Pediatric esophageal motility disorders: studies on (patho)physiology, diagnosis and management

Smits, M.J.

Publication date
2015

Document Version
Final published version

General introduction & Outline of the thesis

Parts of this introduction have been published as

Marije Smits, Clara Loots, Marc Benninga, Taher Omari, Michiel van Wijk
Current Gastroenterology Reports. 2013 Oct;15(10):351
New insights in gastroesophageal reflux, esophageal function and gastric emptying in relation to dysphagia before and after anti-reflux surgery in children.

Rachel van der Pol, Marije Smits, Marc Benninga, Michiel van Wijk.
Journal of Pediatric Gastroenterology and Nutrition. 2011;53:S6-8
Non-pharmacological therapies for GERD in infants and children.

Anatomy, physiology and normal upper gastrointestinal motility

Esophagus

The esophagus is a hollow tubular organ stretching from the upper esophageal sphincter (UES) to the lower esophageal sphincter (LES). The esophagus enables the passage of boluses (e.g. liquid and solid food, saliva) from the mouth cavity towards the stomach. The esophageal musculature comprises of a proximal one third striated muscle and a distal two thirds smooth muscle. Primary peristalsis is the reflex esophageal peristaltic contraction wave after swallowing and involves the oral phase of swallowing, UES relaxation, esophageal propagation and LES relaxation. Autonomic innervated, circular and longitudinal layered muscle fibers lining the esophageal wall propagate the bolus forward after a swallow, followed by a swallow-related relaxation of the LES (SLESR). After bolus passage, the LES returns to its natural contracted state, preventing backflow of stomach contents.[1,2] In case of multiple subsequent swallows, the LES remains relaxed and returns to resting pressure after the last swallow. Residual bolus in the esophagus can be cleared by so-called secondary peristalsis, a contraction wave limited to the esophageal body not involving a full swallow reflex. The control of swallow-induced propagation across the esophagus is fully developed from a gestational age of 26 weeks, but maturation of this esophageal peristaltic patterns and the LES continues throughout the infant/toddler period.[3-5]

Esophago-Gastric Junction

The esophago-gastric junction (EGJ) is situated at the transition of the esophagus to the stomach and consists of the LES and the crural diaphragm (CD), *Figure 1.* It creates a high pressure zone at the end of the esophagus at the transition of the thoracic and abdominal cavity, preventing backflow of gastric contents into the esophagus (gastroesophageal reflux). The EGJ is the main anti-reflux barrier. Basal high pressure is maintained by tonic contraction of the smooth muscles of the LES and extrinsic pressure of the striated muscles of the CD. Relaxation of the EGJ allows the passage of a bolus into the stomach. Changes in the abdomino-thoraric pressure gradient, e.g. as an effect of respiration, lower the main anti-reflux barrier. However, this is compensated by reflex contractions of the CD. [6]

Stomach

The stomach can be divided into three sections (cardia/fundus, corpus and antrum/pylorus), based upon histologic differences and two sections according to their role in the process of digestion (the upper gastric reservoir creating tonic contractions and lower, the gastric pump creating phasic contractions). The proximal reservoir part of the stomach relaxes and expands in reaction to ingested food and has a large share in the total gastric emptying time. The more distal and powerful phasic contractions of the gastric pump serve to grind and mix the food with digestive gastric juices before it is propelled into the duodenum for further digestion and uptake of nutrients.

The gastric mucosa in the fundus and corpus contains cells, which produce digestive secretions. The two main cell types are: acid (HCl) secreting parietal cells and the pepsinogen secreting gastric chief cells. Gastrin-secreting G cells and somatostatin-secreting D cells in the antral mucosa regulate gastric acid secretion in reaction to a meal, together with acetylcholine (vagus nerve) and histamine (enterochromaffin-like cells in fundus/corpus). The acid environment thus created serves as an anti-microbial barrier, but it also activates pepsinogen to form the active protease pepsin which starts the digestive process. The stomach also plays a role in the feeling of satiety by means of ghrelin, an appetite-stimulating hormone that is released by gastric mucosa into the portal circulation when the stomach is empty.[7,8]

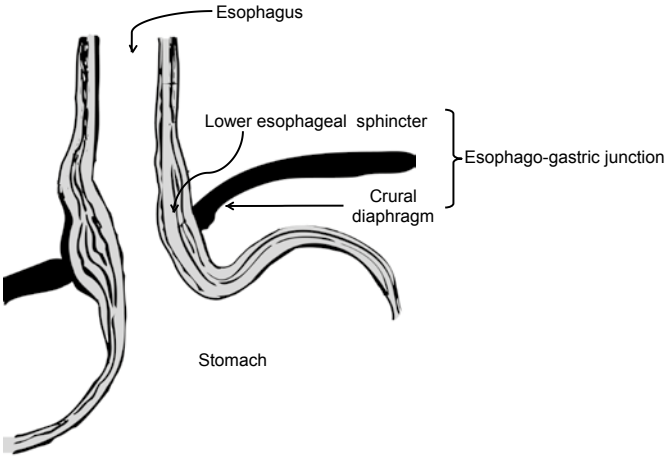

Figure 1. The esophago-gastric junction consisting of the lower esophageal sphincter and the crural diaphragm.

Esophageal motility disorders

Esophageal motility disorders, primarily smooth muscle-related, encompass a broad class of motility abnormalities that might manifest as deviating contractions of the esophageal body as well as abnormal function of both the UES and LES. Motility disorders can be classified in different ways, e.g. by their main symptom or findings on esophageal function assessment. In this thesis, primarily two esophageal motility disorders, gastroesophageal reflux disease (GERD, all age ranges) and achalasia (in children), are discussed. Over the next pages, the pathophysiology, diagnostic tools and management of GERD and achalasia are introduced.

Gastroesophageal reflux disease

(Patho)physiology

Transient Lower Esophageal Sphincter Relaxations

An abrupt decrease in LES pressure, typically longer in duration compared to SLESRs and not preceded by a swallow, is defined as a transient relaxation of the lower esophageal sphincter (TLESR).[9] TLESRs serve as the physiological mechanism to vent gas from the stomach, however they are also the primary mechanism behind up to 90% of liquid gastroesophageal reflux (GER): the passive flow of gastric contents (liquid or mixed) into the esophagus.[10–13] TLESRs, similar to those described in adults, are observed in prematurely born infants >28 weeks.[10,14,15]

TLESRs are mediated by a vago-vagal pathway (*Figure 2*). Activated vagal receptors have central terminals in the Nucleus Tractus Solitarius (NTS) of the brainstem. NTS neurons in their turn, synapse with neurons of the central program generator, where this information is orchestrated with several other inputs, e.g. consciousness and body position.[16–19] Multiple excitory and inhibitory signals are generated, ultimately resulting in LES relaxation and inhibition of esophageal peristalsis. In addition, phrenic efferents to the crural diaphragm result in a laxity of the external part of the sphincter. A number of stimuli are known to induce the vagal activation ultimately leading to a TLESR.[20–22] The primary postulated stimulus is the activation of stretch receptors in the proximal stomach, e.g. after a meal or in case of gas accumulation. Furthermore, cholecystokinin, a hormone released when nutrients enter the duodenum, decreases LES pressure and causes an increase in the number of TLESRs.[23–25] Another trigger is the stimulation of the superior laryngeal nerve in the pharynx.[26] Finally, it was shown that TLESR triggering can be enhanced by relatively minor stimuli such as the presence of a nasogastric tube across the LES[27–29] or distension of the EGJ alone.[30] These observations indicate a more complex mechanism of TLESR triggering than can be explained by gastric distension alone and raise the question which role the EGJ geometry might play in the process of TLESR triggering. Yet undiscovered mucosal receptors at the site of the EGJ might sense luminal contents and accordingly modulate TLESR triggering. In summary, although the neurological pathway underlying a TLESR is now well known, the triggers that lower the threshold for one to occur are complex and not fully understood.

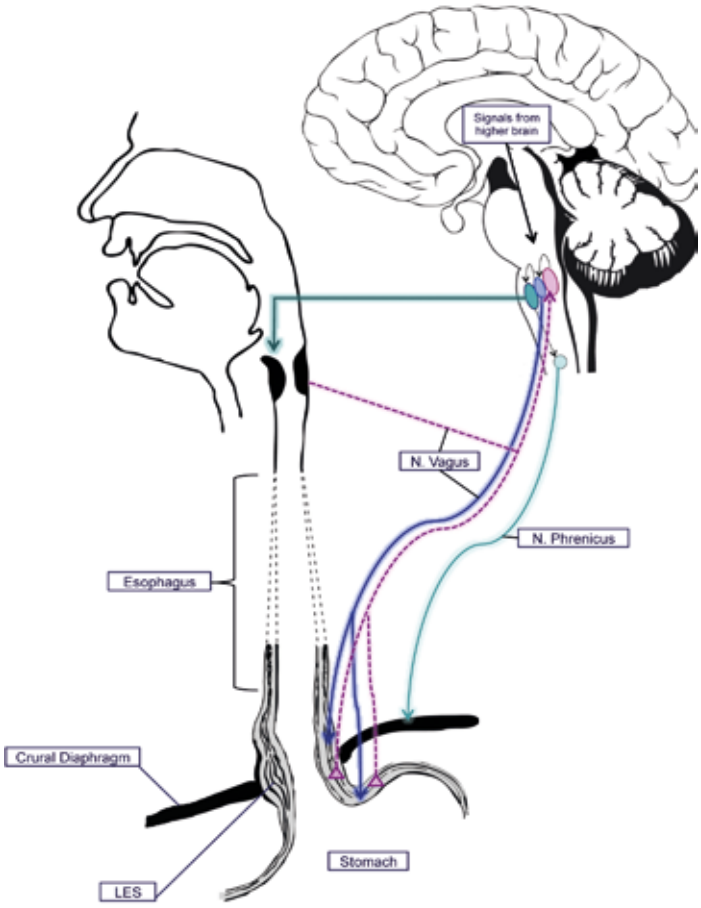

Figure 2. An overview of the vaso-vagal pathway leading to a TLESR. Goyal and Shaker (Nature Publishing Group, Sphincter mechanisms at the lower end of the esophagus. GI Motility online. May 2006) as basis for Figure 2.

