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A comprehensive review and update on ulcerative colitis☆,☆☆

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ABSTRACT

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disorder of the colon that causes continuous mucosal inflammation extending from the rectum to the more proximal colon, with variable extents. UC is characterized by a relapsing and remitting course. UC was first described by Samuel Wilks in 1859 and it is more common than Crohn's disease worldwide. The overall incidence and prevalence of UC is reported to be 1.2–20.3 and 7.6–245 cases per 100,000 persons/year respectively. UC has a bimodal age distribution with an incidence peak in the 2nd or 3rd decades and

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followed by second peak between 50 and 80 years of age. The key risk factors for UC include genetics, environmental factors, autoimmunity and gut microbiota. The classic presentation of UC include bloody diarrhea with or without mucus, rectal urgency, tenesmus, and variable degrees of abdominal pain that is often relieved by defecation. UC is diagnosed based on the combination of clinical presentation, endoscopic findings, histology, and the absence of alternative diagnoses. In addition to confirming the diagnosis of UC, it is also important to define the extent and severity of inflammation, which aids in the selection of appropriate treatment and for predicting the patient's prognosis. Ileocolonoscopy with biopsy is the only way to make a definitive diagnosis of UC. A pathognomonic finding of UC is the presence of continuous colonic inflammation characterized by erythema, loss of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations, with distinct demarcation between inflamed and non-inflamed bowel. Histopathology is the definitive tool in diagnosing UC, assessing the disease severity and identifying intraepithelial neoplasia (dysplasia) or cancer. The classical histological changes in UC include decreased crypt density, crypt architectural distortion, irregular mucosal surface and heavy diffuse transmucosal inflammation, in the absence of genuine granulomas. Abdominal computed tomographic (CT) scanning is the preferred initial radiographic imaging study in UC patients with acute abdominal symptoms. The hallmark CT finding of UC is mural thickening with a mean wall thickness of 8 mm, as opposed to a 2–3 mm mean wall thickness of the normal colon. The Mayo scoring system is a commonly used index to assess disease severity and monitor patients during therapy. The goals of treatment in UC are three fold—improve quality of life, achieve steroid free remission and minimize the risk of cancer. The choice of treatment depends on disease extent, severity and the course of the disease. For proctitis, topical 5-aminosalicylic acid (5-ASA) drugs are used as the first line agents. UC patients with more extensive or severe disease should be treated with a combination of oral and topical 5-ASA drugs $+/-$ corticosteroids to induce remission. Patients with severe UC need to be hospitalized for treatment. The options in these patients include intravenous steroids and if refractory, calcineurin inhibitors (cyclosporine, tacrolimus) or tumor necrosis factor-α antibodies (infliximab) are utilized. Once remission is induced, patients are then continued on appropriate medications to maintain remission. Indications for emergency surgery include refractory toxic megacolon, colonic perforation, or severe colorectal bleeding.

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Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD) of the colon that causes a superficial mucosal inflammation in a continuous fashion extending from the rectum to the more proximal colon, in varying extents.[1] UC is characterized by a relapsing and remitting course.[1] The hallmark symptoms of UC include bloody diarrhea with rectal urgency and

tenesmus. Although the etiology of UC remains a subject of debate, increasing evidence suggests the presence of an underlying autoimmune component.[2,3] Many UC patients experience extraintestinal manifestations (EIM) that involve multiple organs sharing features with other autoimmune disorders. The annual direct and indirect cost related to UC is estimated to be as high as $8.1–14.9 billion in the United States of America (USA).[4] Here, we review the current literature on the pathophysiology, diagnosis, and treatment of UC.

Epidemiology and risk factors

UC was first described by Samuel Wilks in 1859. Worldwide, UC is more common than Crohn's disease (CD).[5] UC is most common in industrialized countries and the incidence has been rising in Asia.[6,7] A prospective study from the United Kingdom (UK) showed that second generation South Asian immigrants to the UK had a higher incidence of UC when compared with the European population (17.2 vs. 7 per 100,000 population/year).[8,9] The overall incidence and prevalence of UC is reported to be 1.2 - 20.3 and 7.6 - 245 cases per 100, 000 persons/year, respectively.[10–12] Based on the Rochester Epidemiology Project, the prevalence of UC in the USA has increased from 214 cases per 100,000 person-years to 286 cases per 100,000 person-years from the year 2000 to 2011.[12, 13] Studies have reported that ethnic and racial differences are more related to environmental influences, food habits and life style rather than the true genetic differences. Population based studies have showed no significant gender differences in UC.[14] UC has a bimodal age distribution with incidence peak in the second or third decades of life followed by a second peak between 50 and 80 years of age.[15] Geographic variations have been observed in Europe and the USA with higher incidence in the northern latitudes when compared with the southern latitudes.[16,17]

The following are the risk factors for UC:

(1) *Age and gender*: UC has a bimodal age distribution with incidence peak in the second or third decades of life followed by a second peak between 50 and 80 years of age.[15] No consistently significant difference has been observed between rates of UC among men and women, however some studies demonstrate a male predominance in UC.[11]

(2) *Race and ethnicity*: Jewish population has a 3-fold higher risk of IBD than non-Jewish populations. Among the Jewish population, Ashkenazi Jews have a higher prevalence compared to the Sephardim, American and European Jewish populations.[19] Initial studies reported a markedly lower prevalence of IBD among African-American and Hispanic ethnicities when compared to the white populations, however recent studies suggest that the gap in incidence between white and non-white populations is narrower than first thought, with comparable phenotypes.[20]

(3) *Genetics*: About 8–14% of patients with UC will have a family history of IBD, more commonly UC (Fig. 1). The Jewish population has an increased frequency of UC when compared with the non-Jewish population. The relative risk of developing UC for first-degree relatives of a patient with UC is estimated to be 4.5% in Jewish probands when compared with 1.6% in non-Jewish probands.[21] Twin studies have shown that the concordance rates in monozygotic twins are estimated at 16% for monozygotic and 4% for dizygotic twins.[22] Several studies have attempted to identify genetic predictors of severe clinical course of UC. Based on genome-wide association study (GWAS), TNFSF15 (TL1A) locus has been reported to increase the risk of severe UC. Other studies have identified polymorphisms in the Il1B gene, ABCB1/MDR17, HSP708 and HLA-DR29 as predictors for severe UC.[23]

(4) *Smoking*: The association between smoking and UC was first reported by Harries et al.[24] In contrary to CD, active smoking has a strong inverse association with active UC (OR 0.58, 95% CI 0.45–0.75).[25,26] In a prospective study, the risk of UC increased within 2–5 years after smoking cessation and remained elevated for 20 years after.[16] Studies have showed that current smoking is associated with later age of onset, milder disease course, need for less immunosuppression, and reduced need for surgery.[27,28] However nicotine

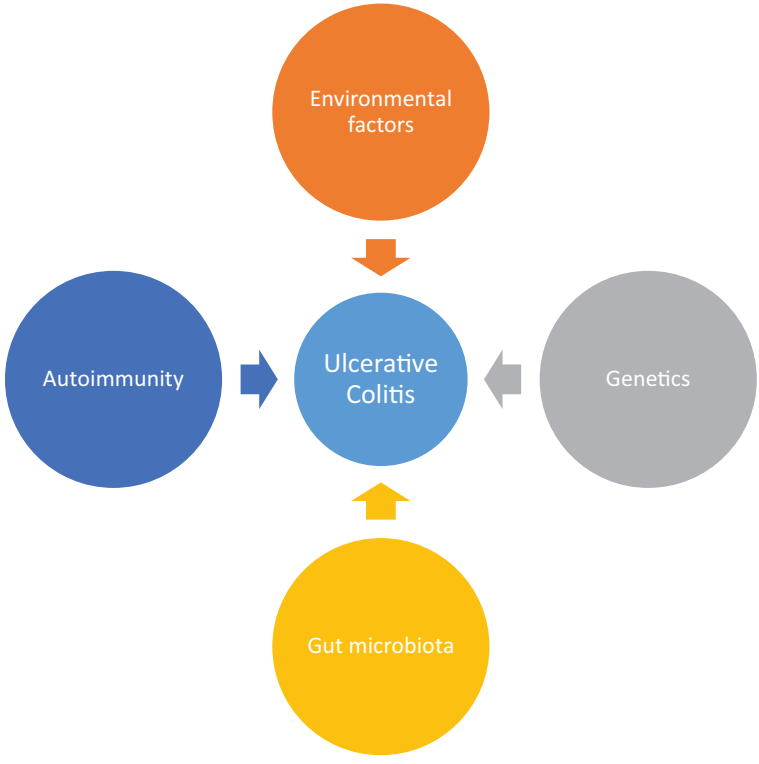

Fig. 1. Key risk factors for the development of ulcerative colitis (figure adapted from Malik,[18] with permission from Elsevier).

replacement in UC has not been found to reduce disease activity, suggesting an effect of tobacco on UC, independent of nicotine.[29,30]

(5) *Diet*: Development of IBD has been postulated to be an immunologic response to food antigens. The association of a "Western" style diet (processed meat, refined carbohydrates, etc) is associated with an increased risk of developing IBD.[31] Cow's milk protein hypersensitivity during infancy has been postulated as a possible cause of UC when compared with controls (21% vs. 3%).[32] Increased dietary intake of total fat, animal fat and polyunsaturated fatty acids are also correlated with an increased incidence of UC.[33]

(6) *Microbiota*: Several epidemiological clues point toward dysbiosis of the intestinal microbiota in IBD. Dysbiosis is defined as an altered composition of the commensal bacterial populations, leading to the dysregulation of the immune response to bacterial antigens. This difference in microbial diversity is greater in CD than in UC. Mucosal transcriptional profile (showing mucosal gene expression) from healthy siblings shows a greater correlation with bacterial gene expression compared to patients with UC or their healthy twins, suggesting a disordered interaction between the mucosa and microbiota in IBD.[34] Also, abnormality in enteric virome has been reported in UC with expansion of bacteriophages belonging to the Caudovirales family independent of bacterial dysbiosis.[35]

(7) *Appendectomy*: Similar to smoking, appendectomy has a divergent effect on UC and CD. Based on a large cohort study, the risk of developing UC was decreased by about 55% in those who underwent appendectomy before they were 20 years old for an inflammatory condition (appendicitis or mesenteric lymphadenitis), but not for nonspecific abdominal pain.[36] In contrast, the risk of CD was increased after appendectomy.[37] In pa-

