In a prospective, randomised, single-blinded, and monocentre study in 200 children aged 3–13 years, the Synera/Rapydan

patch led to superior analgesia during venous puncture than the EMLA patch after a contact time of 35 min.

Local Anaesthetics That Are Used

- Amethocaine patch
- EMLA (Eutectic Mixture of Local Anaesthetics), a mixture of lidocaine 25 mg/g and prilocaine 25 mg/g
- Ethyl chloride spray
- Lidocaine gel
- Lidocaine gel 10 % glycyrrhetinic acid monohemiphthalate disodium (absorption promoter)
- Lidocaine adrenaline tetracaine (LAT) gel
- Lidocaine 15 % and prilocaine 5 % ointment
- Lidocaine 23 % and tetracaine 7 % ointment
- Lidocaine 7 % and tetracaine7 % patch (heated) (Synera™)
- Liquid nitrogen
- Tetracaine adrenaline cocaine (TAC) gel
  Tetracaine cream

Adverse Effects

By using topical anaesthetics, a risk of systemic toxicity should be a concern. Some reasons for inducing systemic toxicity are use of excessive amounts of topical anaesthetics, covering of a large surface area with anaesthetic, occlusion, treated area (mucosal surfaces?), long duration of application, inadequate skin barrier function, and impaired hepatic or renal function. Lidocaine has dose-dependent central nervous system toxicity. An overdose of prilocaine can cause methaemoglobinaemia.

Dermatological Indications of Eutectic Mixture of Local Anaesthetics (EMLA), a Mixture of Lidocaine 25 mg/g and Prilocaine 25 mg/g

EMLA will produce effective analgesia in the skin prior to a variety of superficial skin interventions. Ethyl chloride spray (ECS) has caused more local irritation in a study in which the analgesic and local tolerance of EMLA and ECS before intravenous cannulation in premedicated children were compared.

Several more local anaesthetics are available and have been evaluated. For example, 10 % lidocaine gel containing glycyrrhetinic acid monohemiphthalate disodium as an absorption promoter has reduced the pain upon venous cannulation in adults and in children, although further improvement seemed necessary in order to achieve ideal conditions.

Tetracaine adrenaline cocaine (TAC) gel has been effective in laceration repair, but serious adverse reactions have been reported. Lidocaine adrenaline tetracaine (LAT) gel has worked as well as TAC gel for topical anaesthesia in facial and scalp lacerations in a randomised double-blind study in 95 children aged 5–17 years, but additional studies on its safety have to be done.

Amethocaine in the form of a self-adhesive patch has been evaluated in an open study in children before venous cannulation. A satisfactory anaesthesia was achieved in 80 % of the patients, but 20 % of the patients felt moderate to severe pain.

EMLA cream has been compared with a 4 % tetracaine-containing cream for preventing venipuncture-induced pain in children. It was reported that EMLA reduced the pain more effectively.

EMLA used with glyceryl trinitrate (GTN) ointment which promotes venous dilatation has been found to make intravenous cannulation in adults technically easier. However, adverse effects of GTN include headaches and hypotension. Further studies will be necessary, especially in children, for establishing the efficacy and the safety of this combination.

EMLA is the only topical anaesthetic registered for use in children from the age of 3 months. Studies in neonates indicated that EMLA has also been safely used in neonates. EMLA is approved for anaesthesia of healthy skin in children of 0–3 months, an age range in which it used to be contraindicated. Several studies proved that the use of EMLA cream in neonates is safe when used once a day. Based on available clinical data on the use of EMLA in neonates, infants, and children, maximum dosage recommendations were made (Table 151.2).

EMLA

At present, we prefer to use EMLA for inducing local anaesthesia for superficial interventions in children. Indications for EMLA cream are discussed in the following section.

We have evaluated the efficacy and minimal effective application time for EMLA cream for the removal of mollusca contagiosa in children. Eighty-three children aged 4–12 years, scheduled for curettage of at least five molluscum contagiosum lesions, participated in a double-blind, time (15, 30, and 60 min) response study. The pain was assessed by the children and the physician as none, slight, moderate, or severe. In addition, the children rated the pain on a Visual Analogue Scale (VAS). EMLA effectively prevented the pain for all three application times ($P<0.01$). The proportion of children reporting no pain on the verbal scale increased from 36 % in the 15 min group to 61 % in the 60 min group.

EMLA and Skin Biopsy

It is important to achieve analgesia up to a sufficient skin depth for taking skin biopsies. The maximum depth of analgesia provided by EMLA is about 5 mm. There are controversial reports on the efficacy of EMLA for taking biopsy. We have conducted a double-blind, placebo-controlled study to investigate the analgesic effect of the EMLA patch as a premedication for skin biopsy in 63 children. There were two parallel groups. One group received an EMLA patch and the other placebo on the skin at the site of the biopsy for 60 min. After removal of the patch, the physician infiltrated the skin as usual with 1 ml lidocaine and took the biopsy with a 4 mm biopsy punch. EMLA was significantly more effective in decreasing the pain at the injection site of the lidocaine infiltration. There was no difference in the pain scores for the biopsy.

Other Indications for EMLA

Only the most relevant ones are mentioned here. The efficacy of EMLA analgesia during the treatment of condylomata acuminata by cauterisation or laser treatment has been investigated in a number of clinical studies. Most effective analgesia has been achieved after applying EMLA for 5–15 min on the genital mucosa. Longer application times have resulted in less effective analgesia.

EMLA applied for 60 min has provided analgesia for the treatment of port-wine stains with pulsed-dye laser. EMLA did not affect the efficacy of the removal of the port-wine stain. However, our own experience has been that the analgesic efficacy of EMLA is not adequate.

Effective analgesia has been achieved with EMLA for surgical debridement of leg ulcers of venous or arterial origin.

Other indications are painful inflamed acne lesions, light electrocautery and fulguration of whiteheads, and hair removal by thermolysis in hirsutism.

EMLA has not been effective for removing common warts by curettage. We have observed the EMLA analgesia is not sufficient for the removal of common warts by cryotherapy.

Studies have also been undertaken to investigate the effectiveness of EMLA for (intramuscular) vaccinations. EMLA has been found to significantly reduce the pain of diphtheria, pertussis, and tetanus (DTP) vaccination in children.

We have conducted a double-blind, placebo-controlled study to investigate the analgesic effect of EMLA for the subcutaneous administration of mumps, measles, and rubella (MMR) vaccination in 96 children aged about 9 years. There was no significant difference between the pain scores in the EMLA group and the placebo group, although the difference almost reached significance ($P=0.052$).

There was a trend that in the EMLA group less pain was felt. However, this trend was not significant. Probably the pain of MMR vaccination was not due to skin penetration but due to the injection of the liquid into the subcutaneous space.

The most important dermatological indications for the use of EMLA cream are for the removal of molluscum contagiosum and as premedication for taking skin biopsy in childhood. The biopsy procedure is much easier to perform. Moreover, it may also provide material of improved quality for histological investigation. Other local anaesthetics need to be investigated further.

Adverse Effects

No major adverse effects of EMLA have been reported. A brief period of local redness or pallor of the skin may occur. Despite the frequent and widespread use of EMLA, we have encountered only very few cases in the literature of contact allergy caused by EMLA. In the patients, patch tests were positive for EMLA and prilocaine. For 10 years, we have treated 3,500–4,000 children with EMLA, mainly as an anaesthetic for the removal of molluscum contagiosum. We have observed purpura in five patients, which disappeared within several days. In these patients, patch tests were performed. All tests were negative. We concluded that the purpuric reaction was not of an allergic nature and possibly caused by a toxic effect on the capillary endothelium.

Regimen

The indications and recommended application times for EMLA are shown in Table 151.1. EMLA acts more rapidly in children with atopic dermatitis. Several studies have been undertaken to determine the plasma levels of lidocaine and prilocaine after application of EMLA. In these studies, plasma levels were far below the toxic levels. There is a relative risk for methaemoglobinaemia in children younger than 3 months. Prilocaine can induce methaemoglobinaemia via its *O*-toluidine metabolite. The activity of erythrocyte methaemoglobin reductase does not reach adult levels until after the age of 3 months.

We recommend that the use of EMLA per day is limited to a maximum of 1 g in children aged 0–3 months, 2 g in children to a maximum aged 3–12 months, and 10 g in older children.

Table 151.2 shows the recommendations by the US Food and Drug Administration (FDA) on dose, application area, and application time by age and weight of EMLA, for infants and children based on application to intact skin (source: www.accessdata.fda.gov).

Topical Anaesthetics in Laser Treatment and Intense Pulsed Light (IPL) Treatment

Topical anaesthetics may reduce the pain associated with laser or IPL procedures. The Food and Drug Administration (FDA) has approved mixtures

Table 151.1 Indications and the recommended application times for EMLA

Indication	Application time (min)
Molluscum contagiosum	15–30
Skin biopsy (pretreatment)	60
Condylomata acuminata	5–15
Port-wine stains (pulsed-dye laser)	60
Debridement of leg ulcers	30
Vaccination	60

Table 151.2 EMLA cream maximum recommended dose, application area, and application time by age and weight[a], for infants and children based on application to intact skin

Age and body weight requirements	Maximum total dose of EMLA cream (g)	Maximum application area[b] (cm^2)	Maximum application time (h)
0 up to 3 months or <5 kg	1	10	1
3 up to 12 months and >5 kg	2	20	4
1–6 years and >10 kg	10	100	4
7–12 years and >20 kg	20	200	4

Source: www.accessdata.fda.gov

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of EMLA cream should be restricted to that which corresponds to the patient's weight

[a]These are broad guidelines for avoiding systemic toxicity in applying EMLA cream to patients with normal intact skin and with normal renal and hepatic function

[b]For more individualised calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults: the estimated mean (±SD) absorption of lidocaine is 0.045 (±0.016) mg/cm^2/h. The estimated mean (±SD) absorption of prilocaine is 0.077 (±0.036) mg/cm^2/h

such as 4 % lidocaine cream or 2.5 % lidocaine/2.5 % prilocaine eutectic mixture (EMLA), but these do not always provide adequate topical anaesthesia. The onset action of EMLA is 1–2 h, and occlusion is recommended, which does not permit the brief IPL procedural time that patients desire. Compounded formulations with a higher concentration of the mixture or other topical anaesthetics in an occlusive base are used to increase the onset of action and duration and reduce the pain.

Of the many products used, 23 % lidocaine/7 % tetracaine in an ointment base has become a common formulation for preprocedure anaesthesia in laser therapy. Serum lidocaine levels and cutaneous adverse effects after application of 23 % lidocaine/7 % tetracaine ointment to the face were studied in 52 adult volunteers. The 23 % lidocaine/7 % tetracaine ointment was applied to their faces for 2 h. Eleven of 52 volunteers (21 %) reported a symptom that has been associated with high blood concentrations of lidocaine: dizziness; drowsiness; light-headedness; numbness or tingling other than on the face, lips, or tongue; and back pain. At the time of reported symptoms, only 2 of 11 volunteers had serum lidocaine levels greater than 2 μg/mL. Cutaneous adverse effects of the topical anaesthetic were frequent, a.o. flaking, scaling, peeling, itching, or burning.

Another compound is lidocaine 15 %/prilocaine 5 % ointment. In a single-centre safety study in 20 adults, lidocaine 15 %/prilocaine 5 % topical anaesthetic ointment was applied to the face or face, neck, and chest for 60 ± 15 min before IPL. Toxic levels of lidocaine and prilocaine were not reached.