Gastroesophageal reflux (GER) is a physiological phenomenon occurring at all ages. Physiologic GER in infants is promoted by supine position, frequent liquid feeds and anatomical properties of the infant upper gastrointestinal tract.[33] Mechanical impairment of the EGJ, for example the presence of a hernia diafragmatica and subsequent translocation of (a part of) the proximal stomach in the thoracic cavity, lowers TLESR threshold and promotes the occurrence of GER.[31] If abdominal pressure overcomes EGJ resting pressure, GER occurs more easily. This is especially relevant in cases of low LES resting pressures.[32] When GER causes troublesome, severe symptoms or complications, GER disease (GERD) should be considered. TLESRs are known to be the primary mechanism behind GER episodes.[10–13] Strikingly, the number of TLESRs in GERD patients is equal to those of healthy controls, in children as well as in adults. However, the nature of GER occurring during a TLESR is

more likely to be liquid and acidic in patients with GERD.[10,34,35] The pathophysiological mechanisms underlying this difference are not yet completely understood. Low LES pressures and failure of protective mechanisms (e.g. insufficient clearance or buffering of the refluxate, impaired neural aerodigestive reflexes) might play a role. Recently, in adults, the existence of a so-called acid pocket was suggested to play a pivotal role in the pathophysiology of adult GERD. Accumulating acid in the proximal cardia (especially after a meal) forms a pool (pocket) floating on top of the gastric contents, from which acid GER is more likely to occur in case of a TLESR.[36] In GERD patients, this acid pocket is bigger and extends more proximal compared to healthy controls, especially in the presence of hiatal hernia.[37,38] It is not clear if such an acid pocket exists in infants and children and if, considering the large differences with adults concerning anatomy, posture and feeding, it plays the same role in generating symptomatic GER.

Delayed gastric emptying has been proposed to augment liquid GER and is frequently proposed to play a role in the pathophysiology of GERD.[39-46] However, two studies assessing the influence of body positioning on the occurrence of GER found that, in the presence of delayed gastric emptying, the amount of TLESRs is lessened.[47,48]

Epidemiology

Daily regurgitation occurs in 70% of infants at 4 months of age. [49,50] Generally, infant GER symptoms resolve in the first year of life and only 5% of 12-14 month old children continue to have symptomatic GER. The majorities of these children grow up and develop well. However, GER symptoms are found bothersome and GERD is diagnosed in up to 12% of infants, with a drop in incidence to 1% for children >18 months old.[51,52] A recent national community survey revealed 25.9% of parents reported infant regurgitation matching Rome III criteria for functional gastrointestinal disorders.[53] In addition to the bothersome physical symptoms for children with presumed GERD, it appears to affect psychological well-being, quality of life and financial well-being of the child's parents or caregivers as well.[54,55] The health care costs per pediatric patient are estimated to be USD 2,386 in the first six months following diagnosis, with an overall health care cost burden in the USA of USD 750 million each year.[56] Based on the number of inhabitants and birth-rate statistics, this would approximately translate to an overall health care cost in the European Union of euro 1,1 billion per year for infants only.[57]

Symptoms

The symptoms of GERD vary between infants and older children and can be divided into esophageal (often caused by inflammation of the esophageal mucosa due to acid GER) and extra-esophageal *(Table 1)*. In general, older children are able to report their symptoms adequately. In that age category, predominant symptoms of GERD, heartburn and regurgitation, are typical and resemble those of adults.[58-60] In infants and toddlers, symptoms are often non-specific and the extent to which these symptoms are troublesome is subject to broad interpretation.[61] Non-specific symptoms such as excessive crying, irritability, back-arching and feed refusal in infants and toddlers are often thought to be GER related. However, most of the times they do not correlate with diag-

nostic outcome.[62,63] When alarm symptoms such as failure to thrive or hematemesis exist, or GER symptoms persist beyond 18 months of age, severe GERD might underlie symptoms and should be treated if possible.[64]

Extra-esophageal symptoms of GER in infants and children are thought to be direct consequences of GER extending in the laryngopharynx and beyond (laryngopharyngeal reflux, LPR).[65] Micro-aspiration of LPR is commonly thought to be a causal or aggravating factor in chronic respiratory disease in children, such as chronic cough, bronchitis or even pneumonia.[66,67] For dental erosions and Sandifer's syndrome (paroxysmal dystonic movement disorder), association with GER and hiatal hernia is confirmed.[68-70] However, many other extra-esophageal symptoms *(Table 1)* are inconsistently related to GERD. They contribute significantly to the cost burden of the management of pediatric GERD. Up to 10% of all otorhinolaryngologists referrals are GER related. [71]

In infants admitted for recurrent apneas, presumably underlying GERD is diagnosed in up to 50%, frequently accompanied by costly and invasive diagnostics and even therapeutic approaches like anti-reflux surgery.[72-74] Apneas, cessations of respiratory air flow of clinical significance, are a relative rare phenomenon in mature infants. With a large physiological amount of GER episodes and little apneas, establishing a causal relation between the two entities is challenging and evidence is contradicting.

Symptoms of pediatric GER disease		
	Infants	**Children**
Esophageal	Recurrent regurgitation/vomiting Irritability Excessive crying Feeding refusal	Rumination Heartburn Retrosternal pain Dysphagia Odynophagia
Extra-esophageal	Stridor Chronic cough Hoarseness Halitosis Dental erosions Sandifer's syndrome Back arching	Wheezing
Alarm symptoms	Failure to thrive Hematemesis	

Table 1. Symptoms of GER disease

Differential diagnosis & associated functional motility disorders

Considering the non-specific nature of symptoms as regurgitation and vomiting, a broad differential diagnosis apart from GERD should be considered in infants and children at presentation *(Table 2)*. In infants, regurgitation might be due to overfeeding and GER symptoms might mimic those of cow's

milk protein allergy (CMPA). When atopic symptoms are found (e.g. eczema, loose stools, respiratory symptoms or a positive family history for allergy), CMPA should be considered.[75] Another disease with symptoms that can mimic GERD is eosinophilic esophagitis (EoE).[76] Especially in infants, EoE and GERD can be indistinguishable from each other, while in older children, EoE patients often present with symptoms of dysphagia and/or food impaction. The diagnosis of EoE is confirmed by histologic evidence of eosinophil-predominant inflammation of the esophageal mucosa ($\geq$ 15 eosinophils per high-power field). EoE is chronic immune/antigen mediated inflammatory condition of the esophagus, often associated with atopic characteristics and aerodigestive and respiratory symptoms.[77]

Differential diagnosis of pediatric GER disease		
	Infants	**Children**
Immunologic/ allergic	Cow's milk protein allergy (CMPA) Celiac disease (after gluten introduction) Eosinophilic esophagitis	Celiac disease
Obstructive	Infant colic Pyloric hypertrophy/stenosis Malrotation Duodenal web/stenosis Pancreas annulare Hirschsprung's disease Gastrointestinal atresia Laryngomalacia (with stridor) Constipation Achalasia	EGJ outflow obstruction
Habitual	Overfeeding Infant rumination syndrome Pediatric condition falsification	Supragastric belching Rumination syndrome Aerophagia
Infectious	Gastrointestinal Urinary tract infection Respiratory tract infection Pharyngitis/otitis Meningitis Other infections	
Neurologic	Cerebral process Epilepsy Neuromotor disorder	
Metabolic	Hereditary disorders of metabolism	
Pharmacological	Intoxication	
Other	Necrotizing enterocolitis	

Table 2. Differential diagnosis of regurgitation and vomiting in infants and children.

Regurgitation and vomiting can be associated with motility disorders of the esophagus, such as hypotonic LES, failed peristalsis, EGJ outflow obstruction and achalasia. In addition, unconsciously acquired behavior, the rumination syndrome, aerophagia or the supragastric belching (SGB) syndrome, can generate GER symptoms.[78-82] Rumination is characterized by unintentionally contracting abdominal muscles until gastric pressure exceeds intrathoracic pressure and GER occurs.[78] SGBs are generated by sucking air into the proximal esophagus and consequently rapid expulsion of this air. The air never reaches the gastric cavity, hence the name 'supragastric belch'. Both rumination episodes and SGBs typically occur multiple times a day, especially after a meal and often in bursts.[81] Aerophagia is characterized by the episodic or chronic ingestion of large quantities of air, which accumulate in the gastrointestinal tract to cause abdominal distention and bloating. Symptoms often worsen in the course of day.[82] Due to the involuntarily character of symptoms and unawareness of acquired behavior, all three disorders may become extremely bothersome.