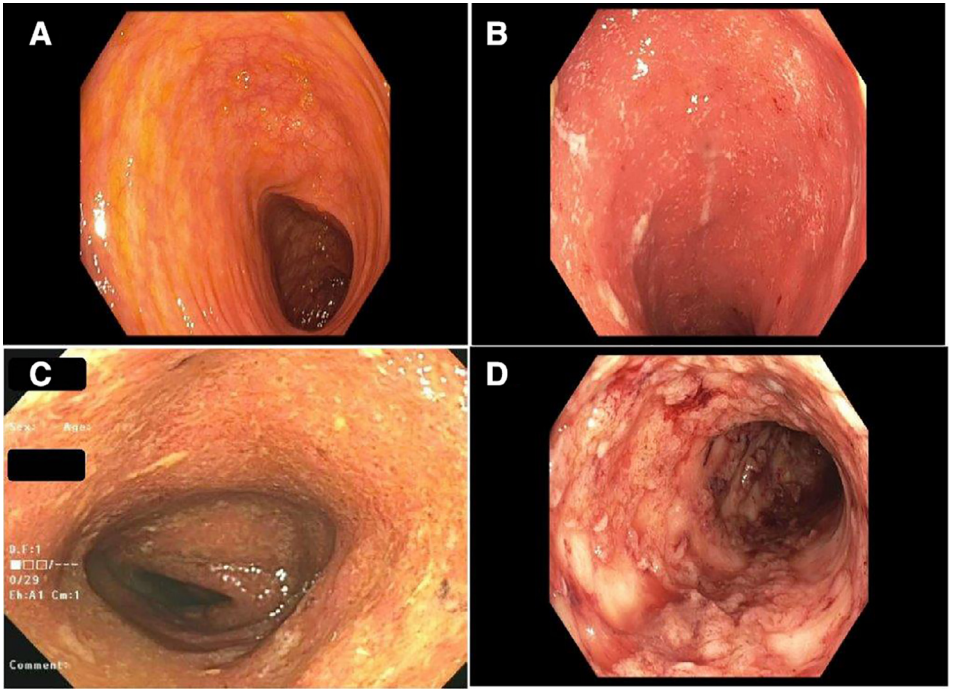

Fig. 2. Colonoscopy images showing (A) normal colon, (B) mild colitis, (C) moderate colitis, (D) severe colitis.

tients with UC, a prior appendectomy was associated with clinically milder disease, lower relapse rates, reduced need for immunosuppression, but had no clear effect on risk of colectomy.[38–40]

Clinical features and extra intestinal manifestations (EIM)

The classic presentation of UC includes symptoms of bloody diarrhea with or without mucus, rectal urgency, tenesmus, and variable degrees of abdominal pain that is often relieved by defecation.[10] Perhaps underappreciated, a minority of patients may present with constipation.[10,41] Ford et al. reported that a combination of anemia, weight loss of more than 5 kg in the past year, and having more than 4 bowel movements daily, had a positive likelihood ratio (LR) of 14.6 for diagnosis of UC; while patients with only anemia and more than 4 daily stools had a LR of 7.87.[42] Typically, symptoms present as intermittent attacks that may become more frequent and occasionally so severe that they require hospitalization.[43] Common laboratory abnormalities among UC patients include iron deficiency anemia, thrombocytosis, hypoalbuminemia and positive autoantibodies such as anti-goblet cell and anti-neutrophil cytoplasmic antibodies (ANCA).[44] Diagnosis depends on the appropriate clinical and histologic findings on endoscopic and biopsy. In some cases, differentiating UC from CD may present a clinical challenge.[45]

UC is often associated with other gastrointestinal (GI) conditions (Table 1). Several studies report an association of UC with Helicobacter pylori gastritis or focal gastritis.[46–48] A feared complication of UC is toxic megacolon, in which the local inflammatory process may be severe enough to disrupt the neuromuscular function of the colon leading to its dilation and subsequent perforation.[49–51] Clinical criteria for diagnosis of toxic megacolon include at least 3 of the following findings: temperature >101.5 °F, pulse rate >120/min, white blood cell count $>10.5 \times 10^9$/l or anemia. In addition to the above findings, the patient should also have one of the following:

Table 1
Differential diagnosis for ulcerative colitis (adapted from Nikolaus and Schreiber[45] with permission from Elsevier).

Symptom	Disease	Characteristics/examples
Bloody diarrhea	Behçet's disease	HLAB51 positive; oral aphthous ulcers
	Crohn's disease	Right-sided pain; abscesses, fistulas; imaging, colonoscopy
	Infectious colitis	Travel history; Stool WBCs, Stool O&P, *Campylobater, Salmonella, Shigella, Enterohemorrhagic E. coli, C. difficile, Entamoeba histolytica*, intestinal tuberculosis
	HIV/AIDS	CD4 count; CMV, HIV, MAC serologies
	Neoplasm	Imaging study; colonoscopy
	Ischemic colitis	Disproportionate pain; angiography
	Sexually transmitted disease	Chlamydia, Gonorrhea
	Radiation colitis	History of cancer treatment; colonoscopy
Non-bloody diarrhea	Irritable bowel syndrome	Normal studies; no nocturnal diarrhea
	Crohn's disease	Non-bloody diarrhea; colonoscopy
	Neoplasm	Imaging studies; colonoscopy
	Pancreatic insufficiency	Alcoholism; increased fecal fat; chronic pancreatitis
	Celiac disease	Food triggers; endomysial/gliadin antibodies; colonoscopy
	Infectious	Stool C&S, Stool O&P; travel history; seasonal (Rotavirus/Norovirus); Giardia; Staphylococcal; *Clostridium perfringens*
	Hyperthyroidism	TSH, free T3 and Free T4
	HIV/AIDS	CD4 count; HIV serology; Cryptosporidiosis, Isospora belli

MAC: Mycobacterium avium complex; O&P: ova and parasites; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; C&S: culture and sensitivity; CMV: Cytomegalovirus; TSH: thyroid-stimulating hormone; T3: triiodothyronine; T4: free thyroxine; CD4: cluster of differentiation 4.

dehydration, hypotension, altered level of consciousness, or electrolyte abnormalities.[51] *Clostridium difficile* has been found in increasing incidence in UC, and physicians should always exclude this condition.[52]

Two key areas of extra-colonic GI involvement include the pancreas and hepatobiliary system. Acute or chronic pancreatitis may precede, occur with, or be a complication of UC.[53–57] There is an association between primary sclerosing cholangitis (PSC) and UC. In a systematic review, Gizard et al. studied the prevalence of PSC and cholelithiasis among UC patients and found rates ranging between 0.76%–5.4% and 4.6%–36.4%, respectively.[58] In the 7 year study by Parente et al., however, there was no difference in the incidence of gallstones in patients with UC (7.48/1000 persons/year; 95% CI 3.41–11.55) when compared with the control population (6.06/1000 persons/year; 95% CI 2.30–9.81).[59] Previous studies have identified gene mutations influencing the levels of IL-10 signaling in both UC and PSC.[60] In the cross sectional study by Halling et al., there was a higher incidence of autoimmune hepatitis, primary biliary cholangitis, and atrophic gastritis among patients with UC when compared to the control group.[2]

Increasing evidence suggests that the relationship of UC with EIM is multifactorial, involving genetic, environmental, and autoimmune components.[61] More than one EIM is common in patients with UC.[62] The most common non-GI system to be involved is the musculoskeletal system, followed by the integument, ocular, and renal systems. Several of these complications may actually precede the development of colitis and the diagnosis of UC. Thus clinicians should maintain a heightened index of suspicion for impending colitis if these symptoms should develop.[63]

As noted, rheumatologic involvement remains one of the most common non-GI-related complaints among patients with UC.[64] Both large and small joints may be affected with the former being more associated with active bowel disease, and the latter often confused with rheumatoid arthritis.[65] Rates of axial spondyloarthritis (ankylosing spondylitis) does not differ between that of UC and CD.[66] The close relationship between IBD and arthritic conditions suggests that both may share genetic and immune alterations.[67]

The skin is the next most affected non-GI system to be involved in patients with UC. Such involvement includes erythema nodosum (most common skin manifestation), pyoderma gangrenosum and recurrent aphthous stomatitis, which may precede UC or occur during times of flare-ups. Other manifestations may represent nutritional deficiencies such as cheilitis, glossitis or pellagra.[68] Melanoma has also been reported with increased frequency in patients with UC.[69] Ocular manifestations including uveitis or episcleritis, can develop prior to the onset of colitis or with the onset of disease. A family history of IBD is a risk factor for ocular involvement. Also, ocular symptoms have been correlated with the presence of other EIMs.[70]

Less common, but important manifestations include renal, pulmonary and vascular complications. Renal conditions include renal insufficiency and nephrolithiasis.[71,72] Frequent pulmonary complications in UC include pulmonary vasculitis, while restrictive disease on pulmonary function testing and pulmonary embolism appear about equally in both UC and CD, but higher than in controls.[73,74] Patients with UC have a higher rate of venous thromboembolic events (deep venous thrombosis and pulmonary embolism) than those without UC, as well as arterial thromboembolic disease such as stroke that may occur at earlier ages; the etiology of this is likely multifactorial.[75–79] Finally, patients with UC have an overall increased risk of developing cancers such as colorectal neoplasms and leukemia.[80]

Natural course

UC is a chronic disease with variable rates of relapse and remission. Multiple factors that play a role in its etiology could be responsible for a unique profile of the disease. The disease manifests by waxing and waning symptoms, with random episodes of varying severity. At the time of presentation, approximately 40% of patients present with proctitis, 30% present with left-sided colitis, and 30% with pancolitis. Disease progression most often follows a gradual course with only 14%–16% of patients going from proctitis directly to pancolitis. Over 10-years, 50%–55% remit, while approximately 37% of patients follow a chronic, intermittent course, 6% develop a chronic continuous course, and only 1% have a period of low activity followed by a severe increase. Generally, 20%–30% of patients require a colectomy after 25 years of disease activity. Yet, overall mortality in patients with UC is similar to that of matched controls. However, those with new disease and those with extensive disease tend to have increased mortality.[43,81]

UC has some distinct features among affected groups. Patients with disease onset after 60 years of age more often present with left-sided disease, have milder disease, and lower rates of disease progression.[82,83] Hispanic populations tend to be older at presentation, female, and have pancolitis at disease onset.[84,85] Damas et al. noted that foreign-born Hispanics had greater severity of disease than US-born Hispanics.[86] In African-American patients, a similar distribution of left-sided and pancolitis was evident compared to non-Hispanic whites.[87,88] Asians also tended to have more left sided colitis and pancolitis at presentation.[89]

Predicting clinical relapse is essential for improving the morbidity associated with UC, as timely interventions can avoid invasive procedures and higher medical costs. Based on the analysis of Nationwide Emergency Department Sample database, UC when compared to CD patients were older, more likely to be hospitalized when they go to emergency department, had longer length of stay in the hospital, and had higher percentage of all comorbidities except bowel obstruction and intraabdominal abscess.[90] Liverani et al. proposed an algorithm based on clinical findings and levels of biological markers to identify patients at high risk for clinical relapse. The study suggested that patients at higher risk for relapse have younger age of onset, extensive disease, prior multiple relapses and fecal calprotectin of greater than 190 ug/g on repeated testing.[91] The risk factors that are associated with increased disease extension in UC include obesity, history of appendectomy and severe disease activity.[92]

It is also thought to be possible to use histologic features to predict clinical outcomes and disease recurrence. Over the years, there have been many scoring systems developed to assess

Table 2
Diagnostic features of UC.