Adverse Effects

Adverse effects are usually caused by high plasma concentrations of topical anaesthetics, resulting from excessive exposure and/or application to abraded or torn skin. Possible adverse effects include:

- Burning or stinging local to the administration site.
- High plasma concentration initially produces central nervous system (CNS) stimulation (including seizures), followed by CNS depression (including respiratory arrest). The CNS stimulatory effect may be absent in some patients, particularly when amides (e.g. tetracaine) are administered. Solutions that contain epinephrine may add to the CNS stimulatory effect.
- High plasma levels depress the heart and may result in bradycardia, arrhythmias, hypotension, cardiovascular collapse, and cardiac arrest. Local anaesthetics that contain epinephrine may cause hypertension, tachycardia, and angina.
- Methaemoglobinaemia (with Prilocaine)

The US Food and Drug Administration (FDA) has issued an advisory regarding the risk of serious adverse effects with the use of topical anaesthetics for cosmetic procedures. Topical anaesthetics are sometimes used in ways not approved and at doses that may pose a risk for serious harm. The FDA reported fatal cases: two women applied topical anaesthetics to their legs to lessen the pain of laser hair removal. These women then wrapped their legs in plastic wrap, as they were instructed, to increase the creams' numbing effect. Both women had seizures, fell into comas, and died from the toxic effects of the anaesthetic drugs. The skin numbing creams used in these two cases contained high amounts of the anaesthetic drugs lidocaine and tetracaine.

Conclusion

Topical anaesthetics are able to decrease pain during different cutaneous procedures. Awareness of the indications, pharmacologic mechanisms, appropriate methods of application, and safety profiles of the available topical anaesthetics is very important.

Careful attention must be paid to the location (skin, mucosa, face, body, a.o.), the total surface area covered, and the duration of anaesthetic skin contact. Adverse outcomes are associated with the use of compounded products, often non-FDA-approved, that have inappropriately high anaesthetic concentrations and with the use of topical anaesthetics on excessively large skin surface areas, for example, during laser treatments.

Serum levels are clearly related to the surface area to which the anaesthetic is applied. Physicians using topical anaesthetics are cautioned to limit the surface area to which they are applied. However, safe use of topical anaesthetics can decrease or eliminate pain during many cutaneous procedures and, also important to keep in mind, will decrease anxiety in patients who fear pain from procedures.

Many studies in children show the effect of EMLA cream as topical anaesthetic in superficial and dermatological procedures. EMLA cream at recommended dosage is a safe and effective topical anaesthetic agent in children.

For optimising the percutaneous absorption of topically applied drugs, different strategies are utilised in formulations. A patch containing a eutectic mixture of lidocaine 70 mg and tetracaine 70 mg (Synera™) consists of a thin, uniform layer of a local anaesthetic formulation with an integrated, oxygen-activated heating component that is intended to enhance the delivery of the local anaesthetic. The safety and effectiveness of Synera™ have been established in paediatric patients aged 3 years and older in well-controlled studies.

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Topical Preparations and Vehicles 152

Marcello Monti and Stefania Motta

Key Points

- As a general consideration, the chemical agents that may be applied to the skin for their local effects belong to two categories: drugs and non-drugs.
- The agents of the first category have a selective action in terms of chemical and pharmacological activity on the skin. Antibiotics, antimycotics, corticosteroids and antineoplastics are some examples.
- The second category is composed of a heterogeneous group of agents showing mostly a non-selective action, has limited chemical and pharmacological activity and, sometimes, has just a physical action.
- Therefore, excluding drugs, topical treatment may be subdivided into non-specific treatment with bases and specific treatment with active agents.
- Dermatological bases or vehicles serve not only as vectors for incorporating active ingredients but also possess some therapeutic effects because of their own physicochemical properties.
- Specific topical treatments are prescribed by dermatologists in so-called magistral formulations. In this case, the topical treatment consists of the local use of some active substances in a suitable vehicle. These locally acting agents include most absorbents, astringents, demulcents, rubefacients, keratolytics and miscellaneous other ingredients.

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General Principles and Classification

Dermatological therapy can be a combination of systemic and topical treatments although topical treatment is often the only therapy prescribed. As a consequence, dermatologists have to be familiar with the use of topical preparations, whether a drug or an active agent needs to be added or not. Tailor-made preparations have undoubtedly a great positive impact on patients, but their use is limited by two main factors: the poor confidence of practising dermatologists to prescribe magistral preparations and the difficulty in finding pharmacists able and willing to provide them. In a recent analysis of compound prescriptions, some mixtures prescribed by dermatologists were questionable either because of the number of active ingredients or the selected

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_152, © Springer-Verlag Berlin Heidelberg 2015

concentrations. As a general consideration, the chemical agents that may be applied to the skin for their local effects belong to two categories:

- Drugs
- Non-drugs

The agents of the first category have a selective action in terms of chemical and pharmacological activity on the skin. Antibiotics, antimycotics, corticosteroids and antineoplastics are some examples. They are prepared by pharmaceutical companies according to strict international rules on suitable vehicles and are ready to use. Their use in combination with other ingredients is neither recommendable nor economically worthwhile.

The second category is composed of a heterogeneous group of agents which, by exclusion, do not belong to the first. They have mostly a non-selective action, have limited chemical and pharmacological activity and, sometimes, have just a physical action. These locally acting agents include most absorbents, astringents, demulcents, rubefacients, keratolytics and miscellaneous other ingredients used in dermatology. The local treatment of skin disorders also includes the exclusive use of vehicles. Therefore, excluding drugs, topical treatment may be subdivided into:

- Non-specific treatment with bases
- Specific treatment with active agents

Non-specific Treatment with Bases

Dermatological bases or vehicles serve not only as vectors for incorporating active ingredients but also possess some therapeutic effects because of their own physicochemical properties. In this case, the bases themselves are the active ingredients. The ideal base should have the following properties:

- Easy to apply and remove
- Non-toxic, irritant or allergenic
- Chemically stable
- Pharmacologically inert
- Cosmetically acceptable

The bases may be liquid, semi-solid or solid. Some bases are utilized in non-specific dermatological treatment, while others are just vehicles.

Table 152.1 Classification of topical preparations

Bases utilized in non-specific treatments	Bases utilized as vehicles
Fatty ointments	Aqueous solutions
Fatty pastes	Tinctures
Powders	Varnishes
Hydrogels	Sprays
Hydroalcoholic lotions	Hydrosoluble ointments
Creams W/O	Creams O/W
Liquid emulsions	
Oils	

Another classification of vehicles is based on their physical phase:

- Monophasic: powders and greases
- Biphasic: paste, status lotions or emulsions
- Triphasic: cooling paste

The main effects, clinical indications and contraindications of bases are discussed according to the categories listed in Table 152.1.

Fatty Ointments

Fatty ointments are anhydrous, lipophilic and hydrophobic bases consisting of mineral, synthetic or plant and animal fats. Paraffin, petrolatum, lanolin, castor oil and olive oil are examples of fats used in ointments. The ointments cover the stratum corneum promoting the inhibition of this layer by softening the skin and promoting drug penetration. They are useful for the treatment of dry skin, hyperkeratotic and scaling dermatoses. The obstruction of the release of heat and water may produce maceration, increase inflammation or produce dyshidrotic eruptions.

Fatty Pastes

Pastes are mixtures of powder and ointment or cream. The powders are at least a 10 % strength, and depending on their concentration, the pastes are subdivided into:

- Pastes: powder/ointment ratio 1:1
- Soft pastes: powder/ointment ratio 1:2
- Hard pastes: powder/ointment ratio 2:1

Zinc oxide, talc and wheat starch are the most utilized powders. The pastes have a cooling, anti-inflammatory and skin-protective action.

They are useful for the treatment of chronic dermatoses, especially when lichenification is present. Some of them have particular secretion absorbing or drying effects. The hard pastes have the same contraindications as ointments.

Powders

Powders are composed of micronized and dispersed granular particles. They can be homogeneously distributed on large body areas directly from a dusting can. Talc, zinc oxide, starch and magnesium carbonate are examples of the most commonly used powders. They have protective antifrictional activity together with cooling and drying effects. They are used in erythematous exanthems and in some pruritic conditions. They dry the skin absorbing water and lipids from the surface, and they crust the skin in oozing and erosive dermatoses.

Hydrogels

Hydrogels are composed of cellulose compounds and derivatives, alginic acid and others that swell with water to produce a gelatinous base. Hydrogels have cooling and slight anti-inflammatory action so they are used in erythematous and pruritic exanthems as well as for the treatment of acute exogenous dermatitis. They may be applied to hairy parts but have a drying effect on prolonged application.

Hydroalcoholic Lotions

Hydroalcoholic lotions are a mixture of ethanol 40–70 % or isopropanol 20–40 % and water. They are mostly used as vehicles for active substances but may be used as is for their defatting and drying effects. They are indicated in seborrhoeic conditions and contraindicated in xerotic and scaling dermatitis.

Creams W/O

Creams (W/O type) are a two-phase system of fatty substances (up to 70 %), water (30 %) and emulsifying agents. They are mainly used as vehicles for active substances, and due to the high concentration of fats, they have a smoothing and softening effect, together with slight cooling and anti-inflammatory action. For these properties, they are employed to counteract xerotic, dry skin and to soften scales and crusts in chronic dermatoses. They are less tolerated with respect to O/W creams on seborrhoeic types of skin.

Liquid Creams

Liquid creams are emulsions with low fatty component (less than 30 %). They appear milky in colour and consistency and usually are employed in cosmetics as cleansing and body lotions. Liquid creams possess a slight anti-inflammatory, antipruritic effect and may be used even in exudative and vesicular dermatoses. However, they dry the skin due to rapid evaporation of water. They are not suitable for chronic scaly dermatosis treatment.

Oils

Oils, as medical preparations, are used for dissolving fat-soluble active ingredients but may be used alone or for suspending powders. Oils have lubricating action and may be used to soften crusts and scales and to remove ointments and pastes. They are indicated in acute superficial dermatoses especially in children and are less indicated in adults especially with seborrhoea or seborrhoeic dermatoses.

In Table 152.2, the bases for dermatological non-specific treatment are listed. Some of these vehicles are rarely used mainly because of their poor cosmetic acceptability; only emulsions are largely used as vehicles for non-specific topical treatment. The most widely used cream in European countries is a base cream called cetomacrogol cream present in many pharmacopoeia. Cetomacrogol cream consists of 30 % soft greases including white soft paraffin and petrolatum. Cetomacrogol 1,000, the emulsifying agent, is a condensation of cetostearyl alcohol with ethylene oxide. Cetomacrogol cream is

Table 152.2 Effects, indications and contraindications of vehicles

Vehicles	Effects	Indications	Contraindications
Fatty ointments	Softening, warming	Hyperkeratotic fissured dermatoses Xerosis Dry skin	Acute inflamed skin Vesicular dermatoses
Pastes	Cooling, anti-inflammatory, secretion absorbing, protective	Chronic dermatoses Lichenified dermatoses	Acute dermatoses Erosive dermatoses
Powders	Cooling, protective, antifrictional, drying	Erythematous exanthems	Dry skin, crusting, oozing, erosive dermatoses
Hydrogels	Cooling, superficial anti-inflammatory, antipruritic	Erythematous or urticarial exanthems Dermatitis solaris	Dry skin
Hydroalcoholic lotions	Drying, cooling	Dermatoses of hairy parts, seborrhoea	Dry skin
Creams O/W	Cooling, anti-inflammatory, emollient	Acute dermatoses, seborrhoeic skin	Dry skin
Creams W/O	Softening, slightly cooling, anti-inflammatory	Chronic inflammation, soft scales and crusts Xerotic dermatoses	Acute inflamed skin Dyshidrosis
Liquid creams	Cooling, anti-inflammatory, emollient	Acute, exudative dermatoses	Scaly or crusty dermatoses
Oils	Lubricating, softening scales and crusts	Superficial inflammation large-area dermatoses. Removal of ointments and pastes	Seborrhoeic dermatoses

non-allergenic, non-greasy, washable, low cost and easy to prepare. Usually, it is prescribed as a vehicle for active ingredients, but it is useful in many non-specific treatments and even as a placebo. Cetomacrogol cream is also produced by pharmaceutical companies.