Finally, a number of conditions are strongly associated with pediatric GERD, or indicate a high probability of developing it.[83] Esophageal atresia, cystic fibrosis (CF) and chronic respiratory disorders such as interstitial fibrosis and bronchopulmonary dysplasia are associated with higher prevalence of GERD.[84-88] Neurological impairment (e.g. cerebral palsy) is clearly associated with GERD.[89,90] Obesity is a risk factor, especially in adults. The association of BMI and reflux esophagitis is children is still under debate, but with increasing numbers of obese children, serious overweight and its contribution to symptoms should be incorporated in diagnostic workup (anamnesis) of pediatric GERD.[91-93]

Diagnosis

History taking & physical examination

Pediatric GERD is primarily a clinical diagnosis, based on history taking and physical examination.[64] This approach might be considered as 'gold standard' and GERD is relatively easy to establish when classical esophageal symptoms, such as regurgitation, vomiting and irritability during or after feeds are accompanied by alarm symptoms such as hematemesis, or failure to thrive. However, in most cases, no alarm symptoms are present (yet) and discerning GERD from physiological GER is difficult. The extent of burden for caregivers should be explored, as capacity to cope with symptoms might vary greatly. Despite GER being physiological and caregivers are informed that symptoms are very likely to disappear spontaneously, many of them are concerned by the number or severity of symptoms and want to exclude disease.[55,83,94,95]

In an attempt to structure history taking in symptomatic infants, the Infant GER questionnaire (I-GERQ) and a revised version, the I-GERQ-R, were developed.[61,96] This questionnaire consists of 12 multiple-choice items scored on a 2-5 scale. The higher the score, the more severe symptoms are. It was proven to be a sensitive and specific tool to monitor symptoms over time. However, the questionnaire does not discriminate infants with pathologic GERD from those with similar symptoms without GERD.[97] No disease-specific symptom questionnaire exists for children >4 years of age.[98]

pH metry and pH impedance metry

Continuous 24-hour esophageal ambulant intraluminal pH-metry is frequently used to diagnose acid GERD.[99] It allows evaluation of esophageal acid exposure (expressed as the reflux index, the percentage during which esophageal pH <4 of total recording time) and association of symptoms with acid GER, especially when measuring extends ≥ 48hr.[100] Currently used normative values in children differ between age groups and from those used in adults. The largest prospective study, using 24hr pH-metry in screening for sudden infant death risks in 509 healthy infants, revealed a normal cut off value for the reflux index during the first 12 months of life of <10%, decreasing from 13% at birth to 8% at 12 months.[101] For older children an RI >7% is considered abnormal, an RI <3% is considered normal, and an RI between ≥ 3% and ≥ 7% is indeterminate.[64] In adults, an RI>4.2% is indicative of pathologic acid GERD. For older teenagers with GER symptoms, adult reference values can be used if pH-metry is indeterminate.[102]

The development of 24-hour esophageal pH multichannel intraluminal impedance metry (pH-MII), first introduced in children in 1996 by Skopnik et al., enabled the detection of weakly acidic (4<pH>7) and non acidic GER (pH>7) besides acid GER, as well as the proximal extent of GER *(Figure 3)*.[103] This might be of special importance to infants receiving frequent milk feedings, a potent buffer of gastric acid up to 2 hours after a feed.[104] Moreover, it has been shown that weakly acidic and non acidic GER is able to induce (extra) esophageal symptoms, to an extent similar to acid GER.[105-110]

A pH-MII catheter consists of six circular electrode pairs placed longitudinal along the catheter. Each pair of electrodes measures impedance, the quotient of voltage and electrical current, which is inversely proportional to ionic concentrations of intraluminal contents passing along the catheter. Gas, with a low ionic content, will produce a high impedance signal, while refluxate or saliva have a higher ionic contents and produce lower impedance signals. The multiple electrode pairs along the catheter allow the assessment of antegrade (swallow) and retrograde (GER) movement. In combination with the pH sensor, pH-MII is able to categorize each GER episode by its acidity (acid, weakly acid or non acidic) and by its nature (liquid, gaseous or mixed). Baseline impedance values represent conductivity of esophageal mucosa, since the esophageal cavity is collapsed when in rest. In adults, baseline impedance values have been related to esophagitis and micro esophageal damage (dilated intracellular spaces).[111] In infants, baseline MII values are lower compared to older children. In older children, the association with esophagitis and low baselines is under debate.[112]

It is generally accepted to define liquid GER on pH-MII recordings as a drop of >50% of baseline impedance signal in the distal two or more channels, moving in retrograde direction.[113] Similarly, gas GER is defined as a retrograde rise of impedance to >3000 Ohm in two or more channels. Mixed GER is a combination of patterns meeting both liquid and gas GER criteria. Although these criteria seem relatively clear cut, certain patterns in pH-MII measurements appear especially hard to interpret.[114] Recent research showed there is a considerable inter- and intra-observer variability in pH-MII analysis and automatic analysis lacks specificity for detecting of GER episodes. [114-116]

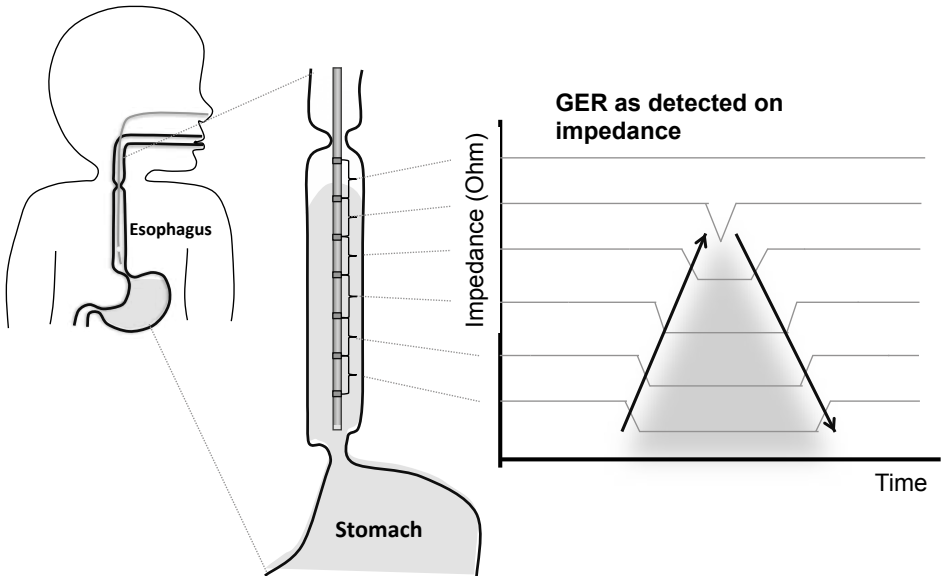

Figure 3. The principle of pH-impedance (pH-MII) metry explained. On the left panel, reference anatomy and the pH-MII katheter is graphically depicted. Note that each pair of electrodes records the conductivity of fluids surrounding the catheter, allowing the detection of GER, even in the absence of a pH drop (red line).

Several indices for symptom association on pH-MII have been developed.[117,118] The three most used indices are: the symptom index (SI),[119] the symptom sensitivity index (SSI)[120] and the symptom association probability (SAP). The latter is most commonly used, and represents the statistical probability that GER and symptoms are in fact temporally related. A time window of 2 minutes to relate GER and symptoms is derived from adult data, but has been shown appropriate for pediatric symptoms of cough and regurgitation.[121,122] However, for crying, a 5 minute window generates optimal symptom association.[122] Recently, the influence of recording time on the association found was clearly shown, confirming the need for prolonged monitoring.[123] Although current available association indices for GER related symptoms all have their limitations, it is indispensable to prove the presence of symptom association.[117,118] Accurate symptom association for pH-MII in children and especially infants is hampered by the fact that it relies on symptoms reported by parents. In contrast to adults, where pH-MII has become the gold standard, pH-MII lacks sensitivity and specificity to diagnose GERD in infants and children and the additional value compared to history taking and physical examination is not as clear.[116,124] The difference in diagnostic accuracy of pH-MII between adults and children can be largely explained by the invasive nature of the test. A pH-MII catheter is passed transnasally through the esophagus towards the stomach. Correct positioning of the catheter in pediatric patients is checked with a thoracic x-ray or preceding esophageal manometry. It would be unethical to study healthy infants and children with this protocol to establish reference values.[125]

Esophageal manometry

Esophageal (high resolution) manometry is used to assess esophageal motility and LES function. The diagnostic value in GERD is limited. However, it can be used to exclude motility disorders such as rumination and SGB syndromes[79,126] or achalasia, in case of additional symptoms. The use of manometry to assess motility disorders is further explained under the subheading 'achalasia' in this introduction.

Diagnosis is primarily based on history taking and exclusion of other causes of GER symptoms. Recently, the combined high-resolution manometry/impedance (HRIM) measurement (see diagnostic tests for pediatric GER disease) has been shown of additional value for the diagnosis of rumination and SGB syndromes and its subtypes.

Endoscopy with biopsies

Esophagogastroscopy can be used to diagnose reflux esophagitis, a complication of GERD. Macroscopically visible mucosal breaks (erosions) are the most reliable evidence for GERD.[127,128] These erosions are classified according to the Los Angeles classification and the Hetzel and Dent scale, similar to adult methods.[129,130] Evidence to use microscopic grading of the esophageal wall is lacking, and currently histology in children is primarily used to exclude other causes of reflux esophagitis and GER symptoms (eosinophilic esophagitis, Crohn's disease and infections).[83,131,132]

Imaging techniques

Barium contrast studies consist of a series of radiographs of the esophagus and stomach using a barium emulsion to track swallows and possible reflux, which sometimes reveal structural anatomic causes underlying GER symptoms.[133] In gastroesophageal nuclear scintigraphy, patients consume a ^{99}technetium labeled meal prior to start of a series of scans, and postprandial reflux becomes visible when labeled stomach contents move upwards in the esophagus.[134] Unfortunately, neither the presence nor absence of GER is indicative of symptom burden or GERD in either of these imaging techniques. Barium swallow studies are neither sensitive nor specific enough compared to pH-metry, which in itself is no gold standard to diagnose GERD in children.[135,136] Scintigraphy can provide information on gastric emptying time, however the correlation between delayed gastric emptying and GERD is under debate in children.[47,48] In addition, there is a lack of standardized techniques and the absence of age-specific normative values for these tests. Therefore, they are of no additional value in the diagnosis of GERD.

Empirical trial with pharmacological therapy

A trial with an anti-reflux agent may be used to diagnose pediatric GERD. A proton pump inhibitor (PPI) is often the agent of choice and an empiric trial of 2-4 weeks is common. In adults, PPIs are more effective compared to other acid inhibitors.[137] Data on sensitivity and specificity in children are scarce, and trials are prone to bias because mild GERD symptoms may improve spontaneously in time or as a result of placebo effect.[64] Dutch and international guidelines advice a trial with PPIs in children <18 months if symptoms persist despite conservative treatment, feed thickeners and only in

the presence of an alarm symptom. In children 18 months to 18 years of age with typical GER related symptoms, a 2-4 weeks trial with PPIs can be started immediately at presentation.[64,138]

Empirical trial with hydrolyzed formula in infants

Considering the similarity of symptoms of GERD and CMPA in infants, a cow's milk free diet or hydrolyzed/semi-elemental formula can be used to exclude CMPA as a cause of symptoms. However, the role of such a diet in GERD is unclear and it should preferably only be considered an approach if other symptoms of CMPA and/or atopy are present to avoid unnecessary and costly treatment.[139] If a cow's milk protein restricted diet reduces symptoms, a double blind placebo controlled test is required to diagnose CMPA with certainty.