Clinical features	Diarrhea, abdominal pain, urgency, tenesmus, hematochezia, blood and mucus in the stool
Lab findings	Inflammatory markers: elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fecal calprotectin, and fecal lactoferrin Nutrition markers: Low ferritin, anemia, and low albumin levels Serology: p-ANCA (+), ASCA (−)
Endoscopic findings	Inflammation begins in the rectum and extends proximally in a circumferential and continuous fashion. Findings include erythema, edema/loss of the fine vascular pattern, increased granularity of the mucosa, friability/spontaneous bleeding, pseudopolyps, erosions, and ulcers (Fig. 2).
Histological findings	Crypt abscesses, crypt branching, crypt shortening, crypt disarray, crypt atrophy, mucin depletion, paneth cell metaplasia, increased lamina propria cellularity, basal plasmacytosis, basal lymphoid aggregates, and lamina propria eosinophils.

disease activity such as the Modified Riley Score, the Gupta Index, and the Geboes scoring system. One review article suggested that such systems that are used to determine the degree of histologic inflammation might play a role in determining a patient's prognosis. For example, in patients with a higher degree of microvascular inflammation, a higher risk of relapse was recorded. Shorter relapse times were associated with the presence of basal plasmacytosis in the biopsy specimens of patients with UC in remission. Lastly, severe eosinophilic infiltration was the strongest predictor of treatment failure in patients with UC.[93]

Diagnosis of ulcerative colitis

UC is diagnosed based on a combination of clinical presentation, endoscopic findings, histology, and the exclusion of alternative diagnoses (Table 2). In addition to confirming and accurately diagnosing UC, it is also important to define the extent and severity of inflammation, which guides the selection of appropriate treatments and for predicting the patient's prognosis.

Laboratory studies

Laboratory measurements are helpful in assessing and monitoring disease activity. Complete blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fecal lactoferrin and fecal calprotectin levels help determine the severity of inflammation. In addition, serum albumin along with iron studies and vitamin B12 levels are used to assess for nutritional status and screen for nutritional deficiencies.[94] Hypoalbuminemia is a marker for severe disease and is a predictor of colectomy and poor response to biological drugs.[95]

Serology

The two most extensively measured antibodies are perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA).[96] In combination, they are used to differentiate between UC and CD. In CD, the usual pattern is ASCA+/p-ANCA−, whereas in UC, the associated pattern is ASCA−/p-ANCA+.[26,96–98] Patients with severe, refractory disease should be assessed for cytomegalovirus infection by serology, histopathology, culture, or DNA PCR testing.

Stool studies

Fecal calprotectin (neutrophil-derived biomarker) and lactoferrin levels are helpful to assess the degree of inflammation and to detect clinical relapse in patients with UC.[99] Infections should be excluded in all patients who are being evaluated for a new diagnosis of UC. These patients should have stool studies to check for *C. difficile* GDH and toxin, routine stool cultures

(*Salmonella, Shigella, Campylobacter, Yersinia*), and specific testing for *Escherichia coli* O157:H7 to rule out infectious causes of their diarrhea. Microscopy for ova and parasites (three samples) and a *Giardia* stool antigen test should also be performed especially for patients with recent travel to endemic places.

Procedural studies

Endoscopy

Ileocolonoscopy with biopsy is the only way to make a definitive diagnosis of UC.[100] It is also the gold standard for monitoring disease in response to medical treatment. A pathognomonic finding of UC is the presence of continuous colonic inflammation characterized by erythema, loss of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations, with a clear distinct demarcation between inflamed and non-inflamed bowel.[101,102] Up to 75% of patients with left sided UC may be accompanied by an isolated area of inflammation around the appendiceal orifice, commonly known as a peri-appendiceal red patch (PARP) or as a cecal patch.[103,104] Backwash ileitis has been reported in 20% of patients with pancolitis and the inflammatory changes are typically mild.[105] For a reliable diagnosis, at least two biopsies should be taken from six different areas (terminal ileum, ascending, transverse, descending, sigmoid colon, and rectum), including normal appearing mucosa.[106] The samples should be fixed immediately by using buffered formalin or an equivalent solution. Salient histological findings in UC include distortion of crypt architecture, crypt shortening, crypt abscesses, cellular infiltrate with plasma cells (basal plasmacytosis), increased lymphocytes in the lamina propria, mucin depletion and paneth cell metaplasia.[107,108] Advanced endoscopic procedures such as high definition endoscopy, narrow band imaging, magnification endoscopy, chromoendoscopy and endomicroscopy that help in detailed assessment of mucosa and the submucosal vasculature can also be utilized.[109] In patients with upper GI tract symptoms, an esophagogastroduodenoscopy (EGD) is recommended to rule out CD.[105]

Surveillance for dysplasia. Colon cancer remains one of the most commonly diagnosed cancers among males and females. In the general average-risk person, a screening colonoscopy is recommended at the age of 50 years in Caucasians and at 45 years in African Americans. In patients who have a normal colonoscopy, a repeat colonoscopy is recommended after 10 years from the initial colonoscopy. Patients who have polyps on their screening colonoscopy will need a surveillance colonoscopy, timing of which will depend on the number, size, and pathology of polyps identified. A surveillance colonoscopy is defined as the interval procedure indicated in those patients at high risk for colorectal cancer (CRC) such as those with a previously diagnosed CRC, a precancerous lesion, or in patients with chronic colitis such as inflammatory bowel disease (IBD) colitis.[110]

Patients with IBD are at increased risk for the development of CRC. Among UC patients, the risk of CRC is 2%, 8% and 18% after 10, 20 and 30 years of disease.[111] Although recent studies suggest that the rates of CRC may be lower than those noted in the past, the risk is still present. An explanation for this lower rate of CRC may be due to the increase in early utilization of medications to control inflammation such as biologics, thiopurines, and aminosalicylates as well as the more aggressive goals targeting mucosal healing. Other reasons to account for this decline in CRC rates among IBD patients include the more proactive referral for surveillance colonoscopy and the improvement in the quality of scopes.

Among IBD patients, there have been several risk factors for the development of CRC identified. Disease extent, histologic activity, and duration of disease are recognized as important risk factors. Specifically, the risk of CRC significantly increases after 8 years of diagnosis.[112,113] Other risk factors include family history of CRC, presence of concomitant PSC, and presence of colonic strictures, shortened colon due to long standing inflammation, and pseudopolyps.[114,115] UC patients with concomitant primary sclerosing cholangitis (PSC) are at a 4-fold increased risk

compared to those UC patients without PSC. Due to this, an annual colonoscopy is recommended in patients with UC and PSC.

The best marker for CRC is dysplasia, and this is found in up to 90% of CRC patients.[114] The purpose of surveillance colonoscopy is to reduce the incidence of CRC, subsequently decreasing the morbidity and mortality associated with it by detecting pre-cancerous lesions to prevent their malignant transformation and advancement.[116]

Current guidelines recommend endoscopic surveillance for dysplasia and colon cancer in IBD patients who have had disease (at least left sided colitis) for 8 years or more every 1–3 years.[114,116] The exception for this interval are patients with concomitant PSC who should be undergoing a yearly colonoscopy from the time of PSC diagnosis.[117] Surveillance colonoscopy can be performed using white light endoscopy (high definition rather than standard definition) and obtaining at least 32 random biopsy specimens from all segments of the colon (i.e. 4 quadrant biopsies every 10 cm) or via chromoendoscopy with targeted biopsies +/− random biopsies.[118–121] The SCENIC guidelines strongly recommend the use of high-definition white light endoscopy or chromoendoscopy over standard-definition white light endoscopy.[111] These guidelines suggest using chromoendoscopy over high-definition white light endoscopy.[111] Chromoendoscopy involves the application of dye (methylene blue or indigo carmine) to the colonic mucosa which provides contrast enhancement and improves visualization of the epithelial surface.[122] Narrow-band imaging (NBI) uses filters to provide narrow bands of blue and green light wavelengths. However, due to lack of benefit, NBI is not recommended in place of white-light colonoscopy.[123] The terminologies used for reporting dysplasia on colonoscopic surveillance of the patients with IBD are described below.[124]

(1) Visible dysplasia: It is identified on targeted biopsies from a lesion visualized at colonoscopy.
   a. Polypoid lesion (lesion protruding from the mucosa into the lumen >2.5 mm)
      i. Pedunculated (lesion attached to the mucosa by a stalk)
      ii. Sessile (lesion not attached to the mucosa by a stalk)
   b. Non-polypoid lesion (lesion with little or no protrusion above the mucosa)
      i. Superficial elevated (lesion with protrusion <2.5 mm above the lumen)
      ii. Flat (lesion without protrusion above the mucosa)
      iii. Depressed (lesion depressed below the level of the mucosa)
(2) Invisible dysplasia: It is identified only on non-targeted random biopsies of colon mucosa without a visible lesion.

Patients with endoscopically non-resectable visible lesions are referred for surgical resection. In those patients with endoscopically resectable polypoid or non-polypoid dysplastic lesions, surveillance colonoscopy is recommended after complete removal of the lesion. For those with endoscopically invisible dysplasia, referral is suggested to a gastroenterologist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy.

Video capsule endoscopy

Small bowel video capsule endoscopy (VCE) is an advanced imaging technique that was originally approved by the Food and Drug Administration (FDA) in 2001 for the evaluation of the small bowel for source of occult bleeding.[26] In 2003, Fireman et al. reported its first use in IBD patients to aid in the diagnosis of CD.[125] In 2006, colon capsule endoscopy (CCE) was first reported to explore the colon for the detection of colonic neoplasms without sedation or air insufflation.[126] In 2009, the second generation of CCE (CCE-2) was released, which provides a larger number of images per second and a broader viewing angle.[127] CCE has an 89% sensitivity and 75% specificity in the detection of active UC.[128] The most common complication of VCE is capsule retention, which is defined as the failure to excrete the capsule for 2 or more weeks. VCE is contraindicated in patients with known bowel stricture, swallowing disorders or history of bowel obstruction.[129]

Histopathology

Histopathology is the definitive tool in diagnosing UC, assessing disease severity and identifying intraepithelial dysplasia, neoplasia or cancer. In UC, the inflammation is restricted to the mucosal layer of the colon, with infiltrates varying in composition and density based on whether the disease is active or in remission. Histologic and endoscopic activity scores closely correlate in severe and inactive disease, but have disparities in mild disease.[130] Several studies have reported a higher sensitivity for histologic grading for determining severity when compared with endoscopic severity.[130,131] There is poor correlation between macroscopic and microscopic disease extent ($r = 0.39$).[132]

In UC, the main infiltrates include lymphocytes, plasma cells and granulocytes. The diagnosis of UC is made in 75% of the cases with two or three of the four following microscopic changes:[133,134]

(a) Severely decreased crypt density
(b) Severe crypt architectural distortion
(c) Irregular mucosal surface
(d) Heavy diffuse transmucosal inflammation, in the absence of genuine granulomas

Early stage disease: Basal plasmacytosis is the earliest diagnostic feature with highest predictive value in early colitis and it is present in up to 38% of the patients in the first 2 weeks of disease onset. Basal plasmacytosis starts with focal distribution and evolves into a diffuse pattern of distribution over a period of time. Only 20% of the patients have crypt distortion in the first 2 weeks of disease onset. If crypt distortion is present, it will help distinguish UC from acute colitis, which is characterized by normal crypts and presence of acute inflammation.

Quiescent or clinically inactive disease: It is characterized by features of chronic mucosal injury including decreased crypt density, crypt distortion, crypt atrophy and paneth cell metaplasia.[135] Histologic mucosal healing is characterized by resolution of the crypt distortion and inflammatory infiltrate.[136]

Some of the histologic features that have been associated with increased relapse rates include:[137]

(a) Epithelial damage with the presence of neutrophils
(b) Increased transmucosal lamina propria cellularity with basal plasmacytosis
(c) Presence of basal lymphoid aggregates
(d) Presence of high number of eosinophils

Imaging

In general, imaging studies are of limited use in establishing the diagnosis of UC, but they play an indispensable role to rule out complications.