Specific Treatment with Active Agents

Specific topical treatments are prescribed by dermatologists in so-called magistral formulations. In this case, the topical treatment consists of the local use of some active substances in a suitable vehicle. The vehicles are the same as proposed in the previous section, and the local acting agents may be differentiated by their specific activity on the skin. There is no international agreement about the terminology for describing activity of these compounds on the skin. Moreover, there is no clear distinction between drugs and non-drugs, so that the limit of a magistral prescription is not well defined.

Theoretically, all topical dermatological treatments can be carried out with extemporaneous preparations. However, some of them are technically difficult to prepare and economically not worthwhile. Others are purchased from pharmaceutical companies and have a high safety profile. The main actions of topical active ingredients are listed in Table 152.3. The actions of active ingredients and the ingredients themselves are discussed in the following sections.

Protectives and Absorbents

Protectives and absorbents are intended to absorb moisture, decrease friction, discourage bacterial growth and absorb fats contributing to a decrease in body odours. These actions are achieved using dusting powders and some mechanical and chemical protectives. Dusting powders considered for this activity are bentonite, calcium carbonate, calcium precipitate, talc, titanium dioxide, zinc oxide and zinc stearate. Other

Table 152.3 Action of topical active ingredients

Recommended for magistral prescription	Difficult to prepare or not economically worthwhile	Use of registered drugs is recommended
Protective and absorbent	Pigmenting	Antibacterial
Lenitive	Depigmenting	Antifungal
Emollient	Sun protecting	Virostatic
Astringent and antiperspirant antipruritic	Depilatories	Anti-inflammatory
Rubefacient	Insect repellent	Cytostatic
Caustic	Antiparasitic	Anaesthetizing
Keratolytic		
Keratoplastic		
Cleansing		
Opacifying, sebum absorbing		

substances such as propylene glycol and glycerol may be added to increase the protective action. An example is zinc paste:

Zinc oxide	10
Propylene glycol	15
Glycerol	40
Purified water	35

Collodion varnish may be used to protect non-affected areas of the skin from topically applied irritants or caustics:

Pyroxylin	4
Ether	71
Ethanol	25

Vaseline and silicones are examples of other chemical protectives. Hydrophilic and lipophilic emulsions containing a variety of constituents, such as allantoin, linoleic acid, pantothenol, urea and vitamins, have been considered by other authors to be protective. However, their activity has not been demonstrated yet.

Lenitives

Lenitives are employed to alleviate skin irritation in many superficial skin dermatoses. They also prevent drying of affected areas. Lenitives are mainly in the form of lotions, wet dressings or simply powders. Alginates, mucilages, gums, dextrins, starches, certain sugars, glycerol and many oils are commonly considered as lenitives. Zinc oxide, talc and calamine are sometimes added for their astringent anti-inflammatory effect. Typical formulations are:

Calamine	15
Zinc oxide	5
Glycerol	5
Water	Up to 100

Zinc oxide	3
Magnesium silicate	3
Cetomacrogol cream	Up to 100

Emollients

Emollients are used to render the skin softer and more pliable and also possess some anti-irritative properties. Oils of mineral, vegetable and animal origin as well as waxes are considered emollients. In particular some vegetable fats, such as karite butter or jojoba liquid wax, possess both a good emollient and cosmetic acceptance. Both creams and ointments are suitable for this purpose. All ointments are considered emollients, and virtually all emulsions, due to the presence of fat components that penetrate easily into stratum corneum layers, are also emollients. For this reason, emulsions instead of ointments are now prescribed as

emollients. Cetomacrogol cream is an example of an emulsion utilized as an emollient:

Karite butter	4
Jojoba liquid wax	4
Avocado oil	4
Cetomacrogol cream	Up to 100

Astringents and Antiperspirants

Astringents are active substances. When applied locally, they are protein precipitants, having low cell penetrability so that their action is limited to the surface. Astringents in dermatology are used to reduce erythema and pruritus; they also have an antiperspirant effect by causing protein precipitation in the sweat ducts. Astringents/antiperspirants also have deodorant properties due to an interaction with odorous fatty acids liberated by bacteria and by suppressing bacterial growth by virtue of low pH. The main astringents are:

- Salt of the cations aluminium, bismuth, iron, manganese and zinc
- Other salts containing these metals such as permanganates
- Tannins or related polyphenolic compounds

Dusting powders, lotions and gels are used for this purpose. An example of a powder is astringent powder:

Tannic acid	10
Zinc oxide	10
Talc	Up to 100

Aluminium chloride hexahydrate aqueous or hydroalcoholic solution 5–10 % may be used as an astringent in many chronic oozing dermatitis cases as well as an antiperspirant at concentrations of 10–20 %.

Antipruritics

Pruritus is a common symptom of different dermatoses of eczema, atopia, urticaria, exanthema type and neurodermitic type, etc. It can also be linked to internal diseases or skin senescence. Most astringents, keratoplastics or rubefacients possess antipruritic activity. Menthol, phenol, salicylic acid, polidocanol and coal tar are used as topical antipruritics in different dermatoses. Some examples of antipruritic formulae are:

Menthol	1
Ethanol 70 %	Up to 100

Aluminium chloride hexahydrate	5
Hydroxyethylcellulose	4
Propylene glycol	5
Ethanol	20
Water	Up to 100

Coal tar is an effective antipruritic agent and can be used in emulsion: coal tar 2 % in cetomacrogol cream.

Rubefacients

Rubefacients are able to induce hyperaemia and slight inflammation that produces a feeling of comfort, warmth, sometimes itching and hyperaesthesia. Most rubefacients in high concentrations are vesicants. Rubefacients are sometimes used for treating the sensory and visible effect of irritation, giving the patient the impression of receiving an effective medication. They are also used to treat pernioses and to promote hair growth especially in alopecia areata. Examples are:

- Alcohol camphor
- Anthralin
- Capsicum
- Benzoin menthol
- Resorcinol
- Methyl salicylate
- Nicotine acid and its esters

Caustics

Caustics are agents that cause the destruction of tissue; therefore, they are used in hyperkeratoses or hyperplastic tissues, but they can be used also for the destruction of tumours such as basaliomas and xanthelasmas. These agents usually precipitate proteins so that they may be considered as

astringents at low concentration. Caustics are also bactericidals. Examples are:

- Trichloroacetic acid
- Glacial acetic acid
- Phenol
- Silver nitrate
- Nitric acid
- Potassium hydroxide

Caustics are usually applied to the skin with a stick swab. Examples are:

- Trichloroacetic acid 50 % aqueous solution is used to remove xanthelasmas.
- Liquefied phenol 20 % in water to bleach hand freckles.

Keratolytics

Keratolytics loosen the keratins or intercellular cement facilitating desquamation of scales and softening horny material or crusts so they may be used in hyperkeratotic conditions. They also eliminate parasites or fungi. However, the real action of some keratolytics is not completely elucidated. Examples are:

- Salicylic acid
- Sulphur
- Urea
- Resorcinol
- Calcium chloride
- Some alkali-containing compounds such as sodium and potassium hydroxide.

Among these, salicylic acid is the most commonly used in a variety of formulations. Around 6–10 % of salicylic acid is needed for a keratolytic effect even if the possibility of toxicity due to absorption has to be considered. Therefore, high concentrations are employed in very small areas incorporated in collodion. Examples are:

- Salicylic acid for pityriasis capitis

Salicylic acid	3
Glycerol	10
Ethanol 50 %	Up to 100

Keratoplastics

Keratolytic agents at low concentrations stimulate the renewal of the horny layer through a slight reducing action and favouring desquamation. Salicylic acid, alpha-hydroxy acids, sulphur, urea and ichthyols are considered keratoplastics.

Examples of formulations with this property are:

- Sulphosalicylic shaking lotion

Salicylic acid	2
Sulphur	2
Ethanol 50 %	Up to 100

- Glycolic salicylic lotion

Salicylic acid	2
Glycolic acid	10
Ethanol 50 %	Up to 100

- Glycolic salicylic cream

Salicylic acid	2
Glycolic acid	10
Cetomacrogol cream	Up to 100

Other ingredients are able, via a toxic event, to reduce DNA synthesis and mitosis, especially in hyperproliferative disorders. Some of these substances, namely, tars, also possess antipruritic-anti-inflammatory action so that they may be used in a variety of skin disorders ranging from psoriasis to atopic dermatitis. This activity should be defined as a reducing activity, but many authors regard it as a keratoplastic activity. Examples of these compounds are coal tar, resorcinol, anthralin, ichthyol and phenols. Examples are:

- Coal tar solution

Coal tar	2
Polysorbate 80	0,5
Ethanol	Up to 100

- Ichthyol pale cetomacrogol cream

Ichthyol pale	10
Cetomacrogol cream	Up to 100

Coal tar can easily be incorporated into cetomacrogol cream up to 4 %. The result is a cosmetically acceptable and washable preparation, useful for outpatient treatment.

Cleansing

Cleansing may be carried out with detergents, solvents, abrasive substances singly or in combination. Soaps and shampoos are often used as vehicles for active agents such as antibacterial, antifungal, salicylic acid or tars. Some detergents are also antibacterial such as benzalkonium chloride. Substances in this group include:

- Ethanol sodium lauryl sulphate
- Isopropanol benzalkonium chloride

A simple example in which it is possible to suspend the active ingredients is:

- Anionic detergent

30 % Sodium lauryl ether sulphate	40
30 % Alkyl amido betaine	10
Distilled water	Up to 100

Liquid creams and creams O/W on cotton swabs are also suitable for cleansing affected skin or for removing topical medicaments or makeup.

Opacifying and Sebum Absorbing

Opacifying and sebum absorbing agents are used to diminish the brightness of oily or seborrhoeic skin. The micronized dusting powders by virtue of their absorbent properties have the action of physically absorbing secretion of both sweat and sebaceous glands. Examples are:

- Bentonite
- Zinc oxide
- Caolin
- Titanium dioxide

Each of these compounds may be incorporated in shake lotions or creams O/W. The amount depends on the degree of micronization of the powder employed. Iron oxide may be added in small quantities to match the skin colour.

Hydrosoluble Ointments

A frequently used vehicle that is not classifiable as a base with non-specific activity is polyethylene glycol ointment. This ointment is classified as a hydrosoluble ointment and is also called a greaseless ointment base. This is composed of water-soluble constituents, namely, polyethylene glycols (PEG). PEG ointment is particularly useful because it is an inert, anhydrous, viscous compound that is completely washable. It is possible to incorporate into a PEG ointment almost all active ingredients and distribute them to all body areas, hairy parts included. Washability of this ointment renders it very acceptable to patients. PEGs are hydrophilic compounds and, when applied to eroded or ulcerated skin, exert an absorbing action on exudates and are usually well tolerated. PEGs do not have cellular toxicity and do not interfere with cell growth and migration during the tissue repair process. Moreover, the use of PEG dressing enables anti-adherence and water vapour permeability properties. For these reasons, PEG ointment has to be considered the ideal dressing for dermatological surgery.

- PEG Ointment

Polyethylen glycol 4000 30 % and polyethylen glycol 400 70 %.

The ratio of the two components can be varied depending on the desired viscosity of the compound.

In the treatment of ulcers, allantoin, which induces healing by stimulating healthy granulations and removing necrotic material, is usually added to PEG ointments up to 5 %.

New medication based on PEG-allantoin–soaked gauze will be useful and practical in the dressing of surgical wounds as well as of ulcers.