Treatment

Non-pharmacological treatment

Although GER symptoms in infants are generally mild and self-limiting, with most infants outgrowing their symptoms before the age of one,[51,52] it can cause so much discomfort that caregivers seek medical advice. When no alarm symptoms are present, the first approach in mild pediatric GERD should include explanation and reassurance of caregivers.[64] Overfeeding must be excluded, as distension of the stomach is able to increase the number of TLESRs and thus GER.[140] Moreover, anatomical properties of the infant gastrointestinal tract make GER more likely to occur in case of overfeeding: a small stomach and relative short esophagus, broad cardiac notch (the angle between the esophagus and stomach) and lesser compliance of the stomach compared to older children.[141]

In preterm born infants with frequent GER, a conservative approach including a switch from bolus to continuous feeds and reduction of flow rate switch from bolus to continuous feeds and reduction of flow rate in case of naso gastric feeding might reduce symptoms might reduce symptoms.[142,143]

Feed thickeners, the most commonly used are locust bean gum or (rice) starch, reduce the number and proximal extension of (non-acid) GER in infants with recurrent regurgitation but was found only moderately effective in treating GER in otherwise healthy infants in a systematic review.[144,145] Moreover, thickening of feeds does not reduce presumed GER-related apnea in preterm infants.[146] On the other hand, a recent placebo controlled trial found (low lactose) rice formula was efficacious in providing a clinically relevant reduction of spit-up frequency in term infants.[147] A safety review of toxicology studies showed locust bean gum is safe for use in term-born infants with mild GERD or GER symptoms from birth onwards.[148] Despite its limited proven efficacy in reducing GER, thickening of feed is cheap and easy and a trial of 2 weeks should be applied first before moving to other treatment for uncomplicated GER symptoms in infants.[64,138]

The influence of body position on the occurrence of GER and symptoms is considerable. GER is exacerbated by upright, sitting position (60°) and decreased by a prone 30° anti-Trendelenburg position.[149,150] However, sudden infant death syndrome (SIDS) is associated with prone position in infants and thus prone positioning of a child should be avoided, unless cardiorespiratory monitoring is present or the infant is over 6 months old (SIDS risk significantly reduced and the infant is generally capable of rolling over).[151] Left lateral positioning significantly reduces liquid and acid GER in

healthy (pre)term infants as well as infants with GERD.[152] A protocol in which the infant is placed in right lateral position after a meal, followed by left lateral positioning promotes gastric emptying and reduces liquid GER in the late postprandial period and has been proposed to reduce symptoms of GERD.[48] On the other hand, a recent sham-controlled trial showed that left lateral positioning (LLP) produces a significant reduction in total GER, but did not result in a significant improvement in symptoms other than vomiting.[153] For older children, only expert opinion-based evidence on positioning is at hand, supporting elevation of the bed and prone or left lateral sleeping position based on adult literature.[64]

Another conservative treatment approach is the avoidance of tobacco smoke in the presence of infants and children with GER symptoms, as it might aggravate esophagitis.[154–156] For these and many other reasons, it should be promoted that caregivers stop smoking, at least near their child.

Current national and international guidelines advice a combination of feed thickeners and conservative measures as a first choice treatment for pediatric GERD.[64,138] However, evidence is based on small trials and further research is needed to establish optimal conservative treatment for infants and children.[157–159]

Pharmacological treatment

When a 2-4 week conservative trial does not resolve GER symptoms or alarm symptoms are present, pharmacological treatment can be considered as a next step. This therapy is still primarily focused on acid suppression of gastric contents, despite the fact that also weakly acidic and non-acid GER can cause symptoms. Agents targeting the main underlying mechanisms of GER, TLESRs, have severe side effects and are currently only used if other treatment options fail *(see TLESR inhibitors)*. The use of acid suppression, mainly PPIs and Histamine-2 receptor antagonists (H2RAs), in pediatrics has increased exponentially over the last decades. Especially in infants, but also in older children, acid inhibitor prescriptions have increased 4-11 times in the USA, Belgium and Australia between 2000-2009.[56,160–162] In The Netherlands, a recent health insurance database research involving 500.000 infants and children showed a sixfold increase in prescriptions issued by general practitioners between 2008 and 2013 for infants <18 months *(Figure 4)*. This upward trend was not reversed after the publication of the (inter)national guidelines in 2009 and 2012 on pediatric GERD, which advice only to prescribe acid suppression in refractory GERD or in case of alarm symptoms.[64,138] Parental distress and desire for a medical intervention in case of pediatric GER symptoms might pressure physicians into prescribing acid inhibiting medication.[55,83,94,95] The infant GER related healthcare burden seems to be influenced geographically: more urban infants are hospitalized for GER symptoms, compared to rural infants.[163] The use of acid suppressive medication is associated with an increase in respiratory tract infections and food allergies in adults and children, compared to placebo.[88,164,165] Hereafter, we briefly discuss the main acid suppressant agents and other pharmacological agents targeting GERD. One of the presumed most effective acid inhibitors, PPI, will be further discussed in Chapter 4 and Chapter 8.

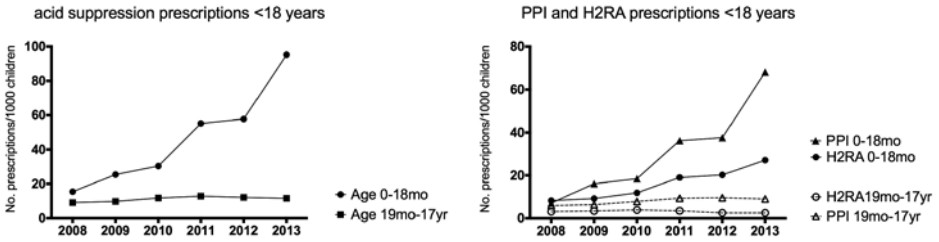

Figure 4. Acid suppression prescriptions issued by general practitioners between 2008 and 2013 for infants <18 months and children 19 months-17 years in the Netherlands. Data are shown for total acid suppression (PPI and H2RA, left panel) and split out for PPI and H2RA separately (right panel). PPI=proton pump inhibitor, H2RA=Histamine-2 receptor antagonists. (Data courtesy of Drs. N.F. Steutel).

Antacids & alginates

Both antacids and alginates (or a combination) are available over-the-counter and therefore broadly used in the treatment of GER symptoms. Antacids consist of alkali complexes (e.g. aluminum and/or magnesium, aluminum and magnesium phosphates, magnesium trisilicate, carbonate and bicarbonate salts) which neutralize gastric acid directly upon contact. The reaction of carbonate antacids with gastric acid cause a release of carbon dioxide (CO_2), which explains a bloated sensation or enhanced burping after ingestion of antacids. Alginate-based formulations contain polysaccharide polymers (derived from brown seaweed) and sodium or potassium bicarbonate. When in touch with acid gastric contents, the alginate forms a viscous gel, thickening gastric contents. When alginates and antacids (usually a bicarbonate) are combined (e.g. Gaviscon®), the CO_2 formed by the antacids becomes entrapped in the alginate based viscous gel, forming a "raft", floating on top of gastric contents.[166] This serves as an anti-reflux barrier, providing an immediate onset of effect.[167–170] Moreover, GER occurring despite the raft is less acidic in nature. Recently, combination formulations (for adults) are reinvented for treatment of GERD as it was shown that these antacid/alginate combinations effectively eliminate or displace the acid pocket downwards.[171–173] The existence of the acid pocket in children is unclear *(see Pathophysiology and symptoms of GER disease)*. Special developed Gaviscon® infant lacks bicarbonate and works thus as a feed thickener, without the forming of a typical raft of top of gastric contacts after administration.[174]

Very little studies have been performed assessing these agents. Especially for antacids, evidence is sparse and inconclusive.[175,176] Because of potential toxicity, prolonged use of antacids should be avoided in children.[64] For alginates, two of four studies show (marginally) beneficial effect on reflux height and vomiting for alginate formulations in children but there is a lack of methodologically sound, well-powered studies.[177–180]

Prokinetics

Evidence for the alleged relation between delayed gastric emptying and severity of GER symptoms is controversial. Right lateral positioning, accelerating gastric emptying, has been shown to enhance TLESRs and GER episodes.[48,181] More recent, gastric emptying rate of milk was found not significantly different between pediatric GERD patients and healthy children.[39]

Nonetheless, prokinetics are frequently used in pediatric GERD aiming to accelerate gastric emptying. Not surprisingly, the three most commonly used agents (domperidone, metoclopramide and erythromycine) all lack convincing evidence for efficacy.[174,178,182,183] Cisapride has never been proven effective in reducing GERD symptoms either and was withdrawn from the market in 2000 because of cardiac adverse events (elongated QT interval).[184] Recent research indicated a small proportion of infants receiving domperidone developed a similar elongated QT interval, but no overall significant effect was found.[185] Administration of amoxicillin/clavulanate directly into the small bowel has a beneficial effect on gastrointestinal motility in children and was therefore suggested as a possible new prokinetic agent.[186] The use of a broad spectrum antibiotics to accelerate gastric emptying, which is inconsistently found related to GERD, should be well founded, as the number of multidrug resistant bacteria is growing.