Plain abdominal radiograph

Plain abdominal radiographs play an important role in UC to rule out toxic megacolon or perforation.[138] In UC, plain abdominal radiographs may exhibit “thumb-printing” because of thickening of the bowel wall from inflammation. Patients with fulminant colitis should have serial radiographs to monitor for toxic megacolon. Toxic megacolon is defined as mid-transverse colon dilation >5.5 cm and is an indication for emergent surgical intervention.[139] In patients with chronic UC, the colon has a “lead-pipe” appearance due to loss of haustral markings and this may be seen on the plain radiographs.

Double-contrast barium enema

Due to its ability to depict fine mucosal detail, double-contrast barium enema examination has been a valuable technique for confirming the diagnosis of UC, for assessing the extent and severity of disease, and for differentiating UC from CD.[26] The earliest finding of mild UC is a

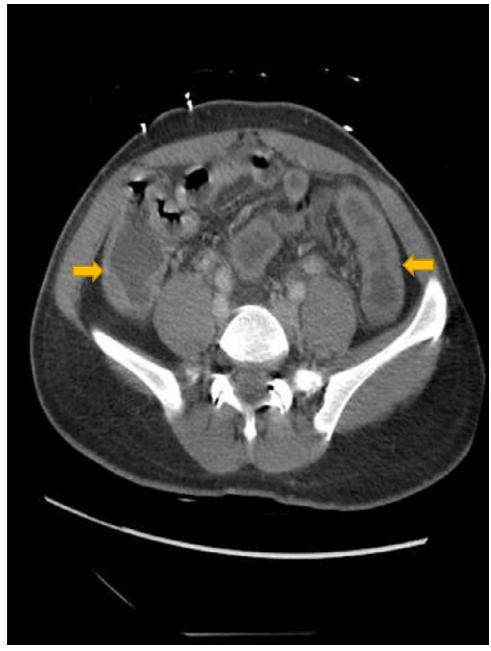

Fig. 3. Axial view computed tomography (CT) scan of a patient with Ulcerative colitis. The patient has pancolitis—the CT scan shows diffuse colitis (yellow arrow). Colitis is more prominent in the left colon when compared to the right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

fine granular appearance of the colon as a result of mucosal edema and hyperemia. In active UC, deeper ulcers may erode into the submucosa and extend laterally resulting in the characteristic spiculated collar button ulcers. Severe UC is characterized by pancolitis, diffuse ulceration, loss of haustral folds, thumb-printing, pseudopolyps, and narrowing of the luminal caliber or shortening of the colon.

Abdominal computed tomography

Abdominal computed tomographic (CT) scanning is the preferred initial radiographic imaging study in UC patients with acute abdominal symptoms. In addition to evaluation of the GI tract, it allows evaluation of other intra-abdominal organs. Abdominal CT is not sensitive for detecting mucosal abnormalities in early UC, although a variety of changes are detected with more advanced disease. The hallmark CT finding of UC is mural thickening with the mean wall thickness of 8 mm (Fig. 3), as opposed to a 2–3 mm mean wall thickness of the normal colon.[140,141] Small bowel wall thickening is almost never observed in UC.

All UC patients who develop severe acute abdominal pain, fever, and peritoneal signs must undergo a CT scan of the abdomen first to exclude any complication of the disease.[142] Studies have shown that magnetic resonance imaging (MRI) and ultrasound studies can also help in the diagnosis of moderate and severe disease activity with high accuracy in UC.[143]

Ileocolonoscopy is the gold standard for assessment of disease activity in UC. Imaging techniques with cross sectional imaging can supplement endoscopic findings in patients with incomplete examination in order to reassess for disease extent. Magnetic resonance colonography (MRC), a non-invasive non-irradiating technique has been shown to be an accurate diagnostic tool for the assessment of disease activity in UC.[144]

An MRI-diffusion-weighted imaging-colonography (MRI-DWI-colonography), a method combining MRI and DWI, without oral or rectal preparation has been showed to be a reliable tool in evaluating colonic inflammation in UC.[145]

Table 3
Montreal classification of ulcerative colitis (UC) based on extent of disease.[147]

- *E1 (Ulcerative proctitis):* Inflammation limited to the rectum
- *E2 (Left-sided UC):* Inflammation limited to the colo-rectum distal to splenic flexure
- *E3 (Extensive UC/Pancolitis):* Inflammation extends proximal to the proximal splenic flexure

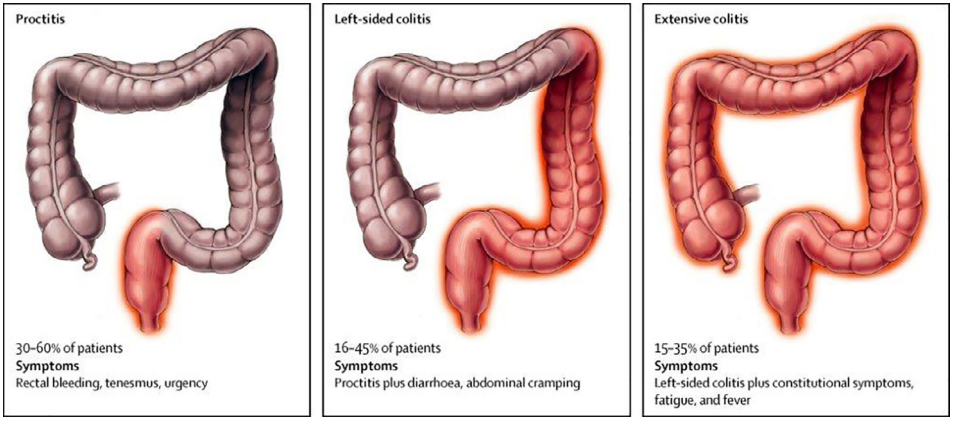

Fig. 4. Montreal classification of ulcerative colitis (UC) based on disease extent (figure reproduced from Ungaro et al.[139] with permission from Elsevier).

Table 4
Montreal classification of ulcerative colitis (UC) based on the severity of disease.[147]

- *S0 (Clinical Remission):* No symptoms
- *S1 (Mild UC):* Four or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- *S2 (Moderate UC):* More than four stools per day, minimal signs of systemic symptoms
- *S3 (Severe UC):* Six or more bloody stools per day, pulse rate of $\geq$90/min, Temp $\geq$37.5 °C, hemoglobin $<$10.5 g/dL, ESR $\geq$30 mm/h

Determining disease activity

It is very crucial to assess the severity of UC objectively in order to guide clinical management and to predict the long term outcomes for these patients. There have been at least ten scoring systems formulated to assess disease activity in UC since the development of the first scoring system by Baron et al.[146] Here we will be describing few of the most commonly used indices to assess the severity of UC.

Montreal classification of UC

The Montreal working party classifies UC based on the extent and the severity of the disease.[147] Table 3 delineates the three subgroups of UC in the Montreal classification based on the extent of disease (Fig. 4). The major drawback of this classification pertains to the dynamic nature of IBD as seen by the changes in the distribution and severity of the disease over a period of time. Progression of disease extent (41–54% over 10 years) as well as regression of disease extent (up to 71% over 10 years) has been reported.[1] Hence the working group proposed to measure the maximal extent of disease involvement as the critical parameter. Table 4 describes the Montreal classification of UC based on the severity of symptoms related to the disease. Of note, the term fulminant colitis was not used in the Montreal classification due to the uncertainty of the prognostic value or clinical utility at that point of time.

Table 5
Mayo score, reproduced from Magro et al.[108,148] with permission from Oxford University Press.

Mayo Index	0	1	2	3
Stool frequency	Normal	1–2/day more than normal	3–4/day more than normal	5/day more than normal
Rectal bleeding	None	Streaks	Blood in stool	Pure blood
Mucosa	Normal	Mild friability	Moderate friability, erosions	Spontaneous bleeding, ulcerations
Physicians global assessment	Normal	Mild	Moderate	Severe

Interpretation of scores: scores should be compared to previous scores for a patient. The score can range from 0 to 12 with higher scores indicating worse severity.

Mayo scoring system for UC severity

The Mayo scoring system is a commonly used index to assess disease severity and to monitor patients during therapy.[148] It utilizes clinical features, physician assessment, and endoscopic features to formulate the score (Table 5). The score ranges from 0 to 12, with higher scores indicating that patients have a more severe disease.

International definitions of disease severity

The American College of Gastroenterology (ACG), European Crohn's and Colitis Organization (ECCO) and Japanese Society of Gastroenterology classify UC into mild, moderate and severe disease based on the Truelove–Witts criteria,[132,149,150]

- Mild UC: Less than 4 stools/day with or without blood, no signs of systemic toxicity and normal ESR. Symptomatically these patients have mild cramping abdominal pain, tenesmus, and rarely, they may experience constipation.
- Moderate UC: More than or equal to 4 loose bloody stools per day associated with abdominal pain that is not severe. These patients may have mild anemia or low-grade fevers. They generally maintain their nutrition and do not have associated weight loss.
- Severe UC: Frequent loose bloody stools ($\geq$6/day) associated with severe abdominal cramps. These patients have systemic toxicity findings such as fever (temperature $\geq$37.5 °C), tachycardia (HR $\geq$90 beats/min), anemia (hemoglobin $<$10.5 g/dL), or an elevated ESR ($\geq$30 mm/h). They generally have coexisting severe weight loss in a short span of time.

The ACG also defines fulminant UC as those patients who have more than 10 stools/day, continuous rectal bleeding, abdominal pain, abdominal distention, and acute, severe toxic symptoms including fever and anorexia. Patients also have colonic dilation on abdominal plain films and often need blood transfusion. These patients are at high risk for progressing to toxic megacolon and bowel perforation.

Definitions

Remission

There is no fully validated definition for disease remission and the definitions vary depending upon the context of use, for example whether used in clinical trials, regulatory, guideline, clinical or patient context. Hence, there are several definitions of remission:

(a) *Clinical remission*: Complete resolution of symptoms and patients has normal stool frequency, no rectal bleeding or urgency. Used in clinical practice.
(b) *Complete remission*: Normal stool frequency, no rectal bleeding or urgency as well as a normal or quiescent appearance of the colonic mucosa endoscopically. Used in clinical trials.

(c) *Registration remission*: Cessation of rectal bleeding and a sigmoidoscopy/endoscopy score of 0 or 1 based on Mayo scoring or UC Disease Activity Index (absence of visible blood and mucosal friability). Used in trials to gain drug license as required by the regulatory authorities. Remission defined by clinical indices alone has an 86% sensitivity and 76% specificity for the regulatory-defined remission.[151]

Response

Response is defined as clinical and endoscopic improvement and measured based on the activity index used in the trial. In general, more than 30% improvement in the activity index plus a decrease in rectal bleeding and endoscopy sub-scores are considered to be an adequate response in clinical trials.[152]

Relapse

Relapse is defined as flare up of symptoms in a patient who is in clinical remission. Typically, these patients have rectal bleeding, increase in stool frequency and abnormal mucosa at sigmoidoscopy.[153] The relapse is considered early if it occurs within 3 months after achieving remission with previous therapy. The pattern of relapse could be infrequent (less than or equal to 2 episodes/year), frequent (more than twice per year), or continuous (persistent symptoms of active UC without a period of remission). The term “chronic active disease” is ambiguous and it should be avoided. Instead, more precise definitions like steroid-refractory or steroid-dependent disease should be used.