Allantoin-PEG ointment is stable and nontoxic, and the treatment of ulcers is painless, simple and inexpensive.

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Vitamins and Nutritional Supplements

153

Alexandru Tataru and Andreea Nicoleta Boca

Key Points

- Complementary and alternative medicine approaches are frequently chosen by patients with various skin conditions.
- An important number of botanical-based preparations and vitamins are used for skin care or dermatological diseases, even if rarely supported by evidence-based science.
- More studies, especially clinical ones, are needed to determine their efficacy and risks.
- Clinicians should be informed of the benefits, as well as specific side effects of natural products and vitamins used for various skin disorders.

General Principles

Complementary and alternative medicine (CAM) represents an array of health-care approaches with a history of use, or origins outside of conventional medicine, as explained by the US National Center for Complementary and Alternative Medicine (NCCAM). According to NCCAM, the most frequently used CAM approaches are natural products. There are numerous diet-based therapies, dietary supplements, and herbal extracts with proven or sometimes only supposed beneficial effects.

Patients with various skin conditions are reported to use CAM, especially herbal remedies, as first therapeutic approach, with higher frequency than general population. For Europe, it is estimated that 35–70 % of them use CAM at least once during their lifetime.

Herbal extracts are also used in conventional dermatology, accepted by historical experience or based on scientific studies: psoralens, podophyllin, and pyrethrins.

This chapter summarizes the use of important CAM approaches, more exactly herbal extracts, dietary supplements, and vitamins, in dermatology. It contains a general presentation of the herbal extracts, their chemical classification, and biological effects, in order to make it more comprehensible in this area of interest, which includes a large number of different substances. In fact,

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_153, © Springer-Verlag Berlin Heidelberg 2015

natural extracts always contain mixtures of organic compounds, belonging to different classes, with different properties. The most used or useful herbal extracts are then presented, each one with their peculiar properties. The last part of this chapter is an overlook on vitamins and their benefits in various skin conditions.

Herbal Extracts

Classification and Biochemistry

Polyphenols are active constituents of many plants, some of them frequently used in CAM. They are a very large class of organic chemicals characterized by the presence of phenol structural units. Polyphenols are mostly natural, but can also be synthetic or semisynthetic, each with unique properties, according to the number and characteristic of their phenol structures.

The wide class of polyphenols includes phenolic acids, flavonoids, stilbenes, or lignans. Flavonoids are probably the most studied among them.

Flavonoids (lat. flavus = yellow) are a class of plant secondary metabolites, found in a large variety of natural sources and including a number of subclasses as shown in Table 153.1. From a chemical point of view, flavonoids can be glycosides (those connected with one or more sugar molecules) and aglycones (those without such connection). In nature, catechins and proanthocyanidins are aglycones, while all others are glycosides.

Starting from the natural compounds, a number of useful semisynthetic and synthetic derivatives have been developed, like diosmin, recommended in chronic venous insufficiency.

The bioavailability of flavonoids is relatively low due to limited absorption and rapid elimination. Isoflavones like those from soy are the most bioavailable ones, as opposed to flavanols like proanthocyanidins and tea catechins.

General Biological Properties of Flavonoids

Direct and Indirect Antioxidant Activity

Diets containing flavonoids are known to have important antioxidant effects. Flavonoids are potent direct scavengers of free radicals of oxygen in vitro. In vivo, most circulating flavonoids are actually flavonoids' metabolites, with lower antioxidant activity than the original molecules, and low plasma and intracellular concentrations. Therefore, the relevance of the flavonoids' direct antioxidant activity in vivo remains questionable. In topical applications, the poor transcutaneous penetration and rapid local metabolization are the main limitations for their beneficial effects.

An indirect antioxidant activity of flavonoids is due to their capacity of metal chelation, especially iron and copper (at least in vitro). Free iron

Table 153.1 Classification of flavonoids

Subclass	Examples	Common herbal sources
Flavones	Apigenin, luteolin	Parsley, thyme, celery, hot peppers
Flavonols	Quercetin, myricetin, isorhamnetin, kaempferol	Yellow onions, scallions, broccoli, apples, berries, teas
Flavanones	Hesperitin, naringenin, eriodictyol	Citrus fruits
Flavanols monomers (catechins)	Catechin, epicatechin, epicatechin gallate, epigallocatechin gallate	Green tea, some cocoas, and chocolate
Flavanols dimers	Theaflavins, thearubigins	Teas (especially oolong black)
Flavanols polymers	Proanthocyanidins	Red grapes, berries, apples, chocolate
Anthocyanidins	Cyanidin, dephinidin, malvidin, pelargonidin, peonidin, petunidin	Red and purple grapes, blue and purple berries
Isoflavones	Genistein, daidzein, glycitein	Soybeans

and copper ions are able to generate radicals of oxygen. In living organisms, most iron and copper ions are bound to specific proteins, limiting their oxidant capacity. Therefore, the importance of such reactions in reducing the oxidative stress in vivo has not been established so far.

Effects on Cell-Signaling Pathways

Data from cell culture experiments suggests that the main biological effect of flavonoids relies in their ability to modulate cell-signaling pathways, including growth, proliferation, angiogenesis, and apoptosis.

Intracellular concentrations of flavonoids required for cell-signaling pathways are lower than those required for antioxidant effects, plus flavonoids' metabolites are also able to interact with cell-signaling proteins.

Studies suggest that flavonoids selectively inhibit protein kinases that catalyze the phosphorylation of specific receptor proteins, like the growth factor receptor. This could help prevent tumor development by inhibiting cell proliferation, neoangiogenesis, tumor invasion, and inducing apoptosis. Flavonoids also promote the excretion of potentially toxic or carcinogenetic chemicals.

By modulation of cell-signaling pathways, flavonoids could prevent cardiovascular diseases by decreasing chronic inflammation associated to atherosclerosis, vascular cell adhesion molecules' expression, platelet aggregation, and increasing endothelial nitric oxide synthase activity.

By decreasing the chronic inflammation and fighting against oxidative stress, they could be helpful in neurodegenerative diseases and least but not last, in a large spectrum of skin conditions.

Adverse Effects of Flavonoids

Due to their low bioavailability, rapid metabolism, and elimination, no significant adverse effects have been associated with normal dietary intake of plant-based flavonoids.

Drug Interactions

Flavonoids quercetin and naringenin, and furanocoumarins, especially dihydroxybergamottin (in grapefruit juice), have a documented potential to inhibit the intestinal cytochrome P450 3A41, both in vitro and in vivo. This results in increased risk of toxicity for a large number of drugs, such as antiarrhythmics, benzodiazepines, carbamazepine, terfenadine, cyclosporine, sildenafil, and statins.

For quercetin, naringenin, and the green tea flavanol epigallocatechin gallate, in vitro inhibition of the P-glycoprotein has been reported. The impairment of P-glycoprotein's (efflux transporter) function can increase the potential toxicity of antihypertensive, antiarrhythmic, antifungal drugs, digoxin, HIV protease inhibitors, and H2 receptor antagonists.

High intakes of flavonoids from purple grape juice and dark chocolate can increase the risk for bleeding when taken with anticoagulant or antiplatelet drugs.

Because all flavonoids have metal chelating properties, the consumption of tea or cocoa decreases the absorption of non-heme iron found in plant foods and iron supplements.

Dietary Sources of Flavonoids

Anthocyanidins are found mainly in blueberry, bilberry, elderberry, black currant, and red grape, but content may vary considerably.

Flavanols are found in all types of teas. Green tea extracts have higher levels of flavanol monomers (catechins), black tea extracts are richer in flavanol polymers (theaflavins and thearubigins), while the oolong tea extracts are in between them. All kinds of teas also contain different concentrations of caffeine.

Flavanones are represented by hesperidin glycosides, naringenin, and eriodictyol, which are found mainly in citrus fruits.

Flavones are represented by tangeretin, nobiletin, and sinensetin and can be found in the citrus peels.

Flavonols, found in citrus and many other vegetables, are represented by quercetin and its glycoside rutin.

Isoflavones are a subclass of flavonoids, belonging to polyphenols. Isoflavones of nutritional and medical interest are derivatives of isoflavone (itself

has no interest) by replacement of two or three hydrogen atoms with hydroxyl groups. Isoflavones are produced almost exclusively by the family of Fabaceae (bean family), the most well known being the soybean. They are genistein, daidzein, naringenin, and naringenin chalcone. These isoflavones are potent antioxidants, because of their ability to trap singlet oxygen, and many act as phytoestrogens in mammals.

Catechins

Catechins belong to the class of flavanols. Their name comes from "catechu," a plant extract from which they were first isolated. The main natural source is the leaves of different types of tea (Camelia sinensis).

According to the processing procedures, teas are classified into white, green, oolong, black, post-fermented, and yellow. The highest quantity of catechins is found in green tea, up to 35 % more than in other type. Black tea contains more flavanols polymers, theaflavins, and thearubigins.

Experimental research on cell cultures and animal models revealed numerous biological effects of catechins; due to their ability to modulate different cell functions, they are involved in DNA transcription, protein expression, DNA repair, cell cycle control, and cell-to-cell communication, plus they possess a potent antioxidant effect.

Regarding skin cancers, data from animal models suggest that catechins from green tea could protect against tumorigenesis induced either by UV radiation or chemicals and could influence the tumors' growth. However, data on humans are insufficient for recommending the use of green tea in the prevention or treatment of skin cancers.

They are some studies reporting good efficacy of topically applied extracts of green tea for the treatment of genital warts, facial telangiectasia, and acne.

Quercetin

Quercetin is one of the most prominent dietary antioxidants. It is present in all vegetables, fruits (especially citrus and berries), tea, and wine. The biological effects are those of flavonoids in general: antioxidant, anti-inflammatory, and anticarcinogenic; via signaling modulation, quercetin is able to downregulate the expression of mutant p53 protein.

For oral administration, quercetin is found in capsules containing 400 mg quercetin and 100 mg bromelain (pineapple extract, increasing intestinal absorption) each. Recommended dose is 500–1,000 mg/day, in intermittent cycles of 8–12 weeks. More than 1,000 mg/day could cause renal toxicity.

Topical application of the quercetin aglycone has been shown experimentally to be effective in the prevention of UV-induced liposome peroxidation and in UVB-induced glutathione depletion.

Genistein

The most studied isoflavone, genistein is abundantly present in soybeans and can be found in smaller amounts in Gingko biloba, fava bean, kudzu, and red clover.

Genistein is known to have good effects on atherosclerosis, cancers, oxidative stress, and helminthic infestations. Several studies have confirmed its efficacy against *Echinococcus* spp. and *Fasciola* spp.

Recent studies on genistein reported skin beneficial effects, such as antiaging, antioxidative, and anti-inflammatory; it has been tested in antiaging cosmetic preparations with interesting results. In addition, results on animal models showed that genistein inhibited the initiation and promotion of chemically induced skin tumorigenesis; there were also promising results on wound healing.

Genistein can be used alone, or more frequently in combination with quercetin and other isoflavones extracted from soybean. The usual dose is 8 mg/day, for 3–12 months.

Terpenes and Terpenoids

Terpenes and terpenoids, also known as isoprenoids, are a large class of organic compounds which are derivatives of the basic molecule

isoprene. Their classification is based on the number of basic isoprene units linked together in linear chains or arranged to form rings:

- Hemiterpenes (a single isoprene unit): prenol and isovaleric acid.
- Monoterpenes (two units): geraniol, limonene, and terpineol.
- Sesquiterpenes (three units): humulene, farnesene, and farnesol.
- Diterpenes (four units): cafestol and taxadiene, important because they are precursors of retinol, retinal, and phytol.
- Sesterpenes (five units): geranylfarnesol.
- Triterpenes (six units): very important because the linear form is squalene, the structural precursor of all steroids. In vegetals, lipophilic triterpenes in combination with hydrophilic glycosides generate saponins, substances with marked antimicrobial and antifungal effects.
- Sesquarterpenes (seven units): less important.
- Tetraterpenes (eight units): the acyclic form is lycopene, and the cyclic forms are the important and studied subclass of carotene and carotenoids; the monocyclic tetraterpene is gamma-carotene, and the bicyclic tetraterpene generates alpha-carotene and beta-carotene.
- Polyterpenes have long chains of isoprene units and generate, for example, the natural rubber.