Histamine-2 receptor antagonists

Histamine-2 receptor antagonists (H2RAs) lower gastric pH by selectively blocking histamine-2 receptors in the gastric parietal cell. This results in decreased production of gastric acid and pepsin and thus a rise in gastric pH.[174] Different H2RAs exists (ranitidine, famotidine, nizatidine, roxatidine, and cimetidine hydrochloride) and even while they are a little less potent in raising gastric pH compared to PPIs,[187] it is an agent used often in treatment of (pediatric) GERD.[188] A recent systematic review showed that evidence supporting the efficacy and safety of H2RAs is sparse.[189] H2RAs have the advantage of easy administration over PPIs (which generally come in tablets or granules). However, for infants and children it should be noted that the usual ranitidine syrup contains 7.5% of alcohol.[64,138]

TLESR inhibitors

Several agents have been developed to target the underlying mechanism of most GER episodes: TLESRs. These include mGluR antagonists, cannabinoid receptor agonists and gamma-aminobutyric acid B (GABAb) receptor agonists. Only the latter, with most pediatric evidence available, will be discussed here.

GABA is one of the main neurotransmitters in the nervous system. One of its three subtypes, GABAb, is involved in the signal transduction of the vagal motor outflow to the LES.[190] The GABAb antagonist baclofen has been shown to significantly reduce TLESRs in adult healthy volunteers and GERD patients on the short and long term (4 weeks).[191-194] In pediatric patients, two studies have shown the potential beneficial effect of baclofen on TLESRs, acid reflux episodes and emesis.[195,196] A recent retrospective study found that baclofen can be beneficial as supplemental therapy to proton pump inhibitors in children with refractory GER.[197] However, severe side effects can occur, due to the pres-

ence of GABAb receptors throughout the central nervous system. Drowsiness, nausea, weakness, and headache often are reason to abate this therapy.[198] Besides, baclofen requires multiple doses per day due to its short half-life. Alternatives to overcome these problems, arbaclofen (requiring only one dosage per day) and lesogaberan (a peripherally active GABab antagonist), have not yet been proven clearly beneficial over PPIs or placebo, although a small proportion of GERD patients can benefit from lesogaberan.[199-201] These latter drugs, however, are no longer available due to marginal effects and have not been tested in children.

Surgical treatment

The primary goal of anti-reflux surgery is to reduce GER without preventing passage into the stomach of swallowed substances. Different types of fundoplication have been developed by Nissen (360° fundic wrap around the esophagus), Thal and Toupet (both partial wraps) which can be performed either via an open procedure or laparoscopic.[202] Similar to adult findings, the few pediatric studies on this subject suggested that total and partial fundoplication produce equivalent GER control in children.[203] The laparoscopic procedure in children has been shown to be superior to the open procedure in terms of length of hospital stay and in-hospital mortality, but cost-effectiveness is comparable.[204,205] Efficacy and safety of fundoplication in children remains poorly investigated. Success rates in terms of complete relief of symptoms <6 months after surgery of 57-100% (median 86%) have been suggested. In neurologically impaired children, success rates are lower, varying from 57-79% (median 70%).[203]

Overall complications during and after fundoplication in children occur in 0-54%, varying from post-operative dysphagia to wound infection and perforation.[203,206] Post-operative dysphagia is the most common complication, occurring in 0-33% of patients in the first months after fundoplication.[207] Dysphagia may occur less frequently in partial versus total fundoplication.[208] Long term follow up studies (up to 5.5 years) report treatment failure, (relapsing GERD) in 1% of non-neurologically impaired children and 12% in neurologically impaired children.[209]

The applicability of fundoplication has been hampered by the inability to predict which patient may benefit from surgery and which patient is likely to develop complications. Studies using a novel pressure-flow analysis technique based on high resolution impedance manometry recently developed the Dysphagia Risk Index (DRI), able to identify pre-operatively esophageal motility parameters that are associated with post-operative complications such as dysphagia.[210–212] In a recent study evaluating 10 neurologically impaired children (age range 1.1-17.1 years) before and after laparoscopic anterior partial fundoplication, the preoperative DRI was significantly higher in patients with post-operative dysphagia (n=4) compared to those without postoperative dysphagia (n=6). Conventional techniques, which analyze bolus movement and pressure generation separately, were not different in both groups. Larger trials are needed to determine the clinical relevance in terms of the prognostic value of this new analysis approach.

Guidelines for pediatric GERD

In 2009, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and nutrition (ESPGHAN), published joint international guidelines for the diagnosis and treatment of GERD in infants and children and in 2012, a Dutch equivalent was published.[64,138] Although the use of acid suppressive medication should be limited to very selected cases according to these guidelines, infants with uncomplicated GER are often treated with acid suppressive medications whilst conservative treatment would have most likely sufficed and pediatric prescriptions continue to rise.[56,93,160–162] A recent survey showed poor adherence to the current international ESPGHAN/NASPGHAN guidelines.[93] This might be due to insufficient knowledge of the guidelines, but other factors are likely to play an additional role, such as the ambiguous definition of GERD, absence of a valid gold standard diagnostic test as well as the absence of pharmacological therapy that is proven effective, and symptom burden for the child and caregivers.

Achalasia

Assessment of motility

Esophageal motility, the relaxation of the UES and LES, esophageal peristalsis and TLESRs, can be assessed using intra-esophageal manometry. A catheter usually contains 6-10 (in case of conventional manometry) capillary tubes, made of polyvinyl chloride or silicone, with their open ends placed longitudinal along the catheter. Each channel is water-perfused by an hydraulic pump, and the pressure in each channel is sensed and converted by a transducer. The catheter is placed transnasally across the EGJ in the stomach allowing the measurement of intraluminal pressure of the esophageal body and LES, displayed in a line plot.[213] Over the past years, more detailed assessment of esophageal function is possible due to the development of high resolution manometry (HRM).[214] HRM catheters contain 22-36 sensors, (water-perfused or with novel solid state) micotransducers with a pressure sensitive surface spaced ≤ 1cm apart. Dedicated software converts the pressure recordings into a detailed line plot. This can be displayed in an intuitively interpretable esophageal pressure topography (EPT) color plot *(Figure 5)*.[215]

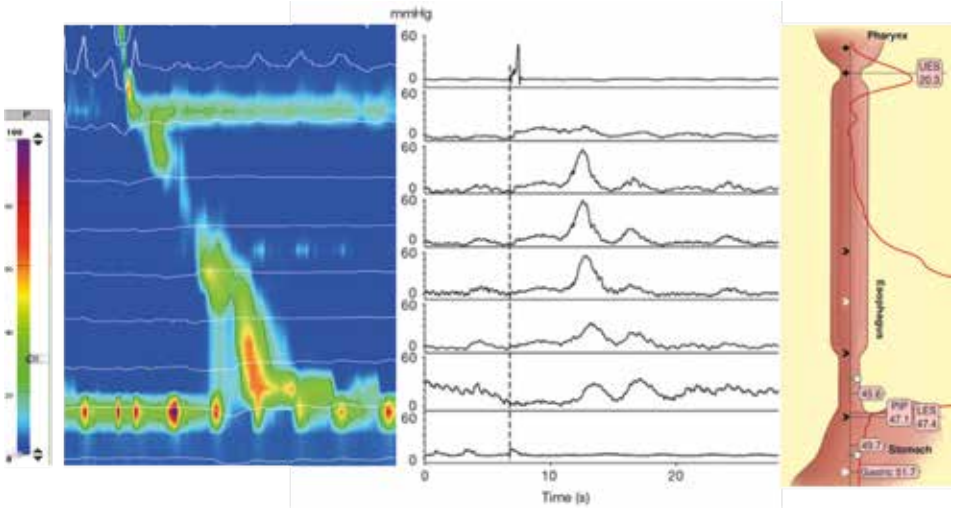

Figure 5. A swallow recorded with high resolution manometry (HRM) versus conventional esophageal manometry (reference anatomy in right panel). The color plot in the left panel is predominantly used for the analysis of HRM recording. Deeper red colors indicates higher pressures, while blue indicates low pressures.

The introduction of HRM allowed for better characterization of esophageal motor function and uniform consensus on diagnosis of esophageal motility disorders for adults using standardized HRM study protocols.[214,216,217] The latter embody 10 liquid, and optional semi-solid and solid, single swallows of 3-5ml each with the patient put in a supine position. The Chicago Classification algorithm (lastly updated 2014) for esophageal motility facilitates diagnostic interpretation of HRM recordings using specific developed EPT metrics derived from an average of recorded swallows.[218-220] In this thesis,

the 2012 version of the Chicago classification system was used, which divides motility disorders of the esophagus into 4 subgroups in order of severity using 5 EPT metrics *(Table 3)*. EPT metrics and interpretation of motility with this classification system are discussed further in Chapter 7. The latest update of the Chicago classification was published recently, in December 2014, and trials with these new criteria have not yet been performed. In this new version, EPT metrics and criteria of motility disorders are simplified.[220]

Chicago classification		
Category 1	Primary motor disorders	Classic achalasia Achalasia with esophageal pressurization Spastic achalasia
Category 2	Potential achalasia phenotype	EGJ outflow obstruction
Category 3	Disorders never observed in healthy (adult) individuals	Absent peristalsis Diffuse esophageal spasm Hypercontractile esophagus
Category 4	Motor patterns outside the normal range (unclear clinical relevance)	Weak peristalsis Frequent failed peristalsis Hypertensive peristalsis Rapid contraction

Table 3. The four categories of the Chicago Classification v2.0 of esophageal motility disorders. Categories 1-3 are never observed in the normal (adult) population, category 4 might be variant of normal and it is not yet clear what the clinical relevance is of motility patterns under category 4.

The use of HRM in infants and children is increasing now that size-adjusted pediatric catheters are available. However, there are a number of limitations when performing manometry in general and HRM specifically in children and thus adult classification of motility cannot simply be copied.[221] Firstly, normative ranges for EPT metrics lack in children, since it is considered unethical to perform these invasive studies in underaged and healthy patients.[125] Moreover, standard HRM protocol might be harder to perform in children because of a lack of cooperation and interpretation might be hampered due to the high amount of incomplete and methodologically imperfect studies (e.g. because of crying and body movement).[222] Catheter diameter, posture and bolus consistency have been shown to have considerable impact on peristaltic patterns.[223,224] Recent research in pediatric patients evaluated with HRM showed EPT metrics are influenced by patient age and size.[221,225,226] This underlines the need for development of specific criteria and classification of motility disorders with HRM in children.