Steroid-refractory colitis

Patients are considered to have steroid-refractory UC if their symptoms do not improve with 40 mg of prednisone daily, administered orally for at least 2 weeks or intravenous steroids for at least 1 week. Steroid-dependent colitis is a term used for patients who are unable to reduce steroids below the equivalent of prednisone 10 mg/day within 3 months of starting steroids without recurrent active disease.[108]

Immunomodulator-refractory colitis

These patients have active disease or relapse despite the use of thiopurines (i.e., azathioprine 2–2.5 mg/kg/day or 6-mercaptopurine 1–1.5 mg/kg/day) for at least 3 months.

Medical management

The goals of treatment in UC focus on improving quality of life, achieving steroid free remission and minimizing the risk of cancer. During the initial endoscopic assessment, it is important to delineate the proximal margin of inflammation. If the inflammation is limited to below the splenic flexure, it is considered to be "distal" and hence within the reach of topical therapy. If the inflammation extends proximal to the splenic flexure, then systemic therapy is warranted. The histologic severity of the inflammation is taken into account when planning a treatment regimen. The basic approach in the treatment of UC is based on severity, distribution, age of onset, disease duration, disease course, relapse frequency, previous medication, side effects of medication and extra-intestinal manifestations. It is important to identify patients with severe UC (Truelove and Witts index is the best validated and most commonly used tool) and hospitalize them for treatment. Remission is defined as cessation of rectal bleeding with improvement in bowel habits, and endoscopic healing (Mayo score of zero or one). Endoscopic healing has been shown to greatly improve long-term clinical remission, decrease risk of colectomy, and limit corticosteroid use.[154]

Table 6
5-Aminosalicylates dosing and site of action, reproduced from Regueiro et al.[182] with permission from Springer Nature.

Medication	Route of administration	Effective dose	Site of action
Sulfasalazine	Oral (500 mg tablet)	Induction: 3–4 g/day in evenly divided doses Maintenance: 2 g/day	Colon
Sulfasalazine DR	Oral (500 mg tablet)	Induction: 3–4 g/day in evenly divided doses Maintenance: 2 g/day	Colon
Mesalamine ER	Oral (375 mg capsule)	1.5 g/day (in 1 dose)	Terminal ileum, colon
Mesalamine DR	Oral (800 mg tablet)	2.4–4.8 g/day (800–600 mg TID)	Terminal ileum, colon
Mesalamine DR	Oral (1200 mg tablet)	Induction: 2.4–4.8 g/day (in 1 dose) Maintenance: 2.4 g/day	Terminal ileum, colon
Mesalamine DR	Oral (400 mg capsule)	Induction: 800 mg TID (2.4 g/day) for 6 weeks Maintenance: 800 mg BID (1 g/day)	Terminal ileum, colon
Mesalamine CR	Oral (500 mg capsule)	2–4 g/day as 500 mg BID to 500 mg QID.	Small intestine, colon
Balsalazide	Oral (750 mg capsule)	Three 750 mg capsules TID (6.75 g/day)	Colon
Olsalazine	Oral (500 mg tablet)	1 g/day in 2 divided doses	Colon
Mesalamine suppository	Rectal (1 g)	1 g, 1 suppository QHS	Rectum
Mesalamine enema	Rectal (4 g)	4 g per unit (60 ml); 1 enema QHS for 3–6 weeks	Rectum to splenic flexure

5-ASA, 5-aminosalicylates; CR, controlled release; DR, delayed release; ER, extended (slow) release; QHS, before bedtime; UC, ulcerative colitis; BID, twice a day; TID, three times a day; QID, four times a day; QHS, every bedtime.

Mild to moderate disease

UC proctitis

Induction of remission. The first line medication to treat mild to moderate UC proctitis includes 5-aminosalicyclic acid (5-ASA) formulations (Fig. 6). There are different 5-ASA formulations with no difference in efficacy or safety profile (Table 6). Patients with UC proctitis should be first treated with topical 5-ASA suppositories, since they are more effective than oral 5-ASA as they directly target the site of inflammation.[155] The topical 5-ASA therapy reaches higher concentration in the rectal mucosa when compared to oral 5-ASA therapy.[156]

Maintenance of remission. Maintenance therapy in UC proctitis is recommended in patients who have more than one relapse per year. For patients who achieved remission on topical 5-ASA therapy, a maintenance regimen with 5-ASA suppository is recommended.[157] Patients who required an oral 5-ASA to achieve remission or have multiple relapses on topical therapy should be treated with oral 5-ASAs to maintain remission.

Left-sided or extensive colitis

Induction of remission. In left-sided or extensive colitis, the first line management is a combination of 5-ASA enemas >1 g/day and oral 5-ASA at a dose greater than 2.4 g/day.[158] This combination is more effective than oral or topical 5-ASA alone. When combination 5-ASA therapy was compared with oral 5-ASA alone, patients in the combination group had a shorter time to remission (11.9 vs. 25.5 days; $P = 2.002$) and had a relative risk for failure to achieve remission of 0.65 (95% CI is equal to 0.47–0.91).[159] In a randomized control trial of 116 patients, the combination therapy of oral 5-ASA 4 g/day with 1 g 5-ASA enema/day had a significantly higher remission rate when compared with oral 5-ASA (64% vs. 43%, $P = 0.03$).[160] In patients with left sided UC, 5-ASA enemas are preferred over 5-ASA suppositories in order to reach the splenic flexure.

In a Cochrane systematic review of 38 clinical trials, 5-ASA was superior to placebo with a pooled OR of 8.3 for symptomatic remission (95% CI 4.28–16.12), 5.3 for endoscopic remission (95% CI 3.15–8.92) and 6.3 for histological remissions (95% CI 2.74–14.40) in UC.[161] The oral 5-ASA has not shown to be better than topical 5-ASA in terms of induction of remission or time to remission, although the combination of oral and topical 5-ASA is more effective than either of them alone.[159,162] Oral 5-ASA are started at a dose of 2.0–2.4 g/day and can be increased up to 4.8 g/day.[163,164] Symptomatic improvement is seen typically within 2 weeks but it might take up to 8 weeks for symptomatic remission.[163] Patients who achieve remission with 5-ASA should be continued on the same medication to maintain remission. The use of oral 5-ASA at diagnosis more than 2 g/day has been shown to be more effective in inducing remission than when started at lower doses (RR for failure to achieve remission at week 4–8 of 0.91, 95% CI 0.85–0.98) and those patients with moderate disease need high dose of 4.8 g/day.[158,161] According to the ASCEND II trial, the median time for cessation of rectal bleeding was 9 days in patients receiving 4.8 g 5-ASA/day, 16 days for patients receiving 2.4 g/day, and 7 days for patients receiving 4.8 g/day of multimatrix (MMX) 5-ASA.[165]

Sulfasalazine is the first drug developed in this class and it is a prodrug composed of 5-ASA and sulfapyridine. It has similar efficacy to the 5-ASA drugs but is less well tolerated.[163] Intolerance to the sulfapyridine moiety of sulfasalazine may result in nausea, vomiting, dyspepsia, anorexia and headache. About 80% of patients intolerant to sulfasalazine are able to tolerate other oral 5-ASA preparations.[166–170] When compared with oral sulfasalazine, oral 5-ASA/mesalamine has similar efficacy but has a better side effect profile (RR for an adverse event 0.48, 95% CI 0.36–0.63).[161]

Topical steroids (2 g budesonide rectal foam) have been found to be superior to placebo in inducing remission at week 6 in patients with mild to moderate procto-sigmoiditis (41.2% vs. 24%, $P < 0.0001$).[171] A meta-analysis showed that topical 5-ASA is more effective than topical steroids for symptomatic, endoscopic, or histological remission.[172] Topical steroids are indicated in patients who have inadequate response or intolerant to topical 5-ASA.[173] Rectal corticosteroids are also used as second-line add-on therapy to induce remission in proctitis or left-sided UC if patients had inadequate response to 5-ASA therapy. Combination therapy with rectal 5-ASA and corticosteroids are shown to be superior to single-agent therapy and causes no increased adverse reactions.[174] Rectal foam formulations are better tolerated than the enema preparations.

A typical time required to attain complete remission with 5-ASA is about 37–45 days of therapy.[175,176] Therefore, in patients who have been treated with appropriate 5-ASA regimen, if the rectal bleeding persists beyond 10–14 days or if patients are not in complete remission within 40 days of therapy, initiating treatment with oral corticosteroids is indicated. Oral steroids with high first pass metabolism such as budesonide-MMX should be used prior to the use of other oral glucocorticoids.[177–179] In two large randomized controlled trials (cores I and II), budesonide-MMX 9 mg daily for 8 weeks was effective in inducing clinical, endoscopic and histologic remission when compared to placebo without significant steroid-related side effects. Subgroup analysis in these trials failed to show any difference between budesonide-MMX and Asacol 2.4 g/day or between budesonide-MMX and non-MMX budesonide.[171,180] Oral prednisolone has been shown to be more effective in inducing remission when compared with sulfasalazine (77% vs. 48%) within 2 weeks of therapy.[181] Prednisone is usually effective within 10–14 days, after which the dose can be tapered gradually. The typical starting dose of prednisone is 40 mg daily and is usually tapered by 5–10 mg/week. Oftentimes, the taper of 5–10 mg/week is continued, whilst in other circumstances, when the prednisone dose reaches 20 mg, the decrease then is by 2.5–5 mg/week until completed.[137,149] The patients who are refractory to all of the above agents in maximal doses or who are systemically ill may require treatment with a biologic agent such as infliximab.