Terpenoids contribute to the resin of conifers, the scent of palms like *Eucalyptus*, the flavors of cinnamon and ginger, the yellow color in sunflower, and the red color in tomatoes.

Well-known terpenoids are the menthol and camphor, the cannabinoids found in *Cannabis indica*, ginkgolide and bilobalide in Gingko biloba, and the curcuminoids in turmeric and mustard seeds.

Curcumin

Curcumin, a low-molecular-weight terpene, is the active ingredient in the spice turmeric and, in smaller amounts, in mustard seeds. In naturopathic Ayurveda Indian medicine, it is applied on the skin to enhance wound healing and to facilitate the process of epithelialization after herpes zoster, sometimes even after autoimmune blistering diseases. Unfortunately, scientific evidence supporting these beneficial roles of curcumin is limited.

Phase II clinical trials used systemic curcumin in psoriasis with limited response. Other studies were focused on topical administration of curcumin in vitiligo, phototoxic dermatitis, and morphea, with some beneficial effects reported, based on its photoprotective effect.

Experimental studies reported antiproliferative and proapoptotic effects of curcumin, which can inhibit the epidermal growth factor receptors, the sonic hedgehog pathway, downstream signaling pathways like nuclear factor kappa-B, and signal transducers and activators of transcription. Future studies will reveal if oral administration of curcumin, alone or with other drugs, could be helpful to treat basal cell carcinoma, melanoma, and primary cutaneous T-cell lymphoma.

Due to its antioxidant and photoprotective properties, curcumin is included in a number of marketed cosmetic products.

For oral administration, curcumin is frequently combined with bromelain, insuring improved intestinal absorption. The dosage is 400–600 mg capsules with standardized powder, three times per day. For preventive purposes, a 900 mg/day life-long treatment is recommended.

Carotenoids

Carotenoids are a group of over 600 liposoluble pigments, divided in two classes, xanthophylls (contain oxygen) and carotenes (purely hydrocarbons). They are widespread, being responsible for the yellow, orange, red, and purple colors of many fruits, flowers, birds, insects, and marine animals.

Although hundreds of carotenoids are found in nature, only few possess the well-known beneficial effects. Actually only about ten of them are found in plasma and tissues, and only two in the retina (lutein and zeaxanthin). The most studied ones are beta-carotene and lycopene (belonging to the subgroup of carotenes), along with lutein, zeaxanthin, and beta-cryptoxanthin (subgroup of xanthophylls). Only few carotenoids,

such as alpha-carotene, beta-carotene, and beta-cryptoxanthin, display a provitamin A activity (can be converted to retinal).

Animals and humans cannot synthesize carotenoids, thus obtaining them from fruits and vegetables. Alpha-carotene is found in carrots; beta-carotene in carrots, squash, and dark-green leafy vegetables; lycopene in gac fruit, tomatoes, and watermelon; lutein in spinach and broccoli; and ß-cryptoxanthin in oranges and papaya. The richest source of carotenoids with provitamin A activity is crude palm oil.

Several epidemiological studies reported association of carotenoid-rich foods consumption and reduced risk to develop cancers, cardiovascular diseases, and aged-related eye macular degeneration. This could be related to their function as vitamin A precursors, for alpha-carotene, beta-carotene, and beta-cryptoxanthin, as well as to their antioxidant effects, modulators of immune response and inducers of gap junctional communications. Carotenoids are able to scavenge free radicals such as singlet molecular oxygen and peroxyl radicals, to protect cellular systems from oxidative damage.

Carotenoids play an important part in the skin's antioxidant defenses; thus, many studies focused on assessing their potential for skin tumor prevention. In vivo carotenoid concentration, evaluated by Raman spectroscopy in basal cell carcinomas, actinic keratosis, and their perilesional skin, was reported to be significantly lower compared to region-matched skin of healthy subjects. Even if there is a clear need for more scientific studies in this direction, dietary supplements claiming photoprotective effect are already marketed.

For beta-carotene, the recommended dose is 50 mg/day, for lutein 4–20 mg/day, and for zeaxanthin 0.2–1 mg/day, without a specific time limit.

Lycopene

The most potent antioxidant among various carotenoids is lycopene. Its health benefits include trapping singlet oxygen, reducing mutagenesis, anti-inflammatory, antimutagenic, and anticarcinogenic effects. In physiological concentrations, lycopene has been proven to inhibit human tumor cell growth, through mechanisms including inhibition of prostatic IGF-I and androgen signaling, as well as IL-6 expression. In addition, lycopene improves gap junctional communication and induces phase II drug metabolizing enzymes and oxidative defense genes. Interestingly, it has been shown that a combination of low concentrations of lycopene with 1.25-dihydroxyvitamin D3 exhibits a synergistic effect on cell proliferation and differentiation.

Regarding its benefits for the skin, some studies reported promising results for topically applied lycopene in protecting against UVB radiations. Mechanisms involved include suppressing ornithine decarboxylase and reversing the reduction of proliferating cell nuclear antigen (vital for DNA synthesis and cell repair) caused by UVB exposure.

Likely due to its immunostimulant and anti-inflammatory properties, lycopene has also been reported as efficient adjuvant therapy in HPV infections of the genital area.

Lycopene is available in capsules of 10 mg; doses of 10–30 mg should be taken three times per day, for 3–6 months. Alternatively, one cup of tomato juice provides an intake of approximately 23 mg lycopene. For lycopene from direct natural sources, there is no limit in quantity or intake period.

Resveratrol

Resveratrol is a stilbenoid, a resorcinol derivative produced naturally by several plants; being a phytoalexin, it protects them against insects and pathogenic microbes. Stilbenoids are hydroxylated derivatives from stilbene; they share most of the biosynthesis pathway with chalcones, all belonging to the large family of polyphenols.

It is present in high concentrations in red wines produced from grapes of *Vitis vinifera* (skin of red grapes), *Polygonum cuspidatum* (roots), and *Muscadinia rotundifolia* (skin and seeds).

Resveratrol is known and used especially for its antioxidant effect and beneficial cardiovascular protective potential. Some derma-cosmeceutical products use topical resveratrol to improve the aspect in women cellulitis, periocular cernes, and

striae. Still, there is limited scientific evidence with regard to its efficacy in these indications.

Resveratrol is available in capsules of 20, 30, or 100 mg. It is recommended in a single dose, of up to a maximum of 100 mg/day.

Silymarin

Silymarin is a mixture of flavonolignans, polyphenolic substances derived from phenylalanine via dimerization of cinnamic alcohols. Lignans are good antioxidants and act as a class of phytoestrogens, along with the isoflavones.

The main sources of silymarin are the seeds and fruits of milk thistle (*Silybum marianum*). Silymarin has a good efficacy on hepatotoxicity caused by agents like *Amanita phalloides*, ethanol, and paracetamol, as well as in chronic active hepatitis of various causes.

Regarding skin conditions, silymarin has been extensively studied for its photoprotective capacity. It has been proven to have chemopreventive effects against chemical and photocarcinogenesis in various animal tumor models. In vivo studies report antioxidant, anti-inflammatory, and immunomodulatory properties of silymarin. Available experimental data suggest that silymarin may supplement sunscreen protection, increasing anti-photocarcinogenic defenses, and be useful in conditions associated with UV radiation-induced inflammation, oxidative stress, and immunomodulatory impairment.

According to different clinical trials, silymarin dosage varies between 230 and 600 mg/day, for a standard period of 8 weeks.

Aloe vera

The active components of *Aloe vera* leaves are saponin, a triterpene with antimicrobial activity, anthraquinones (especially aloesin) with a moderate photoprotective effect, and polymannan, a polysaccharide derived from sugar mannose, with anti-inflammatory and immunostimulatory properties.

Aloe vera leaf extract is used topically for wound healing, including first-degree burns, and minor cutaneous infections like herpes simplex, rarely microbial or fungal ones. It was tried for plaque psoriasis, atopic dermatitis, seborrheic dermatitis, acne, diaper dermatitis, lichen planus, aphthous stomatitis, human papilloma virus, and frostbite, with various results. With respect to topical applications of *Aloe vera* for prevention of radiation-induced injuries or photoprotection, studies show conflicting results. Though there are some promising data regarding its use for some dermatologic conditions, clinical effectiveness of oral and topical aloe vera need more scientific confirmation.

Use of topical aloe vera gel may cause allergic reaction. It should be avoided in patients with known hypersensitivity to *Aloe vera* or plants of the Liliaceae family (e.g., garlic, onions, tulips). Taken orally, it may lower blood sugar levels; caution is advised in patients with diabetes, hypoglycemia, or glucose intolerance.

Marigold

Marigold (*Calendula officinalis*) is used topically as water solution from leaves, containing: triterpene saponins, with antimicrobial effect, and flavonoids and carotenoids, with moderate anti-inflammatory effects.

It can be useful in the treatment of wounds, burns, ulcers, mouth and throat inflammation, and seborrheic dermatitis, reducing residual erythematic and inflammation after herpes zoster and carbuncles. There is evidence that marigold can be efficient as prophylaxis for acute radiation dermatitis. Studies on animal models suggest that marigold has a good efficiency against UVB irradiation-induced skin damage, most likely associated to improvement in collagen synthesis in the subepidermal connective tissue.

There are reports of contact dermatitis, as well as aggravation of chronic leg eczema in venous insufficiency after the use of marigold extracts.

Arnica

Arnica (*Arnica montana*) is a plant belonging to the Compositae (Asteraceae) family. It is used in topical application only on intact skin, because of

its direct irritant effect. The active components are sesquiterpene lactones, with potent anti-inflammatory properties.

Arnica extracts are used topically for treatment of myalgia, arthralgia, bruises, insect bites, sometimes gingivitis, hemorrhoids, acne, and less frequent seborrheic dermatitis and psoriasis. The scientific evidence supporting its efficacy is still limited.

Arnica is available as standardized gel at a 50 % concentration.

If ingested, *Arnica* has a high toxic risk. There are reported cases of contact dermatitis following topical arnica applications.

Chamomile

Chamomile is the common name given to daisy-like plants of the Asteraceae family (*Matricaria recutita*, *Chamomilla recutita*). It is widely used all over the world, either orally, as tea, or in topical applications.

There are an important number of chemical compounds present within chamomile, each with different effects. The known antiseptic properties are due mainly to monocyclic sesquiterpene alcohols alpha-bisabolol, bisabolol oxides A and B, and secondary to other sesquiterpenes: chamazulene, farnesene, and matricin. The anti-inflammatory effects are due to a number of flavonoids: apigenin, quercetin, luteolin, and patuletin. These flavonoids have a proven moderate inhibitory effect on cyclooxygenase and lipoxygenase, on histamine release and also in promoting granulation tissue formation. For topical chamomile, studies reported an anti-inflammatory effect comparable to that of topical hydrocortisone 0.25 %. Apigenin has also been shown to have strong chemopreventive effects. Coumarin compounds such as herniarin and umbelliferone may have blood-thinning properties, and umbelliferone has also been reported to be fungistatic.

Chamomile extracts have been used for various inflammatory skin conditions like atopic dermatitis and psoriasis, mucous membrane inflammations, for rosacea, seborrheic dermatitis, and also for promoting wound healing, with variable results and scientific evidence.