The integration of high resolution manometry and impedance (HRIM) allows the assessment of the relation between esophageal pressures and bolus flow. Recently, its additional diagnostic value in detecting rumination and supragastric belching *(see above, Differential diagnosis & associated functional motility disorders of GERD)* was shown.[78,126,227] Additionally, advanced analysis of HRIM studies enable the assessment of subtle changes in bolus flow and motility not reaching current diagnostic

criteria for a motility disorder in relation to present symptoms.[210,211] Moreover, the HRIM derived Dysphagia Risk Index seems to be able to predict postoperative dysphagia in both adults and children undergoing fundoplication.[212,228]

Pathophysiology of achalasia

Achalasia is a rare, severe motor disorder of the esophagus, characterized by the absence of peristalsis and a defective relaxation of the LES.[229] This results in progressive dysphagia and stasis of food due to impaired bolus flow to the stomach. The pathophysiology of achalasia is not completely understood. Histopathological studies indicate an association with gradual disappearance of myenteric neurons in the distal esophagus, most likely due to a cytotoxic T-cell mediated ganglionitis.[230] Adults studies now indicate an auto-immune mediated origin of this ganglionitis as the most likely mechanism behind the development of achalasia with a possible role of human herpes simpex virus type 1.[231-233] Especially in genetically susceptible individuals, aberrant immune response triggered by a viral infection might induce disease.[234] However, the exact causative stimuli and antigen(s) have not yet been identified.

Epidemiology

The incidence of achalasia in adults is estimated 1 per 100,000 per year with a possible rise in incidence over the past decade.[235,236] For children, very little prevalence data exist. One study from the United Kingdom estimates the incidence of achalasia in children <16 years to be 0.18/100,000 per year.[237] Achalasia is a chronic disease, which can have a great impact on patients. Wellbeing and quality of life might be markedly reduced, even when adequate treatment is applied.[238] Children with achalasia experience a lower quality of life compared to healthy children and children suffering from irritable bowel disease (IBD).[239]

Symptoms and diagnosis

Typical symptoms of achalasia include progressive dysphagia, regurgitation and weight loss. Younger patients might also express symptoms of vomiting, chest pain, cough and respiratory problems.[240-242] Syndromal disorders associated with achalasia are trisomy 21, congenital hypoventilation syndrome, glucocorticoid insufficiency, eosinophilic esophagitis, familial dysautonomia, Chagas' disease, and the triple "A" syndrome (achalasia, alacrima, and ACTH insensitivity).[240,243] Esophageal manometry, preferable high resolution manometry, is the gold standard to diagnose achalasia.[244] Typically, impaired LES relaxation, elevated LES resting pressure and an aperistaltic esophageal body is observed. Recently, it was shown in adults that HRM enables the division of achalasia into three subtypes based on the pattern of esophageal compression *(Figure 6):* Type 1 achalasia (classic achalasia: absence of peristalsis, high LES resting and relaxation pressures and no esophageal compression), type 2 (Pressurization achalasia: high LES resting and relaxation pressures with esophageal compression) and type 3 (Spastic achalasia: high LES resting and relaxation pressures with spastic contraction mimicking motor patterns in the esophageal body).[245] It is yet unknown whether achalasia in children can be divided in similar subtypes.

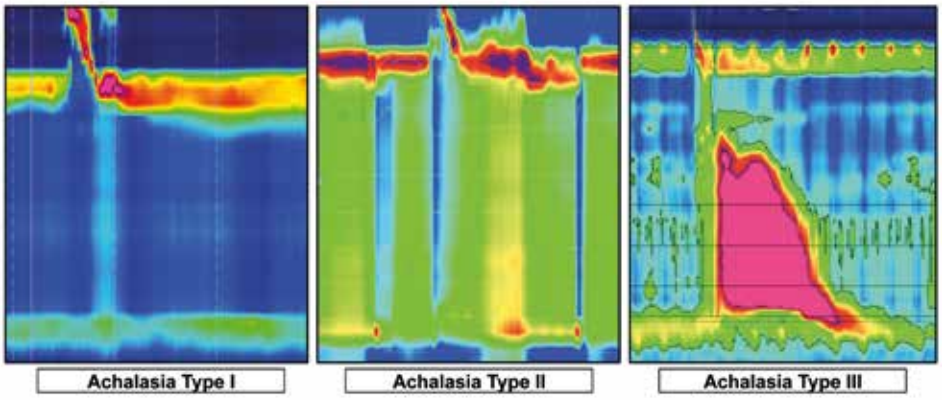

Figure 6. Different types of achalasia as diagnosed with HRM. In adults, treatment success depends upon type of achalasia as diagnosed with HRM.

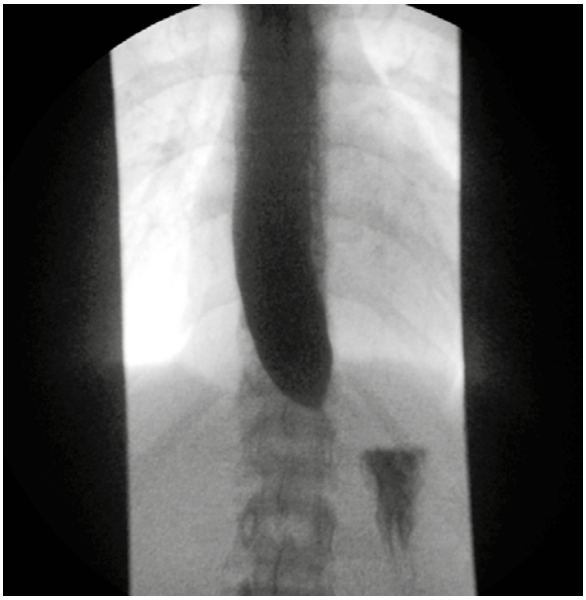

Figure 7. 'Bird-beak' sign in a patient (male, 16 years old) with achalasia. Stasis of barium contrast with marginal flow to the stomach can be observed in patients with achalasia. Image courtesy of Dr. M.P. van Wijk.

Other diagnostic methods can be used to substantiate the diagnosis and to rule out other causes of dysphagia (e.g. eosinophilic esophagitis and pseudo-achalasia). Esophagogastroscopy may reveal a dilated esophagus and increased resistance of the LES. Barium contrast study of the upper gastrointestinal tract might show a dilated esophagus as a typical 'bird-beak' sign at the junction of the LES and stomach *(Figure 7)*. Timed barium swallows with X-rays on 1, 2 and 5 minutes might show stasis

of barium in the esophagus. However, in early stages, these additional tests might be completely normal, even with clear achalasia on manometry.[246,247]

Treatment

The loss of myenteric plexus neurons in achalasia is permanent and current therapy focuses on ensuring bolus passage across the LES. Medical approaches to lower LES pressure, such as botulinum toxin injection in the LES and nifedipine, are only temporally effective and rarely used in children.[248,249] Currently, treatment is primarily focused on mechanical disruption of the LES, either with pneumatic balloon dilation (PD) or laparoscopic Heller's myotomy (HM). In PD, the LES is disrupted by forceful inflation of an air-filled balloon ø 20-40mm). A graded distension protocol with increasing balloon sizes is standard for adult PD. In HM, the EGJ is laparoscopically approached and the LES muscle layers are cleaved. Treatment success in adults is ≈90% for HM and ≈85% for PD.[250] Adult studies report a higher relapse risk for young men [251,252] In addition, it was shown in adults that treatment success depends upon which type of achalasia (1,2 or 3) is diagnosed on HRM.[253] In general, patients with Type 2 achalasia show a better response to treatment than patients with Type 1 or 3. Limited data are available that evaluate PD and HM in children.[254] In a recent prospective study with 24 children, Di Nardo et al. describe a 67% success rate after one PD and 87.5% after more than one PD.[255] Symptom relief after HM ranged from 60 to 95% in long term follow-up.[256-258]

Recently, peroral endoscopic myotomy (POEM) was developed to less invasively cleave the LES muscles.[259] An endoscopist creates a submucosal tunnel to reach the LES and dissect the circular muscle fibers over a variable length. This new technique was found safe and effective up to 6 months after the POEM procedure in adults.[260] In children, 2 case reports involving 4 patients have reported successful procedures and symptom free follow up for up to 12 months.[261,262] However, future prospective evaluation will need to be conducted to ascertain whether POEM is safe and effective in children.

Current treatment of achalasia disrupts the LES mechanically, and therefore might impede the anti-reflux barrier. Symptoms of gastroesophageal reflux disease postoperatively occur regularly in adults as well as in children.[250,254,263] Conducting a (partial) fundoplication simultaneously with the HM is commonly used to prevent symptoms of gastroesophageal reflux,[250,254,263,264] however evidence to support this is lacking.[265-267] Other complications of treatment might involve esophageal perforation and recurrent dysphagia, since treatment is only symptomatic.[250,254,263]

On the whole, data on pediatric achalasia are sparse. It remains largely unknown what the predominant symptoms of pediatric achalasia are, what diagnostic and treatment approach should be used and what the quality of life is of affected children. Furthermore, no data exist regarding their clinical course and quality of life when they grow into adulthood.

Outline of the thesis

In this thesis, a common -gastroesophageal reflux disease (GERD)- and a rare -achalasia- pediatric esophageal motility disorders are studied. **Part I - (Patho)physiology** comprises of studies on underlying mechanisms of GER-related disorders in infants and adults. In **Part II - diagnosis and management**, studies evaluating diagnosis of esophageal motility disorders with accepted and novel technologies are presented, as well as studies on the management of pediatric GERD with proton pump inhibitors and a combined retrospective and prospective study on Dutch pediatric achalasia patients.