Maintenance of remission. Maintenance therapy is recommended in all patients with proctosigmoiditis, left sided colitis, extensive colitis, or pancolitis once remission is achieved. If remission is achieved using corticosteroids, options for maintenance treatment include 5-ASA, thiopurines, or biologics. The 5-ASA can be considered for maintenance in patients with mild UC who are

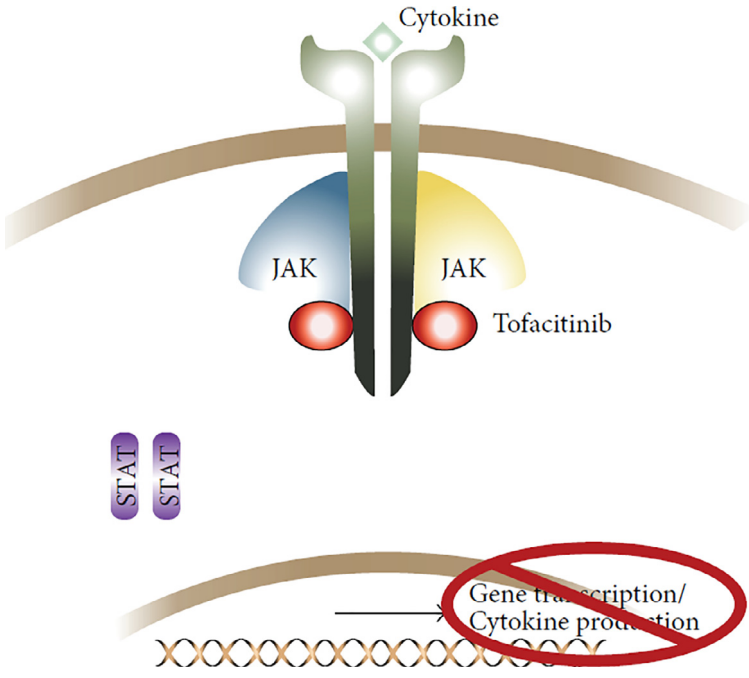

Fig. 5. The mechanism of action of tofacitinib. Reproduced from Hsu and Armstrong.[194] (Open access article distributed under the Creative Commons Attribution License.) Tofacitinib inhibits the phosphorylation and activation of Janus family kinases (JAK), hence preventing the phosphorylation of the cytokine receptors. Therefore, the cytokine receptors cannot dock the Signal Transducer and Activator of Transcription (STAT) and the process of gene transcription and cytokine production are halted.

naive to 5-ASA medications. However, those patients with poor prognostic factors such as young age at disease onset, extensive colitis, deep ulcerations, those who require two or more courses of steroids in a year or steroid dependence, should be started on maintenance treatment with thiopurines and/or biological treatment (anti-TNF-α or anti-integrin therapy).[163]

Moderate to severe disease

Patients with moderate to severe colitis should be treated with oral corticosteroids (40 mg of prednisone per day) or intravenous steroids (300 mg hydrocortisone or 60 mg methylprednisolone) to achieve remission (Fig. 7). If there is no response, then the next option is induction with biological therapy (anti-TNF-α or anti-integrin). Anti-TNF-α drugs, such as infliximab, adalimumab, and golimumab, are effective at inducing remission in patients with moderate to severe UC.[183–186] Infliximab is the most widely used biological agent to induce remission in UC patients admitted to the hospital with severe UC.[183,187] According to the SUCCESS trial, azathioprine and infliximab combination therapy is more effective than azathioprine or infliximab alone to achieve both clinical remission (39.7% vs. 23.7% vs. 22.1%, $P = 0.032$) and endoscopic healing by week 16 (62.8% vs. 36.8% vs. 54.6%, $P = 0.001$).[188] Vedolizumab is an anti-adhesion molecule inhibitor and acts by blocking the $\alpha 4\beta 7$ integrin in the gut. It is approved for the treatment of moderate to severe UC.[189,190]

Tofacitinib is the newest class of medication approved in 2018 for treatment of moderate to severe UC.[191,192] It is a small-molecule Janus kinase (JAK) inhibitor that targets all JAKs (JAK1/JAK2/JAK3/TYK2), but preferentially JAK1 and JAK3 (Fig. 5).[193] Tofacitinib is a promising

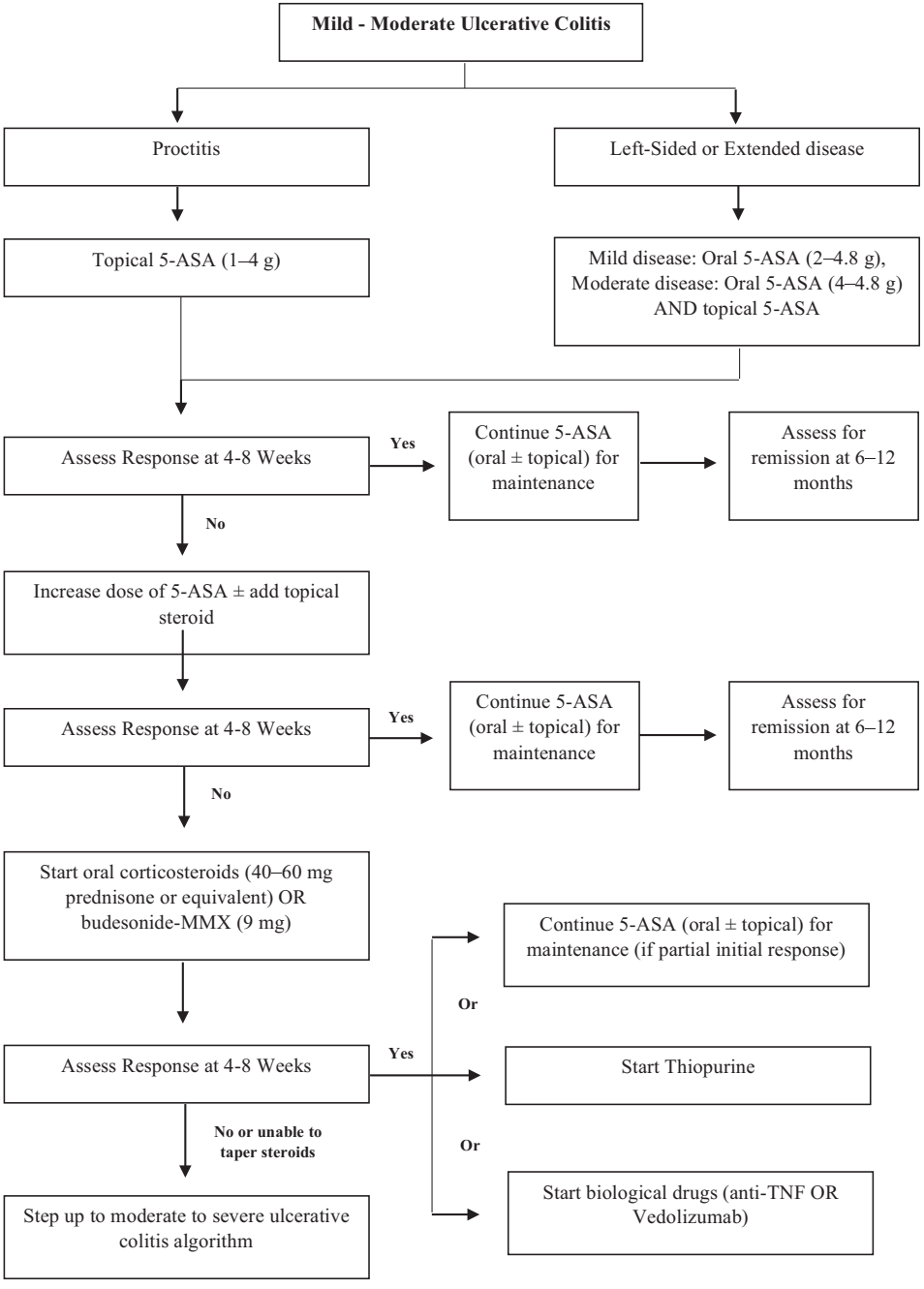

Fig. 6. Treatment approach for mild to moderate ulcerative colitis based on Toronto Consensus and European Crohn's and Colitis Organization guidelines (figure adapted from Ungaro et al.,[139] with permission from Elsevier).

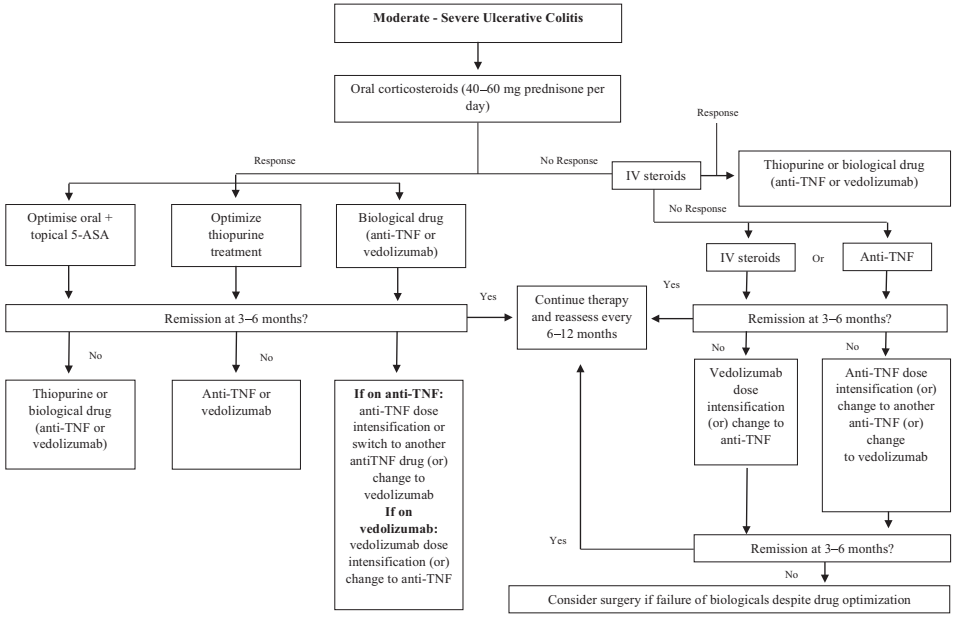

Fig. 7. Treatment approach for moderate to severe ulcerative colitis based on Toronto Consensus and European Crohn's and Colitis Organization guidelines (figure adapted from Ungaro et al.,[139] with permission from Elsevier).

option for patients who have failed other biological therapies; however, prior use of biologic therapy is not a requirement. It is available as an immediate-release tablet and is rapidly absorbed after oral administration with relatively rapid onset of action. In the OCTAVE 1 induction trial, patients with moderate to severe UC who received tofacitinib 10 mg twice daily had higher remission rates at 8 weeks when compared with placebo (18.5% vs. 8.2%; $P = 0.007$). Similarly in the OCTAVE 2 induction trial, remission rates were higher in the tofacitinib group when compared with placebo (16.6% vs. 3.6%; $P < 0.001$).[191] The OCTAVE Sustain trial included 593 patients who had initial clinical response to induction therapy.[191] At 52 weeks, remission occurred more frequently in patients receiving tofacitinib 5 mg or 10 mg daily (34.3% and 40.6%, respectively) compared with placebo (11.1%, $P < 0.001$ for both comparisons with placebo). As compared with placebo, tofacitinib was associated with more overall infections and more cases of herpes zoster, although the absolute risk differences were low. Due to the increased incidence of herpes zoster in patients receiving tofacitinib, it is recommended to vaccinate patients with the non-live recombinant zoster vaccine prior to or shortly after initiating therapy.[191]

Maintenance therapy

Once remission is induced, patients with moderate to severe UC should be continued on maintenance therapy. Patients who are induced with steroids may be transitioned to thiopurines and/or biologic therapy. Thiopurines (azathioprine or 6-mercaptopurine) are effective in maintaining remission in patients with UC. Results on the use of methotrexate, however, were conflicting based on clinical trials, and it is currently not used for maintaining remission.[195] Patients who receive biological therapy to induce remission should continue on that same drug, whether an anti-TNF-α agent or vedolizumab to maintain remission as they are both effective in maintaining remission.[183–186] Similarly, patients who achieved remission with tofacitinib can continue that drug.[196] The anti-TNF-α agents are considered to be one of the most effective agents for maintenance of remission in UC. According to the ACT study, infliximab resulted in significantly higher rates of clinical response and remission when compared with placebo.[187]

GEMINI 1 study evaluated the efficacy of vedolizumab for maintenance of clinical remission (Mayo clinic score <2 and no sub-score >1).[190] At 52 weeks the rate of clinical remission for patient's receiving vedolizumab every 8 weeks was 41.8% and those receiving vedolizumab every 4 weeks was 44.8%, when compared to 15.9% remission rate for those patients receiving placebo after initial induction ($P < 0.001$ for both groups vs. placebo). The rates of durable clinical response (defined as response at both weeks 6 and 52), durable clinical remission, mucosal healing and steroid free remission were all significantly higher in the vedolizumab groups when compared with placebo, however there was no significant difference in efficacy between the two vedolizumab dosing regimens.[197] The vedolizumab group did not have higher frequency of adverse events when compared with the placebo groups. The benefit of vedolizumab over placebo was consistent regardless of previous anti-TNF use.[198] Currently there is no reliable evidence to guide the choice of biologic agents for maintenance treatment in UC. In the network meta-analysis infliximab, adalimumab, golimumab, and vedolizumab were all superior to placebo for maintenance of remission and response; however to date there is no study comparing the superiority of one agent over the other.[199]

Management of refractory proctitis and distal colitis

Refractory distal colitis is defined as persistence of colonic inflammation in the rectum or left-side of the colon, despite treatment with oral plus topical steroids and 5-ASA for 4–8 weeks.