Because chamomile can cause uterine contractions, leading to miscarriage, pregnant women are advised not to consume it. There is also risk of allergic reaction, contact dermatitis, or even anaphylaxis. It is still unclear whether individuals with reported allergies to chamomile were actually exposed to it, or to plants with similar appearance.

Horse Chestnut

The seed extract from horse chestnut (*Aesculus hippocastanum*) contains escin, a mixture of triterpene saponins with vasoconstrictor and vasoprotective effect, and also esculin, a coumarin glucoside which potentiates anticoagulation and has marked renal and liver toxicity. The esculin must be removed by adequate procession of the horse chestnut seed extract (HCSE).

The escin inhibits the release of elastase and hyaluronidase from leukocytes, thus preventing vascular leakage and degradation of proteoglycans from the vascular wall. Because of these favorable effects, oral HCSE escin is indicated in the treatment of chronic venous insufficiency, and topical HCSE escin can be used for varicose veins, phlebitis, and hemorrhoids.

Licorice

The extract from licorice root (*Glycyrrhiza glabra*, *G. uralensis*, and *G. inflata*) contains three xenoestrogens: liquiritin (a flavanone), glabrene and glabridin (isoflavonoids), and a peculiar compound, glycyrrhizic acid, with a sweet taste and marked antiviral properties.

Glycyrrhizic acid is used in Japan for the treatment of chronic viral hepatitis, and recent studies indicate that oral glycyrrhizic acid disrupts latent Kaposi's sarcoma.

Glycyrrhizic acid has also mineralocorticoid effects, so overdose could lead to the so-called syndrome of apparent mineralocorticoid excess

(hypertension, edema, congestive heart failure, and hypokalemia).

Topical use of licorice has also been investigated. Studies report good results for topical licorice extract 7 % in the treatment of melasma and other pigmentary abnormalities and glabridin inhibiting tyrosinase activity in melanocytes.

Licorice is available as tablets, tincture, or dried root for decoction. Recommended doses are 0.4–1.6 g three times per day for tablets, 2–4 ml three times per day the tincture, and 1–5 g three times per day as decoction, in repeated cycles of 3 months/year.

Olive Oil and Olive Leaves Extract

The extract of the fruit and leaves of the olive tree (*Olea europaea*) has been used since ancient times to moisturize and help rejuvenate damaged skin. Nowadays, the health benefits of olive oil are extensive, and new positive attributes keep being discovered.

Both olive oil and olive leaves extract contain oleic and palmitic acids and a spectrum of polyphenols: flavonoids, lignans, and especially a type of monoterpene called secoiridoid glucosides. These compounds have anti-inflammatory and antioxidant effects, benefiting a number of skin conditions. Olive oil and olive leaves extract are mostly used for hydration, but also for treating sunburns, atopic dermatitis, psoriasis, seborrheic dermatitis, acne, diaper dermatitis, calluses, stretch marks, and scars. Additional research is needed to confirm their benefits in these indications; still, cosmetic products containing olive oil and olive leaves extract have been extensively marketed for many years.

Capsaicin

Capsaicin, a mixture of vanillyl amides and isodecenoic acid, is found in hot peppers. Its most important biological effect is decreasing the intensity of different types of neurologically induced pain.

Topical capsaicin is used for a variety of neuralgias: post herpes zoster neuralgia, diabetic neuropathy, notalgia paresthetica, reflex sympathetic dystrophy, and also for hemodialysis-induced pruritus. Few reports mentioned some beneficial effects on plaque psoriasis and in the treatment of verrucae.

The use of topical capsaicin can be limited by the temporary erythema and burning sensation on the site of application.

Capsaicin is available as gels and creams with variable concentrations of 0.1–8 %. For the treatment of neuralgias, the 8 % concentration is recommended.

Vitamins and Their Use in Various Skin Conditions

Definition and Epidemiology

Vitamins are organic compounds required by our organism as a vital nutrient. Together with minerals, they are also called micronutrients, because in comparison with the major nutrients (water, proteins, fat, and carbohydrates) they are required in smaller amounts.

Role

They can serve as precursors to various cofactors, or directly as coenzymes. In addition, some vitamins have also other functions like antioxidants or hormones. Tiny as the amounts are, they are essential for the production of enzymes, hormones, and other substances essential for proper cell function, growth, and development; therefore, consequences of their absence can be severe.

Vitamins and Medical Conditions

Any disease caused by a vitamin deficiency is called hypovitaminosis.

A chronic vitamin deficiency is called avitaminosis.

Table 153.2 Reference daily intake chart for vitamins (Institute of Medicine, Washington, DC)

Vitamin	0–6 months	7–12 months	1–3 years	4–8 years	9–13 years	Male 14–18 years	Female 14–18 years	Male adult	Female adult
A (μg)	400	500	300	400	600	900	700	900	700
B1 (mg)	0.2	0.3	0.5	0.6	0.9	1.2	1	1.2	1.1
B2 (mg)	0.3	0.4	0.5	0.6	0.9	1.3	1	1.3	1.1
B3 (mg)	2	4	6	8	12	16	14	16	14
B5 (mg)	1.7	1.8	2	3	4	5	5	5	5
B6 (mg)	0.1	0.3	0.5	0.6	1	1.3	1.2	1.3	1.3
B7 (μg)	5	6	8	12	20	25	25	30	30
B9 (μg)	65	80	150	200	300	400	400	400	400
B12 (μg)	0.4	0.5	0.9	1.2	1.8	2.4	2.4	2.4	2.4
C (mg)	40	50	15	25	45	75	65	90	75
D (μg)	5	5	5	5	5	5	5	5	5
E (mg)	4	5	6	7	11	15	15	15	15
K (μg)	2	2.5	30	55	60	75	75	120	90

Hypervitaminosis is the condition that can result from chronic excessive intake of vitamins.

Reference Daily Intake (RDI) represents the average daily level of intake that is sufficient to meet the nutrient requirements of 97–98 % of healthy people (Table 153.2).

Classification

Vitamins are classified according to their biological and chemical activity, not their structure. Therefore, each vitamin includes a number of vitamer compounds, with biological activity associated with that particular vitamin. In the body, they are convertible to the active form of the vitamin, and sometimes interconvertible.

Until the mid-1930s, vitamins were available only through food intake, from various natural sources (the most important ones presented in Table 153.3). Then, vitamin B complex (from yeast extract) and semisynthetic vitamin C supplements became available, all others following. Currently, vitamins are commercially produced as semisynthetic and synthetic preparations, containing one vitamin, or a multivitamin complex.

According to their solubility, vitamins can be classified as:

- Fat soluble: vitamins A, D, E, and K
- Water soluble: vitamins B1, B2, B3, B5, B6, B7, B9, B12, and C

Vitamins in Dermatology

The use of vitamins as prophylactic and therapeutic agents in the management of multiple medical conditions increased over the years. As research on their implication in various diseases continued, it became clear that many vitamin deficiencies had cutaneous manifestations. Currently, all 13 vitamins are used also for skin disorders.

Vitamin A

Vitamers: retinol, retinal, retinoic acid, and several provitamin A carotenoids, among which beta-carotene is the most important.

Function: These fat-soluble retinoids are involved in immune function, vision, reproduction, cell growth and differentiation, bone remodeling, hematopoiesis, and antioxidant activity. They also exert a significant influence on the skin, due to their anti-inflammatory effect, seborrhea control, effects on keratinocyte differentiation and proliferation, and support of natural reparative processes in photodamaged skin.

Deficiency and Health Benefits: Vitamin A deficiency is quite rare in developed countries. However, it is still common in many developing countries due to limited access to animal-based foods containing preformed vitamin A, as well as

Table 153.3 Vitamins' natural sources

Vitamin	Natural sources
A	Cod liver oil, turkey liver, beef, pork, fish liver, carrot, sweet potato, butter, spinach, pumpkin, egg, apricot, papaya, mango
B1	Whole-wheat flour, oatmeal, flax, sunflower seeds, brown rice, whole grain rye, asparagus, cauliflower, potatoes, oranges, liver (beef, pork, and chicken), eggs
B2	Dairy products, eggs, nuts, meat, enriched flour, bananas, popcorn, broccoli, green beans, asparagus
B3	Yeast extract spread, bran (rice, wheat), fish, liver, paprika, peanuts, meat (mostly veal), tomatoes
B5	Small quantities are found in almost all foods, but higher amounts are found in whole grains, broccoli, avocado, eggs, meat, yogurt, and yeasts
B6	Chickpeas, beef liver and other organ meats, fish, chicken, cereals, potatoes, turkey, bananas
B7	Raw egg yolk, Swiss chard, liver, peanuts, seeds, soya
B9	Leafy vegetables (folic acid—from lat. folium = leaf), egg yolk, yeast, bread, cereal, sunflower seeds, liver
B12	Beef, other meats (especially liver), seafood, dairy products, eggs, fortified foods (e.g., fortified breakfast cereals, soy products, energy bars)
C	Acerola, sea buckthorn, rose hip, blackcurrant, red pepper, parsley, kiwifruit, broccoli, redcurrant, Brussels sprouts, strawberries, citrus fruits, cantaloupes, berries, spinach, tomatoes, potatoes
D	Cod liver oil, fish, milk, yogurt and other dairy products, egg yolks, beef liver
E	Oils (wheat germ, sunflower, nut), nuts, leafy vegetables: spinach, turnip, beet greens, avocado, asparagus, kiwifruit, broccoli, pumpkin, tomato
K	K1: green leafy vegetables, mustard, plant oils, soybeans, kiwifruit and grapes; K2: liver, soft cheese, egg yolk, butter, goose, chicken

to sources fresh vegetables and fruits containing beta-carotene.

Not only lack of exogenous supply can lead to lower vitamin A levels but also genetics and lifestyle factors such as smoking. A number of drugs (e.g., aspirin, phenobarbital, arsenicals) can also decrease vitamin A levels. Vitamin A plasma level drop only after the deficiency has been prolonged, so blood analyses are not very helpful for early diagnosis.

Excessive intake of vitamin A can also have severe consequences. Beta-carotene hypervitaminosis increases the risk for lung cancer in smokers and leads to skin discoloration. Chronic excess of retinoids can cause birth defects, liver toxicity, reduced bone mineral density, as well as hair loss, excessive skin dryness, and peeling. Vitamin A supplements should be avoided in people allergic to any of the products' ingredients. Same is valid for all other vitamin supplements.

The therapeutic use of vitamin A in dermatology began almost at the time of its discovery. Currently, synthetic retinoids, especially retinoic acid, are used for a number of dermatologic conditions including severe forms of psoriasis, many forms of acne, and various keratinization disorders and other dermatoses. Moreover, retinoids show antineoplastic activity.

Systemic and local administration of retinoids promotes epidermal cell growth and differentiation and sebaceous gland activity and exhibits immunomodulatory and anti-inflammatory properties, but their exact mechanisms of action are not fully understood. Intracellularly, they interact with cytosolic proteins and specific nuclear receptors, RARs and RXRs. These receptors are tissue specific, skin expressing mainly RAR gamma and RXR alpha. This could lead to development of receptor-selective retinoids, improving their therapeutic profile.

Their major adverse effect is teratogenicity, all others being dose dependent and controllable. Therefore, contraception is essential during treatment. Side effects of topical retinoids include local irritation, dry skin and mucous membranes, rashes, hair loss, skin atrophy, and easy bruising.

In psoriasis, retinoids have been established as effective systemic therapy since their introduction for clinical use. Preparations are available both for systemic and topical use. Available

preparations include acitretin, isotretinoin, and tazarotene. Despite their clear clinical efficacy, their mechanism of action has not been fully elucidated. They are known to induce keratinocyte differentiation and reduce epidermal hyperplasia, leading to the slowing of cell reproduction.