PART I – (Patho)physiology

Although it is generally accepted that the predominant underlying mechanism of a GER episode is transient lower esophageal sphincter relaxation (TLESR), not all different triggers of TLESRs are completely understood. The primary postulated stimulus is the activation of stretch receptors in the proximal stomach.[20-22] However, triggers far too small to cause gastric distension, such as a nasogastric tube and small amounts of feed, have been shown to induce TLESRs.[27-30] **Chapter 1** and **2** further elucidate the underlying mechanisms behind this enhanced rate of TLESRs. Number of GER episodes and TLESRs are assessed after LES distension and the consumption of carbonated drinks **(Chapter 1)** and after the infusions of small volumes in left or right sided position **(Chapter 2).**

Not only external stimuli (position, feed) can induce TLESRs and subsequently GER, but it also has been postulated that internal stimuli such as apnea could be caused by or in itself cause GER to occur. Especially in premature infants, pathologic apneas are frequently encountered and thought to be GER related. In **Chapter 3**, literature on the relationship between GER episodes and apneas in premature infants is systematically reviewed.

Several studies have demonstrated a significantly higher occurrence of respiratory complications in proton pump inhibitor (PPI)-treated children and adults compared to those not using PPIs.[88,164,268] The postulated mechanism is (micro)aspiration of non-acid GER components (bile acids, pepsin, bacterial compounds), which might be more deleterious to bronchial cells as compared to acid refluxate.[269,270] In **Chapter 4**, a laboratory study is presented, assessing the mechanisms by which gastric juice from children without or with acute or long-term acid suppression treatment modulates the inflammatory response of bronchial cells.

PART II - Diagnosis and management

The use of invasive and costly diagnostic tools in pediatric GERD is questioned in national and international guidelines.[64,138] Diagnostic accuracy of the most commonly used tests (pH-metry, pH-impedance metry, barium contrast study, scintigraphy and a diagnostic trial with PPIs) is systematically compared to history taking and physical examination in **Chapter 5.**

One of the available diagnostic tools to evaluate GER, 24-hour ambulatory multichannel intraluminal esophageal pH-impedance metry, has been shown to be superior to pH-metry alone as it can detect

not only acid GER but also weakly acid and non-acid GER.[103,271] While this increases the diagnostic yield of GER detection, the interpretation of pH impedance tracings show poor inter- and intraobserver agreement, especially for difficult impedance patterns.[114,272] **Chapter 6** identifies parameters of difficult to analyze pH-impedance patterns and combines these into a statistical model that can identify GER episodes with an international consensus as gold standard.

In **Chapter 7**, a recent technique to assess esophageal motility is evaluated. High resolution manometry has only recently been introduced in pediatric gastroenterology and there are no age-adjusted normative values.[219] We assessed how international experts and non-experts use the (adult) Chicago Classification criteria to judge pediatric HRM tracings and how automated assigned diagnoses as well as subjective diagnoses differ between different raters.

Proton-pump inhibitors (PPIs) inhibit gastric acid secretion by selectively blocking the gastric parietal cell H+K+ ATPase (also called the proton pump). PPI use in infants and children with GERD has increased steadily during the last decade.[56,160-162] The effectiveness and safety of PPIs in children are under debate and in **Chapter 8** we evaluate the evidence for the use of PPIs in infants, children and adolescents with presumed GERD.

The last chapter **(Chapter 9)** presents a study on pediatric achalasia, a rare and severe motor disorder of the esophagus. Achalasia is characterized by the absence of peristalsis and a defective relaxation of the lower esophageal sphincter, resulting in progressive dysphagia.[254,273] Treatment is limited to mechanical disruption of the LES muscle fibers, either by surgery or pneumatic dilation. Data on this motility disorder specific to the pediatric population are sparse. We studied the prevalence and incidence of pediatric achalasia in The Netherlands (1990-2013). In addition, we present main symptoms, diagnostic methods, treatment, clinical course, current symptom burden and quality of life of all registered Dutch patients diagnosed with achalasia at a pediatric age.

REFERENCES

1. Dodds WJ. Physiology of swallowing. Dysphagia. 1989;3(4):171-8
2. Dodds WJ, Stewart ET, Logemann JA. Physiology and radiology of the normal oral and pharyngeal phases of swallowing. Am J Roentgenol. 1990;154(5):953-63
3. Gupta A, Gulati P, Kim W, et al. Effect of postnatal maturation on the mechanisms of esophageal propulsion in preterm human neonates: primary and secondary peristalsis. Am J Gastroenterol. 2009;104(2):411-9
4. Jadcherla SR, Hoffmann RG, Shaker R. Effect of maturation of the magnitude of mechanosensitive and chemosensitive reflexes in the premature human esophagus. J Pediatr. 2006;149(1):77-82
5. Jadcherla SR, Duong HQ, Hoffmann RG, Shaker R. Esophageal body and upper esophageal sphincter motor responses to esophageal provocation during maturation in preterm newborns. J Pediatr. 2003;143(1):31-8
6. Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;336(13):924-32.
7. Soybel DI. Anatomy and physiology of the stomach. Surg Clin North Am. 2005;85(5):875-94
8. Ramsay PT, Carr A. Gastric acid and digestive physiology. Surg Clin North Am. 2011;91(5):977-82
9. Mittal RK, Holloway RH, Penagini R, et al. Transient lower esophageal sphincter relaxation. Gastroenterology. 1995;109(2):601-10.
10. Omari TI, Barnett C, Snel A, et al. Mechanisms of gastro-esophageal reflux in healthy premature infants. J Pediatr. 1998;133(5):650-4
11. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest. 1980;65(2):256-67
12. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut. 1988;29(8):1020-8
13. Omari TI, Barnett CP, Benninga MA, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut. 2002;51(4):475-9
14. Omari TI, Benninga MA, Barnett CP, et al. Characterization of esophageal body and lower esophageal sphincter motor function in the very premature neonate. J Pediatr. 1999;135(4):517-21
15. Omari TI, Miki K, Davidson G, et al. Characterisation of relaxation of the lower oesophageal sphincter in healthy premature infants. Gut. 1997;40(3):370-5
16. Holloway RH, Penagini R, Ireland AC. Criteria for objective definition of transient lower esophageal sphincter relaxation. Am J Physiol. 1995;268(1 Pt 1):G128-33
17. Holloway RH, Hongo M, Berger K, McCallum RW. Gastric distention: a mechanism for postprandial gastroesophageal reflux. Gastroenterology. 1985;89(4):779-84
18. Holloway RH, Kocyan P, Dent J. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux. Dig Dis Sci. 1991;36(8):1034-9
19. Scheffer RCH, Akkermans LMA, Bais JE, et al. Elicitation of transient lower oesophageal sphincter relaxations in response to gastric distension and meal ingestion. Neurogastroenterol Motil. 2002;14(6):647-55
20. Hirsch DP, Tytgat GNJ, Boeckxstaens GEE. Is glutamate involved in transient lower esophageal sphincter relaxations? Dig Dis Sci. 2002;47(3):661-6
21. Zhang Q, Horowitz M, Rigda R, et al. Effect of hyperglycemia on triggering of transient lower esophageal sphincter relaxations. Am J Physiol Gastrointest Liver Physiol. 2004;286(5):G797-803
22. Straathof JW, Ringers J, Lamers CB, Masclee AA. Provocation of transient lower esophageal sphincter relaxations by gastric distension with air. Am J Gastroenterol. 2001;96(8):2317-23
23. Zerbib F, Bruley Des Varannes S, Scarpignato C, et al. Endogenous cholecystokinin in postprandial lower esophageal sphincter function and fundic tone in humans. Am J Physiol. 1998;275(6 Pt 1):G1266-73
24. Boeckxstaens GE, Hirsch DP, Fakhry N, et al. Involvement of cholecystokininA receptors in transient lower esophageal sphincter relaxations triggered by gastric distension. Am J Gastroenterol. 1998;93(10):1823-8
25. Lacy BE, Carter J, Weiss JE, Crowell MD. The effects of intraduodenal nutrient infusion on serum CCK, LES pressure, and gastroesophageal reflux. Neurogastroenterol Motil. 2011;23(7):631-e256
26. Goyal RK, Padmanabhan R, Sang Q. Neural circuits in swallowing and abdominal vagal afferent-mediated lower esophageal sphincter relaxation. Am J Med. 2001;111 Suppl :95S-105S
27. Peter CS, Wiechers C, Bohnhorst B, et al. Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: a multiple intraluminal impedance study. J Pediatr. 2002;141(2):277-9
28. Manning BJ, Winter DC, McGreal G, et al. Nasogastric intubation causes gastroesophageal reflux in patients undergoing elective laparotomy. Surgery. 2001;130(5):788-91
29. Noviski N, Yehuda YB, Serour F, et al. Does the size of nasogastric tubes affect gastroesophageal reflux in children? J Pediatr Gastroenterol Nutr. 1999;29(4):448-51
30. Van Wijk MP, Blackshaw LA, Dent J, et al. Distension of the esophagogastric junction augments triggering of transient lower esophageal sphincter relaxation. AJP Gastrointest Liver Physiol. 2011;301(4):G713-G718
31. Kahrilas PJ, Shi G, Manka M, Joehl RJ. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology. 2000;118(4):688-95
32. Holloway RH, Dent J. Pathophysiology of gastroesophageal reflux. Lower esophageal sphincter dysfunction in gastroesophageal reflux disease. Gastroenterol Clin North Am. 1990;19(3):517-35
33. Kramer SS, Eicher PM. The evaluation of pediatric feeding abnormalities. Dysphagia. 1993;8(3):215-24
34. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol. 2001;96(9):2569-74
35. Sifrim D, Holloway R, Silny J, et al. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96(3):647-55