There are several other possibilities for failure of conventional first-line therapies, which include:

(a) Incorrect diagnosis (eg: CD, cancer, irritable bowel syndrome)
(b) Noncompliance to prescribed medications
(c) Undiagnosed complications (infection, proximal constipation)
(d) Wrong formulation or dosage resulting in inadequate concentration of medication to the inflamed mucosa

Some of the initial steps in the evaluation of refractory disease include:

(a) Complete review of symptoms, treatment history and adherence to medical therapy
(b) Re-assessment of the disease by stool culture, endoscopy and biopsy
(c) Verifying if the previously used therapy had the right dosage and formulation
(d) Obtaining an abdominal x-ray to rule out proximal constipation
(e) Flexible sigmoidoscopy or colonoscopy to document active distal colitis or proctitis

The mainstay treatment option in patients with refractory disease is systemic steroids to induce remission.[200] Other alternative options include cyclosporine, tacrolimus or infliximab.[201–205] If disease persists despite salvage medical therapy, then the patient might need surgical intervention with colectomy. Up to 10% of patients end up requiring colectomy with pouch formation for refractory distal colitis and have good outcomes.[206]

Management of acute severe ulcerative colitis (ASUC)

Acute severe ulcerative colitis (ASUC) is a life-threatening condition with a historical mortality rate as high as 75% in the early 1900s. With the use of steroid therapy, mortality rates improved to 7% in 1950. The current mortality rate of patients admitted with ASUC is less than 1% in tertiary care centers.[207] ASUC is defined as six or more bloody bowel movements per day plus at least one of the following: (a) pulse rate >90 beats/min, (b) temperature >37·8 °C, (c) hemoglobin <10·5 g/dL, or (d) ESR >30 mm/h.[132] The therapeutic approach for patients admitted with severe ASUC includes timely diagnosis and exclusion of enteric infections.[208] Intravenous corticosteroid are the mainstay of conventional therapy with a response rate of 65%.[209]

Methylprednisolone 60 mg over 24 hours or hydrocortisone 100 mg four times a day are typically used as initial therapy.[210,211] Higher doses have not shown any benefit while lower doses are less effective.[210,211] A systematic review of 32 trials from 1974 to 2006 reported an overall response rate to steroids of 67% (95% CI 65–69%) with colectomy rates of 29% (95% CI 28–31%) and a mortality rate of 1% (95% CI 0.7–1.6%).[211] For patients unresponsive to intravenous corticosteroids within 3–5 days, rescue medical therapy with either cyclosporine or infliximab should be considered and both these medications are equally efficacious.[212,213] If there is no response to one of these drugs, colectomy should be performed as delays in surgery can increase postoperative complications and mortality increases significantly after 7 days.[214,215] Other important measures include intravenous fluids, electrolyte replacement, flexible sigmoidoscopy to rule out cytomegalovirus infection, checking stool cultures and *Clostridium difficile* toxin, use of deep vein thrombosis prophylaxis with enoxaparin, nutritional support, maintaining a hemoglobin above 8 g/dL, and avoidance of anticholinergics, opiates and non-steroidal anti-inflammatory drugs (NSAIDs).[49,51,216–220]

Surgery

Advances in medical therapy have allowed UC to be treated more effectively and thereby decreased the surgical rates. However, 10% of UC patients will require surgery within the first year of diagnosis and up to 30% will require surgical intervention in their lifetime.[221] The most commonly performed surgery for UC is restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA).[221] Most studies have reported improvement in health-related quality of life (QOL) in patients with severe UC after IPAA.[222] There is no data available to-date in terms of healthcare utilization patterns in UC patients who underwent surgery. However it has been shown in CD, that there is a significant healthcare utilization in the 2-year postoperative time period with up to one-third of the patients requiring hospitalization and one-half of the patients requiring abdominal imaging with CT scans.[223] It is important to have a multidisciplinary team including gastroenterologists, surgeons, pathologists, enterostomal therapists, and nutritionist to effectively manage complicated UC patients. This team approach should begin at the time of diagnosis and especially in the case of hospital admission.

Elective surgery indications

The major indications for elective surgery include failure of medical management, CRC or dysplastic lesions not amenable to endoscopic removal.[114,149] CRC occurs in UC patients at an overall rate of 3.7%. This risk increases with time.

- 2% at 10 years[111]
- 8% at 20 years[111]
- 18% at 30 years[111]

Similar to dysplasia, UC patients carry a 14% synchronous carcinoma rate and also an increased risk for metachronous carcinoma when compared to the sporadic CRC population.[224] The recommended surgical treatment is proctocolectomy with end ileostomy or IPAA. Review of current practice by Randall et al. concluded that the threshold for elective surgery is too high.[215] In comparing 3-year mortality rates of hospitalized UC patients, those who underwent urgent colectomy had a significantly higher mortality rate when compared to those who underwent elective colectomy (13.2% vs. 3.7%, $P < 0.001$).[225]

Emergent surgery indications

The emergent indications for surgery include perforation, uncontrolled hemorrhage, fulminant disease failure of medical therapy, and toxic megacolon.[114,149]

Toxic megacolon is a highly morbid complication of UC.[226] The immediate involvement of a colorectal surgeon is imperative. Medical therapy for 24–48 h with intravenous hydration, broad-spectrum antibiotics, bowel rest, and intensive care monitoring may be carefully trialed.[226] Cyclosporine and infliximab have been shown to successfully treat toxic megacolon in only 25–40% of the population.[227] The threshold for surgical intervention must be extremely low. Clinical deterioration, increasing colonic dilation, colonic "thumb printing", or pneumatosis intestinalis on imaging studies are indications for emergent surgery.

Patients with fulminant UC are commonly treated with steroids, and other rescue therapies.[226] *Clostridium difficle* and cytomegalovirus must be excluded by laboratory studies and treated if positive.[226] Monitoring should include CRP levels, stool frequency, frequent abdominal exams, and abdominal imaging. Clinical instability and limited improvement in 4–7 days are indications for surgical intervention.[228]

The most common surgical procedure in the emergent setting of fulminant colitis or toxic megacolon is total abdominal colectomy (TAC) with end ileostomy.[226] TAC significantly reduces the disease burden and symptoms associated with UC. Immunosuppressive medications can be stopped and nutritional status should be improved pre-operatively.[226] Proctectomy (resection of the rectum) should not be performed in the emergent setting as it increases the procedural time, risk of injury to pelvic nerves, risk of bleeding, and negatively affects the future of IPAA.[226]

Staged operations in the surgical treatment of UC are widely practiced. Patient factors including disease stage, age, sex, and continence affect the selection. The stages are as follows:

- 1 stage
  1 Total proctocolectomy (TPC) and IPAA *(performed very selectively)*
- 2 stage
  1 TPC and IPAA with diverting loop ileostomy (DLI)
  2 DLI reversal
- 3 stage
  1 Total abdominal colectomy (TAC) and end ileostomy
  2 Proctectomy, IPAA and DLI
  3 DLI reversal

The indications for a staged surgical approach include: obesity, medical treatment (patient on biologics or steroids), fulminant disease, toxic megacolon, or presence of other patient comorbidities. Steroids, infliximab, and immunomodulators have been associated with pouch-related complications.[229–233] Lim and Hanauer showed that steroids are an independent risk factor for complications after pouch creation in a dose-dependent fashion.[229] Lim and Hanauer concluded that patients on more than 20 mg/day of prednisone should undergo a staged pouch creation.[229] Patients with severe colitis are often malnourished and immunocompromised when they are referred to a colorectal surgeon.[226,232] UC patients treated with biologics before IPAA have substantially increased odds of postoperative pouch-related and infectious complications.[232] These findings were confirmed by Mor et al. who demonstrated that the odds of post-operative septic complications were 13.8 times greater and the odds of late complications 2.19 times greater in those patients receiving biologic therapy compared to patients who are not receiving such medications.[233] Yang et al. demonstrated in a meta-analysis that biologic therapy increased short-term overall postoperative complications in UC.[233]

The staged approach decreases the incidence of pelvic sepsis caused by anastomotic leak at the ileal-anal anastomosis and its resultant long-term effects on pouch function.[234] The 3-stage approach provides an opportunity to optimize the patient's nutritional status and wean off medical therapy following the TAC, prior to proceeding with completion proctectomy and IPAA creation. When comparing a 2-stage procedure to a 3-stage procedure, Pandey et al. reported that the overall complication rates were similar, while infectious specific complications were higher in the 2-stage procedure group when compared to the 3-stage procedure group (21% vs. 38.2%; $P < 0.05$), respectively.[235]

Operative planning and considerations

Preoperative preparation

Preoperative evaluation by anesthesia and medical specialists maybe needed based on patient comorbidities to optimize their condition.[236,237] Patients who will be receiving a temporary or permanent ileostomy must meet with an enterostomal therapist for proper siting of the ileostomy to reduce stoma related complications.[236,237] Mechanical bowel preparation is completed the day before surgery. Stress-dose steroids maybe required in certain patients prior to induction of anesthesia.[236,237]

Ileostomy

Despite the perceived negative impact of an ileostomy, Camilleri-Brennan and Steele showed that the UC patients who underwent proctocolectomy and permanent ileostomy had similar quality of life to that of the general population in all dimensions and the overall scores.[238,239] The Brooke ileostomy is the common small bowel stoma in which the ileostomy prevents skin excoriation by eversion of the small bowel, elevating the exit site of intestinal contents above the level of the skin.[236,237] Kock pouch was first described in 1969 as a continent ileostomy, which has an internal valve that controls the flow of intestinal contents into the ostomy bag.[236,237] Candidates for Koch pouch include patients with low rectal cancer that will require adjuvant therapy, patients with a Brooke ileostomy after a proctocolectomy who wish to improve their quality of life, and patients who are not candidates for IPAA due to poor sphincter function.[240,241] Two long-term problems with a continent ileostomy are pouchitis and pouch malfunction. The incidence and treatment of pouchitis is similar to that of IPAA.[236,237] Malfunction of the valve may cause incontinence or difficult intubation. A functional obstruction due to a “slipped valve” may require surgery for revision or conversion to a Brooke ileostomy.