Topical retinoids are a mainstay of acne treatments, showing anti-inflammatory effects, reducing the size and secretion of the sebaceous glands and the bacterial population in ducts and skin surface, expelling mature comedones, and reducing microcomedone formation. Starting from the first-generation retinoid tretinoin, to isotretinoin, and the third-generation adapalene and tazarotene, all have a favorable safety profile compared to the systemic ones. Their broad anti-acne efficacy and good safety profile justifies their use as first-line treatment in most acne types.

Severe rosacea cases can benefit from isotretinoin as well. It is used also in pyoderma faciale after initial oral steroids, and good results have been reported in its use for granulomatous perioral dermatitis. Isotretinoin is also the regimen of choice in severe seborrhea, majorly reducing sebocyte lipid synthesis. Contraception is of course essential for all women of childbearing age.

Other dermatologic conditions such as keratosis pilaris, Darier's disease, familial benign chronic pemphigus, pityriasis rubra pilaris, ichthyosis, condylomata acuminata, granuloma annulare, lupus erythematosus, lichen planus, lichen sclerosus and atrophicus, and chronic hand eczema have been shown to respond to the immunomodulatory and anti-inflammatory activities of retinoids.

Retinoids were also proved to have antitumor activity. Bexarotene is used for the skin manifestations of advanced-stage cutaneous T-cell lymphoma. Retinoids like acitretin and isotretinoin are effective for chemoprevention of nonmelanoma skin cancer. Isotretinoin is preferred in xeroderma pigmentosum and nevoid basal cell carcinoma syndrome, whereas acitretin is used more in transplant recipients and severe sun damage.

Cosmetic skin issues such as wrinkles can also benefit from treatment with vitamin A. Tretinoin is probably the most potent for photoaging therapy. It works by increasing the production of new collagen, stimulating new blood vessels in the skin, in some cases even reducing actinic keratosis. Although retinoids show good results, irritant reactions limit their acceptance by patients.

Available options for topical use include adapalene (0.1 % gel, cream and solution; for acne), bexarotene (0.1 % gel; for cutaneous T-cell lymphoma), isotretinoin (0.05 % gel, 0.05 or 0.1 % cream; for acne), retinaldehyde (0.05, 0.1, or 0.2 % cream, gel, and lotion; cosmetic indications), retinol (0.01–4 %, serum and cream; cosmetic indications), retinol palmitate (0.5–5 % cream and lotion; cosmetic indications), tazarotene (0.05 or 0.1 % gel; for psoriasis, acne), and tretinoin (0.01–0.4 % cream, gel, solution, lotion, and ointment; for acne and photoaging).

For systemic use, medical options include acitretin (psoriasis, disorders of keratinization), bexarotene (cutaneous T-cell lymphoma resistant to other treatments), isotretinoin (severe acne and acne-related dermatoses), retinol (prevention and treatment of hypovitaminosis A), tretinoin (acute promyelocytic leukemia), and alitretinoin (chronic hand eczema).

The recent development of vitamin A derivates is likely to improve actual skin therapies. Highly receptor-selective molecules, receptor inducers, antagonists, and inverse agonists will probably be part of retinoid development in the near future. More effective and less toxic retinoids, alone or in combination and new delivery systems, may provide improved therapeutic solutions for various skin disorders.

Vitamin B1

Vitamer: thiamine and its phosphate derivatives.

Function: Thiamine phosphate derivatives are involved in a number of important cellular processes. Thiamine pyrophosphate is a coenzyme in the catabolism of carbohydrates and branched-chain amino acids. Thiamine is also important for the protein metabolism. Human body uses thiamine for the biosynthesis of acetylcholine and gamma-aminobutyric acid.

Deficiency and Health Benefits: Thiamine is the main transport form of the vitamin, while the

active forms are its phosphorylated derivatives. Thiamine derivatives are present in most cells of the body; therefore, a thiamine deficiency would be expected to have a high impact on most systems. However, only the nervous system is particularly sensitive to thiamine deficiency, due to its dependence on the oxidative metabolism.

Well-known syndromes caused by thiamine deficiency include beriberi, Wernicke-Korsakoff syndrome, and optic neuropathy. Since it is known to increase the capacity of cells to generate energy and help metabolize fats and proteins, it is also considered important for maintaining healthy skin and hair. It has been tried in cases of psoriasis, seborrheic dermatitis, acne, and hair loss, but to present no clear scientific evidence recommends thiamine supplementation for any cutaneous pathologies.

Vitamin B2

Vitamers: riboflavin, flavin mononucleotide, and flavin adenine dinucleotide.

Function: Vitamin B2 is mostly found as coenzymes flavin mononucleotide and flavin adenine dinucleotide, and only in a small percentage as riboflavin. It has a crucial role in oxidation-reduction and metabolic reactions. It is also involved in the metabolism of lipids, proteins, ketone bodies and carbohydrates, vitamin B6, and in red blood cell production. Riboflavin is critical for normal cell growth, development, and tissue repair.

Deficiency and Health Benefits: Riboflavin is mostly used in ariboflavinosis (B2 deficiency), cervical cancer, and migraine headaches.

Regarding skin, ariboflavinosis can result in dry cracked lips, inflammation of the mouth lining, glossitis, mouth ulcers, angular cheilitis, seborrhea around the nose, eyes, and ears, as well as scaling skin (affecting mostly the scrotum, labia majora, or nasolabial folds); it can also cause scrotal dermatitis, mucositis, and, in some cases, even epidermal necrolysis. Thus, riboflavin deficiency is classically associated with the oral-ocular-genital syndrome. All mentioned signs and symptoms disappear after administration of B2 supplements.

Riboflavin has been reported to help clear up cases of rosacea, acne, and seborrheic dermatitis and also accelerate the healing of various skin lesions like ulcers or burns. Recent studies focused on the therapeutic effects of systemic riboflavin in psoriasis, reporting various percentages of improvement.

Vitamin B3

Vitamers: niacin and nicotinamide.

Function: Niacin and nicotinamide are precursors of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). NAD is essential in the catabolism of lipids, proteins, and carbohydrates and also in DNA repair and cell signaling, while NADP mostly in fatty acid and cholesterol synthesis.

Deficiency and Health Benefits: Nowadays, B3 deficiency occurs rarely, mostly in conditions of malnutrition. Severe deficiency of niacin causes pellagra, a disease classically characterized by diarrhea, dermatitis, dementia, and death. Other symptoms and signs include digestive disturbances, photosensitivity, ataxia, peripheral neuritis, insomnia, mental confusion, depression, and delirium.

Pellagra, the oldest known cutaneous manifestation among vitamin deficiencies, includes skin lesion like the "Casal's necklace" (hyperpigmentation and thickening of the lower neck's skin), or dermatitis on sun-exposed areas, characteristically bilateral and symmetrical on the dorsum of the hands, but also described on the elbows, knees, axillae, perianal, and genital region. These lesions are sharply demarcated; the skin is erythematous, rough, with scaling, and fissures, and sometimes angular cheilitis, stomatitis, glossitis, oral ulcers, or alopecia can be associated. In most cases, niacin requires association of thiamine and riboflavin to clear up the pellagra lesions.

Nicotinamide has been used for more than 40 years for various dermatological conditions. Currently, systemic but also topical nicotinamide preparations, due to their anti-inflammatory and sebum-reducing properties, have proved useful in various forms of acne, rosacea, seborrheic dermatitis, atopic dermatitis, autoimmune bullous

dermatoses, psoriasis, and granuloma annulare. It also improves skin barrier function, decreasing water loss through the epidermis, thus increasing skin hydration, and improves the pigmentation, blotchiness, and redness of aging skin; therefore, it is also included in a number of cosmeceutical products.

Recently, nicotinamide has shown benefits also in the treatment and prevention of photoaging and photoimmunosuppression; it reduces solar keratoses and possibly the risk of skin cancer.

Overdose of vitamin B3 should not be overlooked, since it can lead to skin rashes, xerosis, and various digestive disorders; it also has teratogenic risks.

Vitamin B5

Vitamers: pantothenic acid, panthenol, and pantethine.

Function: Pantothenic acid is required for the synthesis of coenzyme A (CoA), important in energy metabolism and also in the biosynthesis of acetylcholine. CoA also serves as a cofactor for a variety of reactions important in the metabolism of carbohydrates, fatty acids, proteins, sterols, steroid hormones, and porphyrins.

Deficiency and Health Benefits: Vitamin B5 deficiency is exceptional, due to its widespread distribution; thus, it has not been thoroughly studied.

Pantothenic acid is important for a normal epithelial function, so it is included in preparations used in various skin disorders. Dexpanthenol, stable alcoholic analog of pantothenic acid, is suitable for topical use due to its good skin penetration. It acts as moisturizer, activates fibroblast proliferation, and accelerates reepithelization, promoting wound healing both in vitro and in vivo. Dexpanthenol has also been shown to have an anti-inflammatory effect. Its efficacy has been shown in patients with skin grafts, burn injuries, scar treatment, and different dermatoses. As an adjuvant, dexpanthenol improved skin dryness, roughness, scaling, pruritus, erythema, and erosions, proving helpful also in itching, insect bites, poison ivy, diaper rash, and acne. Regarding its benefits on gray hair or dandruff, although cosmetic industry began adding pantothenic acid to various cosmetic products, including shampoos, there are no scientific data supporting it.

Vitamin B6

Vitamers: pyridoxine, pyridoxine 5′-phosphate, pyridoxal, pyridoxal 5′-phosphate, pyridoxamine, pyridoxamine 5′-phosphate, and 4-pyridoxic acid.

Function: Vitamin B6 through its active form, pyridoxal phosphate (PLP), acts as a coenzyme for many enzymes involved predominantly in macronutrient metabolism. PLP is also an essential for the biosynthesis neurotransmitters, conversion of tryptophan to niacin, hemoglobin synthesis and function, as well as gene expression.

Deficiency and Health Benefits: Vitamin B6 deficiency is rare, being usually associated with other B complex vitamin deficiencies. It is associated with microcytic anemia, electroencephalographic abnormalities, confusion, irritability, depression, and weakened immune function.

Cutaneous signs of vitamin B6 deficiency include seborrheic eruptions localized mostly on the face, neck, and shoulders, glossitis, oral ulcerations, cheilitis, intertrigo, and a pellagra-like dermatitis. For these conditions, and others like psoriasis, or acne, treatment with oral or parenteral pyridoxine has been tried, with variable and unconfirmed results.

Pyridoxine is also used topically, being included in a number of cosmetics, both hair and skin care products, but there is no scientific evidence of their efficacy.

Vitamin B7

Vitamers: biotin.

Function: Biotin is essential for cell growth; it plays a key role in critical metabolic pathways, including gluconeogenesis, fatty acid synthesis, and amino acid catabolism. It is also a cofactor for enzymes involved in carboxylation reactions. Biotin interacts with nuclear histone proteins and

thus seems to be important in DNA replication and transcription.

Deficiency and Health Benefits: The rare cases of biotin deficiencies can be seen in alcoholics, gastrectomy, inflammatory bowel disease, metabolic disorders, long-term antibiotic or antiepileptic use, and sometimes increased consumption of raw egg whites. Pregnant women are exposed to a higher risk of biotin deficiency.

Biotin deficiency can cause neurological symptoms, increased susceptibility to bacterial and fungal infections, hair loss, and a typical periorificial dermatitis, as seen also in zinc deficiency. The characteristic facial rash, with a particular facial fat distribution, has been named the "biotin-deficient face." Biotin deficiency generally improves with supplementation.

Additionally, biotin has been tried as adjunctive therapy in palmoplantar pustulosis, seborrheic dermatitis, acne rosacea, psoriasis, systemic lupus erythematosus, and atopic dermatitis, with little and conflicting reported result.

Biotin deficiency can cause hair loss, and deficient subjects reported nails to break easily. Thus, biotin is often recommended as a dietary supplement for strengthening hair and nails, and found in many cosmetics, though there is little scientific data supporting its efficacy in these conditions.

Vitamin B9

Vitamers: folic acid, folinic acid, and 5-methyltetrahydrofolate.

Function: Vitamin B9 is important for nucleotide biosynthesis, DNA synthesis, repair, and production of healthy erythrocytes. It also acts as a cofactor in a number of biological reactions, and it is crucial in periods of rapid cell division and growth, such as infancy and pregnancy.

Deficiency and Health Benefits: Folate deficiency is more common in chronic alcohol consumers, morbidly obese patients, patients with celiac disease and cobalamin deficiency, or due to drugs which interfere with its biosynthesis (e.g., methotrexate, trimethoprim, valproic acid).

Concerning skin conditions, folic acid has been reported useful in the treatment of aged and photoaged skin, topical formulations containing folic acid exerting sustained effects on collagen metabolism. Folate has also been used for oral ulcers from methotrexate and for gingival hyperplasia from phenytoin. It is also used in acne and hair loss, but there is no scientific evidence to support this.

Side effects of folate are rare and include gastrointestinal disorders and allergic reactions. There is concern that very high doses might increase the risk of lung and prostate cancer.

Vitamin B12

Vitamers: cyanocobalamin, hydroxocobalamin, methylcobalamin, and adenosylcobalamin.

Function: Vitamin B12 is crucial for the normal function of the nervous system and the synthesis of erythrocytes. It is involved in DNA synthesis and regulation, fatty acid synthesis, and energy production. Recently vitamin B12 has also been proven to have an immunomodulatory effect on T lymphocytes and cytokines.

Deficiency and Health Benefits: Deficiency is generally due to decreased intrinsic factor production (atrophic gastritis, gastrectomy), decreased acid secretion, microbial competition, or impaired absorption, and only in exceptional cases can be caused by insufficient intake.

Vitamin B12 deficiency is characterized principally by megaloblastic anemia. Neurological findings are also common and can occur before anemia, allowing early diagnosis.

Dermatological signs of vitamin B12 deficiency include cutaneous hyperpigmentation, commonly affecting the face, hands, flexural regions, and pressure points, angular cheilitis, Hunter glossitis, and hair depigmentation; all tend to remit after a proper vitamin B12 treatment.

Studies have also noted low levels of this vitamin in psoriatic plaques. Thus, the potential use of vitamin B12 in psoriasis therapy has recently started to be evaluated.

Vitamin B12 has also been tried as supplemental therapy for stomatitis, seborrheic dermatitis, erythema nodosum, herpes zoster, hyperpigmentation, trophic ulcers, burns, and hair loss, with various and conflicting results.

Vitamin C

Vitamers: ascorbic acid, dehydroascorbic acid, calcium ascorbate, sodium ascorbate, and other salts of ascorbic acid.

Function: Vitamin C acts as an essential cofactor in enzymatic reactions forming hydroxyproline, which is critical for collagen stability. It has many other functions, including antioxidant effects, decreasing UV-induced DNA damage and lipid peroxidation, and increasing the immune's system activity, iron absorption, and steroidogenesis. Essential also for the proper functioning of the skin barrier, vitamin C normalizes epidermal lipid formation, including glucosphingolipids and ceramides, crucial for the stratum corneum.

Deficiency and Health Benefits: The avitaminosis resulting from the lack of vitamin C is scurvy, and its manifestations are mostly due to the impaired synthesis of collagen. Generally, the first cutaneous signs characterizing scurvy are the bruise-like spots surrounding hair follicles, perifollicular hyperkeratotic papules, appearing generally on the shins. The central hairs are very fragile, twisted like corkscrews. Progressing, these papules form large purpuric areas. Gums may swell, become erythematous, fragile and bleed easily. Other possible signs include xerostomia, keratoconjunctivitis sicca, and salivary glands hyperplasia, mimicking Sjogren syndrome. Scurvy responds well to treatment with ascorbic acid.

A number of dermatologic diseases seem to benefit from systemic and topical vitamin C supplementation; conditions might be improved due to its anti-inflammatory action (e.g., postinflammatory hyperpigmentation, acne, rosacea, psoriasis), depigmenting effect (melasma, postinflammatory hyperpigmentation), as well as its effect on collagen synthesis (wound healing, especially pressure ulcers). Some cases of dyskeratoses, such as keratosis pilaris and Darier's disease, which failed to respond to vitamin A, were also reported to respond to vitamin C. Studies also focused on the protective role of vitamin C in nonmelanoma skin cancer, but their results are still contradictory.

Aging and excessive exposures to UV light have been reported to lower vitamin C skin levels; studies assessing the antiaging and photoprotective effects of vitamin C showed promising but not conclusive results.

Topical products such as creams, gels, serums, etc., containing various concentrations of vitamin C generally ranging from 5 to 20 % are widely marketed. Their claimed indications are multiple, few of these having scientific support.

Overdose of vitamin C can cause stomach disturbances, abdominal cramps, diarrhea, flushes, headache, and increased urination. For topical use, rare side effects include discoloration of the skin, hypopigmented hair, stinging, erythema, and dryness.

Vitamin D

Vitamers: ergocalciferol (D2) and cholecalciferol (D3).

Function: Vitamin D is mainly responsible for promoting intestinal absorption and maintaining adequate serum levels of calcium and phosphate. It is also important for cell growth, proper function of the neuromuscular and immune systems, and inhibition of the inflammatory response.

Both vitamin D and its analogs can bind to specific nuclear receptors, enhancing keratinocyte differentiation, inhibiting keratinocyte proliferation, promoting proapoptotic effects, and regulating the local immune response.

Deficiency and Health Benefits: Vitamin D deficiencies can result from insufficient dietary intake, impaired absorption or function, increased requirements, as well as limited exposure to sunlight and dark skin.

The classical forms of vitamin D deficiency are rickets and osteomalacia. Osteoporosis is generally associated with low calcium intake, but insufficient vitamin D also contributes to this condition.

Due to the multiple effects that vitamin D has on the skin, a number of analogs have been tried in various dermatological conditions. Such molecules were proved to be a therapeutic success in psoriasis, at present the main cutaneous

indication. Due to their immunomodulatory effect, oral calcitriol and calcipotriene have been reported useful in the treatment of morphea, and topical calcipotriene in a number of lichen sclerosus cases. Favorable effect of topical calcipotriol on actinic keratoses has also been described.

Vitamin D and its analogs have been investigated for chemoprevention in melanoma and metastasis of malignant tumors. The results of the various studies are conflicting, so more research on the topic is needed.

Recently, it has been shown that calcitriol, the active form of the vitamin D, is responsible for regulating antimicrobial peptides, a major component of the antimicrobial innate immune responses. Bacteria hardly develop resistance against them; based on this, a new class of antimicrobial agents is being developed.

Although the specific mechanism of action is not fully known, a number of studies stress the association of vitamin D and nonmelanoma skin cancers. Other researches focused on the benefit of the vitamin in cases of rosacea, seborrheic dermatitis, and atopic dermatitis. Unfortunately, clear scientific data supporting the benefit of vitamin D in these indications is still required.

Three vitamin D analogs, namely, calcipotriol, calcitriol, and tacalcitol, are currently marketed for topical use, main indication being psoriasis. Calcipotriol is available as ointment, cream (both at the concentration of 50 mcg/g), and scalp lotion (50 mcg/ml). Once or twice/day applications are recommended, with improvement usually within 2 weeks. This can often be maintained by continuing treatment. The maximum dose, by the manufacturer's recommendations, is 100 g/week for adults, 75 g for children over 12 years, and 50 g for children of 6–12 years. Under 6 years, the use is not recommended. Calcipotriol is also available in combination with betamethasone dipropionate, having greater efficacy than either constituent alone.

Calcitriol is available as ointment, containing 3 mcg/g of 1:25 dihydroxycholecalciferol. It is less irritant but also less effective than calcipotriol. It can be useful for the face and flexures, but it should not exceed 30 g/day and should not be applied on more than 35 % of the body surface. Tacalcitol is also less irritant than calcipotriol. It is available in 4 mcg/g concentration, suitable for the face and flexures. Amount applied should not exceed 10 g/day.

Vitamin E

Vitamers: tocopherols and tocotrienols (alpha, beta, gamma, delta).

Function: Vitamin E is mostly known for its antioxidant function, acting as a scavenger of free radicals. Being fat soluble, it is incorporated into cell membranes, protecting them from oxidative damage. Throughout the body, it is involved in many other processes, including gene expression, enzymatic activities, neurologic functions, inhibition of platelet aggregation, and cell signaling (the most important activity, according to recent studies).

Deficiency and Health Benefits: Vitamin E deficiency is very rare and almost never due to a poor intake. It can be caused by genetic abnormalities of tocopherol transfer protein, fat malabsorption conditions, or protein-calorie malnutrition.

Various dermatological conditions have been reported to benefit from vitamin E supplementation. Due to its anti-inflammatory action, vitamin E has been used in atopic dermatitis, psoriasis, discoid lupus erythematosus, granuloma annulare, and lichen sclerosus et atrophicus, with various results. It also seems to reduce sebum production in seborrheic skin, being efficient in seborrheic dermatitis and acne. In addition, it has been reported to decrease pruritus, improve wound healing, limit hypertrophic scar formation, and promote hair growth. There is a definite need for more scientific data to support the efficacy of vitamin E in these conditions.

Based on vitamin E's antioxidant effect, oral and topical preparations containing it have been evaluated for their potential in antiaging, photoaging, skin tumors, and photoprotection. Cosmeceutical products such as creams, serums, or gels, containing various concentrations of vitamin E, are already marketed claiming these indications, but more research is actually needed to confirm such benefits.

Skin conditions such as contact dermatitis with topical use of vitamin E and pruritus following oral supplementation have been reported.

Vitamin K

Vitamers: phytomenadione (K1), menaquinones (K2), and menadiones (K3-5, synthetic forms).

Function: Vitamin K is crucial for the synthesis of a number of coagulation factors, like factors II, VII, IX, and X, and protein C and S. It is also involved in the bone and other tissues' metabolic pathways.

Deficiency and Health Benefits: Primary vitamin K deficiency is very rare in healthy adults. This deficiency impairs the coagulation cascade, which results in hemorrhagic events, purpura, ecchymosis, hematomas, anemia, and bleeding.

A number of skin conditions seem to benefit from systemic and also from topical application of vitamin K, which has been reported to accelerate wound healing, reduce bruising and swelling and hyperpigmentation, improve venous circulation, and relieve itching accompanying biliary cirrhosis. Commercial vitamin K formulations are already marketed, claiming to remove spider veins, bruises, scars, and stretch marks, heal wounds, treat rosacea, or improve the elasticity of the skin, but more scientific evidence is needed to properly rate vitamin K for these uses.

Vitamins K1 and K2 have a good safety profile, but vitamin K3 (synthetic form) has known toxicity. In large doses, it can cause allergic reactions, hemolytic anemia, and cytotoxicity.

Future Perspectives

- Further research including clinical assessment of selected active compounds from natural sources will supply more scientific evidence, supporting their efficacy in various dermatological conditions.
- New delivery systems with increased topical absorption and improved stability might increase the efficacy of these natural remedies.
- The World Health Organization stresses on global awareness by upgrading and expanding the Vitamin and Mineral Nutrition Information System (VMNIS).
- Increasing the knowledge on their mechanisms of action and scientifically proven benefits will help include nutritional supplements and vitamins in the daily clinical practice.

Further Reading

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