TAC with ileorectal anastomosis (IRA)

TAC with IRA may be offered to patients with limited rectal involvement, good rectal compliance, and no dysplasia or cancer.[236,237] The overall morbidity is between 8 and 28%.[242–245] An IRA obviates the need for pelvic dissection and minimizes the risk of sexual and urinary dysfunction resulting in higher fertility rates. As a result, this procedure should be discussed with female patients in their reproductive age.[243] Disease recurrence in the rectal remnant is significant and these patients should be endoscopically monitored. The cumulative probability of rectal dysplasia at 10 years is 9% and 25% at 20 years.[242] The incidence of cancer was 0, 2, 5, and 14% at 5, 10, 15, and 20 years respectively.[242] Rectal biopsies every 6–12 months are recommended in these patients and if dysplasia is found, completion proctectomy is indicated.[237] Patients not willing to undergo surveillance, or with preexisting dysplasia or cancer should not undergo IRA.[246] An exception to this rule are those with limited life expectancy due to their advanced metastatic disease.[237] TAC with IRA is not favored compared with TAC/IPAA or completion TPC/end ileostomy.

Total proctocolectomy (TPC) with end ileostomy or IPAA

TPC with end ileostomy removes all diseased epithelium including the anus, cures the patient of UC, and eliminates the associated risk of malignancy. The risks associated with this procedure include the potential for pelvic nerve injury and possible problems with perineal wound healing.[237] TPC with end ileostomy is indicated in patients with contraindications to IPAA or patients whose work and daily activities preclude them from having frequent bowel movements that are often associated with IPAA.[237]

Contraindications to surgery

Fecal continence must be assessed prior to IPAA. Females with multiple vaginal deliveries and history of episiotomies or lacerations are at higher risk for impaired continence.[237] During

an acute UC flare, fecal continence is frequently impaired.[237] As a result, evaluation by a colorectal surgeon is of utmost importance in determining the need for manometry or endoanal ultrasound.[247]

UC patients with low rectal cancer should be treated according to standard oncologic principles of rectal cancer.[237] Neoadjuvant chemoradiation therapy should be applied to Stage II-III disease to decrease the risk of local recurrence.[248,249] Neoadjuvant chemoradiation therapy is not an absolute contraindication to IPAA, but it does place the patient at high-risk for pouch failure. Wu et al. reported a 42.9% pouch failure rate in patients who received radiation compared to 17.6% in those that did not.[250]

Obesity is a relative contraindication to immediate IPAA.[251] A staged approach in obese patients may provide time for weight loss to avoid permanent ileostomy. If steroids are the cause of obesity, they can be discontinued during this period.[237] A goal BMI of 28 or less should be targeted before IPAA creation.[237]

Pouch configuration/anastomosis type

The majority of pouches are in the "J" shape due to technical ease and speed of creation.[252,253] "S" shaped pouch is occasionally required in tall male patients with short mesentery.[254] Two types of IPAA exist: stapled and hand sewn. Stapled anastomosis requires a short rectal cuff, retaining rectal mucosa and the highly sensitive anal transition zone (ATZ).[255] Continence, defecatory function, and quality of life are improved in these patients when compared to those with a hand sewn anastomosis where mucosectomy is performed.[256] In this scenario, inflammation may occur in the retained rectal 'cuff' mucosa and has been reported to occur in 14.7% of these patients.[257,258] Medical management with topical 5-ASA or topical steroids is usually successful. However, transanal mucosectomy with ileal pouch advancement may be performed with good results if medical management fails.[257]

In the hand sewn IPAA, a mucosectomy is performed to remove the risk for future dysplasia and cancer.[237] A mucosectomy entails removal of the entire diseased anorectal mucosa including the ATZ. However, at times, mucosectomy may not guarantee complete elimination of the rectal mucosa, due to variability at the ATZ.[259] Therefore, dysplasia may still occur with or without a mucosectomy, but at lower rates in those patients who undergo a mucosectomy compared to those with a rectal cuff and a stapled IPAA.

In their study of 210 patients with a stapled IPAA, O'Riordain et al. noted dysplasia development in 3.3% of patients only at a median of 11 months postoperatively.[260] In this same group of patients, none of the patients developed cancer after 5–10 years of follow-up.[260] As a result, surveillance of the ATZ has been recommended between 1–3 years.[256,261] The preservation of the ATZ can be individualized. Patients with high grade rectal dysplasia or cancer, PSC, and in the pediatric population are recommended to have a mucosectomy secondary to the known high risk that these have for dysplasia and cancer.[262]

Post-operative management of UC

Surgical management of UC through TPC with IPAA is curative but is associated with short-term ($\leq$30 days) and long-term ($>$30 days) complications that require monitoring and management.[263] Short-term complications include bleeding, pouch leakage, pelvic abscess, anastomotic stricture, and small bowel obstruction.[236] Common long-term complications include pouchitis, cuffitis, anastomotic ulcer, pouch fistula, fecal incontinence, irritable pouch syndrome, sexual dysfunction, and CD of the pouch.[236,264] A meta-analysis by Peyrin-Biroulet et al. showed early complication rate of 9%–65% and late complication rate of 17%–55% depending upon the type of surgery.[264] Infectious complications ranged from 10% to 45% and pouch-related complications ranged from 0% to 19%.[264] A study by de Silva et al. revealed that age $>$64 years, presence of $>$2 comorbidities, and emergent colectomy were independent predictors of post-operative complications.[265]

Pouchitis

Pouchitis is an idiopathic and nonspecific inflammation of the ileal pouch, and is the most common complication after IPAA.[266,267] Peyrin-Biroulet et al. reported that the frequency of pouchitis ranges from 8% to 41%.[264] Nearly 50% of patients develop pouchitis within 10 years of surgery and is associated with increased healthcare resource utilization.[268–270] Risk factors for pouchitis include extensive and severe colitis, backwash ileitis, presence of p-ANCA, mutations of interleukin (IL)-1 receptor antagonist or NOD2/CARD15, EIMs like PSC, non-smoking status, and use of NSAIDs.[267,271] It is proposed that pouchitis results from fecal stasis and bacterial overgrowth in the setting of a compromised host immune system.[267] A subset of pouchitis shares some pathogenic pathways of IBD and may be secondary to recurrence of UC-like disease in the ileal pouch.[267,272]

Pouchitis is characterized by nonspecific symptoms like fever, lower abdominal cramps/discomfort, increased frequency of bowel movements, and mucus/blood in stools, making it difficult to differentiate from other conditions like infectious enteritis, cuffitis, irritable pouch syndrome, and Crohn's disease of the pouch.[266,271] Diagnosis is established through a combination of clinical assessment, endoscopic and histologic evaluation. Separate biopsies should be obtained from the pouch, afferent ileal limb, and retained rectal cuff (if present).[266] Absence of endoscopic and histologic evidence of inflammation suggests a diagnosis of irritable pouch syndrome.[267] The most commonly used diagnostic instrument for pouchitis is the pouchitis disease activity index (PDAI). The PDAI is an 18-point standardized scale that includes clinical, endoscopic, and histologic criteria. A total PDAI score of 7 or higher indicates presence of pouchitis.[273] Other diagnostic modalities include retrograde pouchography, CT/MRI, and exam under anesthesia.[267]

Pouchitis can be classified into antibiotic-responsive and antibiotic-refractory (fails to respond to a 2- to 4-week course of a single antibiotic) based on the patient's response to antibiotics.[267] Metronidazole and ciprofloxacin are used as first-line agents for treatment of antibiotic-responsive acute pouchitis.[274] Ciprofloxacin has been shown to cause significantly greater reduction in PDAI score and fewer side effects when compared with metronidazole.[275] Patients with chronic pouchitis (symptoms lasting greater than 4 weeks) are initially treated with a 2- to 4-week course of ciprofloxacin and metronidazole.[266] Chronic treatment-refractory pouchitis requires the use of 5-ASA medications, topical steroids immunomodulators or anti-TNF agents.[271] Patients with more than 2 episodes of pouchitis per year are said to have recurrent or relapsing pouchitis.[266] These patients usually respond to antibiotic therapy but develop recurrent symptoms upon discontinuing antibiotics. They are said to have antibiotic-dependent pouchitis and require long-term antibiotic therapy to maintain remission.[267]

Severe antibiotic-refractory pouchitis is difficult to treat and can lead to pouch loss, pouch failure, or pouch excision.[267] It is important to rule out use of NSAIDs, concurrent infection with *Clostridium difficile* or cytomegalovirus, and CD in patients with refractory disease.[267] Probiotics have been shown to be beneficial in preventing flare-ups and maintaining remission in pouchitis, especially relapsing and antibiotic-dependent pouchitis.[276,277] The therapeutic mechanism through which probiotics prevent flare-ups and maintain remission is unclear. Further studies are needed into the efficacy and mechanism of action of probiotics in pouchitis.

Cuffitis

When the "stapled technique" is used for anastomosing the ileal pouch to the anal canal, a 1–2 cm cuff of rectal mucosa is left behind, which can develop recurrent inflammation and dysplasia. It is difficult to differential the symptoms of cuffitis, pouchitis, and CD of the pouch, though cuffitis tends to present with rectal bleeding and has an increased incidence of EIMs.[278] The rectal cuff should be carefully examined during endoscopy to avoid any delay in diagnosis. The Cuffitis Disease Activity Index (CDAI) is used to assess disease severity. Topical mesalamine has been shown to be effective and is well tolerated in the treatment of cuffitis.[279] Refractory

cuffitis or dysplasia of the rectal cuff can be managed by converting the stapled IPAA to a hand-sewn IPAA after resecting the cuff.[266]

Irritable pouch syndrome

Irritable pouch syndrome is characterized by presence of lower abdominal discomfort, increased stool frequency and urgency, with a PDAI of less than 7.[266] This condition is often diagnosed after failure of therapy for pouchitis. Low fecal lactoferrin level ($<7\,\mu g/mL$) strongly suggests non-inflammatory cause of symptoms and is strongly suggestive of irritable pouch syndrome.[280] Management includes increasing dietary fiber, antidiarrheal agents, anticholinergics, and antidepressants.[266]

Crohn's disease of the pouch

Patients with chronic treatment-refractory or relapsing pouchitis should be evaluated for CD of the pouch.[266] Findings suggestive of CD like ulcerations of the afferent ileal limb, granulomas, and distorted mucosal architecture can be found on endoscopy.[26,266] Retrograde pouchography (modified barium enema) will reveal characteristic findings of CD like cobblestoning, ulceration, nodularity, thickened mucosal folds, and strictures or fistulae.[281] EIMs of CD like fatigue and pyoderma gangrenosum can be the presenting symptoms. High titers of ASCA and outer-membrane porin C (omp-C) are suggestive of CD.[266] A combination of infliximab and azathioprine appears to offer the best clinical response.[26,282] A meta-analysis by Huguet et al. revealed that anti-TNF agents are associated with higher and faster efficacy in CD-like complications of the pouch compared to refractory pouchitis.[283] Pouch excision should be considered for patients with refractory disease and poor quality of life and is associated with excellent long-tern outcomes.[266]

Conclusion

In summary, it is difficult to predict the prognosis of patients with UC. It is necessary to individualize each patients' assessment and treatment plan in order to produce the best health outcomes. Not one approach is a perfect fit for every patient and one patient may require multiple treatment modalities to achieve remission. It is also essential to be able to identify higher risk patients, as their treatment approach may require more frequent and aggressive interventions.

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