36. Boeckxstaens GE, Rohof WO. Pathophysiology of gastro-esophageal reflux disease. Gastroenterol Clin North Am. 2014;43(1):15-25
37. Clarke AT, Wirz AA, Manning JJ, et al. Severe reflux disease is associated with an enlarged unbuffered proximal gastric acid pocket. Gut. 2008;57(3):292-7
38. Beaumont H, Bennink RJ, de Jong J, Boeckxstaens GE. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut. 2010;59(4):441-51
39. Knatten CK, Avitsland TL, Medhus AW, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. J Pediatr Surg. 2013;48(9):1856-61
40. Sager S, Halac M, Selcuk N, et al. Temporal relationship between gastroesophageal reflux and rate of gastric emptying in children. Nucl Med Commun. 2010;31(12):1059-62
41. Cresi F, de Sanctis L, Savino F, et al. Relationship between gastro-oesophageal reflux and gastric activity in newborns assessed by combined intraluminal impedance, pH metry and epigastric impedance. Neurogastroenterol Motil. 2006;18(5):361-8
42. Argon M, Duygun U, Daglioz G, et al. Relationship between gastric emptying and gastroesophageal reflux in infants and children. Clin Nucl Med. 2006;31(5):262-5
43. Di Ciaula A, Portincasa P, Di Terlizzi L, et al. Ultrasonographic study of postcibal gastro-esophageal reflux and gastric emptying in infants with recurrent respiratory disease. World J Gastroenterol. 2005;11(46):7296-301
44. Aktas A, ÇCiftçi I, Caner B. The relation between the degree of gastro-oesophageal reflux and the rate of gastric emptying. Nucl Med Commun. 1999;20(10):907-10
45. Ewer AK, Durbin GM, Morgan ME, Booth IW. Gastric emptying and gastro-oesophageal reflux in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1996;75(2):F117-21
46. Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastro-oesophageal reflux according to the type of milk. Eur J Clin Nutr. 1990;44(8):577-83
47. Omari TI, Rommel N, Staunton E, et al. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr. 2004;145(2):194-200
48. Van Wijk MP, Benninga M a, Dent J, et al. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr. 2007;151(6):585-90, 590.e1-2
49. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med. 2000;154(2):150-4
50. Osatakul S, Sriplung H, Puetpaiboon A, et al. Prevalence and natural course of gastroesophageal reflux symptoms: a 1-year cohort study in Thai infants. J Pediatr Gastroenterol Nutr. 2002;34(1):63-7
51. Nelson SP, Chen EH, Syniar GM, Christoffel KK. One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group. Pediatrics. 1998;102(6):E67
52. Orenstein SR, Shalaby TM, Kelsey SF, Frankel E. Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy. Am J Gastroenterol. 2006;101(3):628-40
53. van Tilburg MAL, Hyman PE, Walker L, et al. Prevalence of Functional Gastrointestinal Disorders in Infants and Toddlers. J Pediatr. 2014
54. Marlais M, Fishman JR, Köglmeier J, et al. Reduced quality of life in children with gastro-oesophageal reflux disease. Acta Paediatr. 2010;99(3):418-21
55. Karacetin G, Demir T, Erkan T, et al. Maternal psychopathology and psychomotor development of children with GERD. J Pediatr Gastroenterol Nutr. 2011;53(4):380-5
56. Barron JJ, Tan H, Spalding J, et al. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr. 2007;45(4):421-7
57. European Commission (2014). Eurostat. at epp.eurostat.ec.europa.eu, accessed 27-06-2014
58. Gupta SK, Hassall E, Chiu YL, et al. Presenting symptoms of nonerosive and erosive esophagitis in pediatric patients. Dig Dis Sci. 2006;51(5):858-63
59. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain. 2007;127(1-2):140-50
60. Gunasekaran TS, Dahlberg M, Ramesh P, Namachivayam G. Prevalence and associated features of gastroesophageal reflux symptoms in a Caucasian-predominant adolescent school population. Dig Dis Sci. 2008;53(9):2373-9
61. Orenstein SR, Shalaby TM, Cohn JF. Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire. Clin Pediatr (Phila). 1996;35(12):607-14
62. Salvatore S, Hauser B, Vandemaele K, et al. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr. 2005;40(2):210-5
63. Vandenplas Y, Salvatore S, Hauser B. The diagnosis and management of gastro-oesophageal reflux in infants. Early Hum Dev. 2005;81(12):1011-24
64. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498-547
65. Stavroulaki P. Diagnostic and management problems of laryngopharyngeal reflux disease in children. Int J Pediatr Otorhinolaryngol. 2006;70(4):579-90
66. Decalmer S, Stovold R, Houghton LA, et al. Chronic cough: relationship between microaspiration, gastroesophageal reflux, and cough frequency. Chest. 2012;142(4):958-64
67. Soyer T, Soyer OU, Birben E, et al. Pepsin levels and oxidative stress markers in exhaled breath condensate of patients with gastroesophageal reflux disease. J Pediatr Surg. 2013;48(11):2247-50
68. Frankel EA, Shalaby TM, Orenstein SR. Sandifer syndrome posturing: relation to abdominal wall contractions, gastroesophageal reflux, and fundoplication. Dig Dis Sci. 2006;51(4):635-40

69. Dahshan A, Patel H, Delaney J, et al. Gastroesophageal reflux disease and dental erosion in children. J Pediatr. 2002;140(4):474-8
70. Aine L, Baer M, Mäki M. Dental erosions caused by gastroesophageal reflux disease in children. ASDC J Dent Child. 60(3):210-4
71. Greifer M, Ng K, Levine J. Impedance and extraesophageal manifestations of reflux in pediatrics. Laryngoscope. 2012;122(6):1397-400
72. Machado R, Woodley FW, Skaggs B, et al. Gastroesophageal reflux causing sleep interruptions in infants. J Pediatr Gastroenterol Nutr. 2013;56(4):431-5
73. Tieder JS, Cowan CA, Garrison MM, Christakis DA. Variation in inpatient resource utilization and management of apparent life-threatening events. J Pediatr. 2008;152(5):629-35, 635.e1-2
74. Doshi A, Bernard-Stover L, Kuelbs C, et al. Apparent life-threatening event admissions and gastroesophageal reflux disease: the value of hospitalization. Pediatr Emerg Care. 2012;28(1):17-21
75. Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? Pediatrics. 2002;110(5):972-84
76. Soon IS, Butzner JD, Kaplan GG, deBruyn JCC. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2013;57(1):72-80
77. Hill CA, Ramakrishna J, Fracchia MS, et al. Prevalence of eosinophilic esophagitis in children with refractory aerodigestive symptoms. JAMA Otolaryngol Head Neck Surg. 2013;139(9):903-6
78. Rommel N, Tack J, Arts J, et al. Rumination or belching-regurgitation? Differential diagnosis using oesophageal impedance-manometry. Neurogastroenterol Motil. 2010;22(4):e97-104
79. Tack J, Blondeau K, Boecxstaens V, Rommel N. Review article: the pathophysiology, differential diagnosis and management of rumination syndrome. Aliment Pharmacol Ther. 2011;33(7):782-8
80. Bredenoord AJ. Management of belching, hiccups, and aerophagia. Clin Gastroenterol Hepatol. 2013;11(1):6-12
81. Kessing BF, Bredenoord AJ, Velosa M, Smout AJPM. Supragastric belches are the main determinants of troublesome belching symptoms in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2012;35(9):1073-9
82. Morabito G, Romeo C, Romano C. Functional aerophagia in children: a frequent, atypical disorder. Case Rep Gastroenterol. 2014;8(1):123-8
83. Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104(5):1278-95; quiz 1296
84. Van Wijk M, Knüppe F, Omari T, et al. Evaluation of gastroesophageal function and mechanisms underlying gastroesophageal reflux in infants and adults born with esophageal atresia. J Pediatr Surg. 2013;48(12):2496-505
85. Sistonen SJ, Pakarinen MP, Rintala RJ. Long-term results of esophageal atresia: Helsinki experience and review of literature. Pediatr Surg Int. 2011;27(11):1141-9
86. Mousa HM, Woodley FW. Gastroesophageal reflux in cystic fibrosis: current understandings of mechanisms and management. Curr Gastroenterol Rep. 2012;14(3):226-35
87. Thakkar K, Boatright RO, Gilger MA, El-Serag HB. Gastroesophageal reflux and asthma in children: a systematic review. Pediatrics. 2010;125(4):e925-30
88. Holbrook JT, Wise RA, Gold BD, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307(4):373-81
89. Böhmer CJ, Niezen-de Boer MC, Klinkenberg-Knol EC, et al. Gastro-oesophageal reflux disease in institutionalised intellectually disabled individuals. Neth J Med. 1997;51(4):134-9
90. Staiano A, Cucchiara S, Del Giudice E, et al. Disorders of oesophageal motility in children with psychomotor retardation and gastro-oesophageal reflux. Eur J Pediatr. 1991;150(9):638-41
91. Koebnick C, Getahun D, Smith N, et al. Extreme childhood obesity is associated with increased risk for gastroesophageal reflux disease in a large population-based study. Int J Pediatr Obes. 2011;6(2-2):e257-63
92. Elitsur Y, Dementieva Y, Elitsur R, Rewalt M. Obesity is not a risk factor in children with reflux esophagitis: a retrospective analysis of 738 children. Metab Syndr Relat Disord. 2009;7(3):211-4
93. Quitadamo P, Papadopoulou A, Wenzl T, et al. European Pediatricians' Approach to Children With GER Symptoms: Survey of the Implementation of 2009 NASPGHAN-ESPGHAN Guidelines. J Pediatr Gastroenterol Nutr. 2014;58(4):505-9
94. Hassall E. Uses and abuses of acid-suppression therapy in children. J Pediatr Gastroenterol Nutr. 2011;53 Suppl 2:S8-9
95. Hassall E. Over-prescription of acid-suppressing medications in infants: how it came about, why it's wrong, and what to do about it. J Pediatr. 2012;160(2):193-8
96. Kleinman L, Rothman M, Strauss R, et al. The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument. Clin Gastroenterol Hepatol. 2006;4(5):588-96
97. Orenstein SR. Symptoms and reflux in infants: Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) -utility for symptom tracking and diagnosis. Curr Gastroenterol Rep. 2010;12(6):431-6
98. Bolier EA, Kessing BF, Smout AJ, Bredenoord AJ. Systematic review: questionnaires for assessment of gastroesophageal reflux disease. Dis Esophagus. 2015 Feb-Mar;28(2):105-20
99. Euler AR, Ament ME. Detection of gastroesophageal reflux in the pediatric-age patient by esophageal intraluminal pH probe measurement (Tuttle test). Pediatrics. 1977;60(1):65-8
100. Swidnicka-Siergiejko A, Dabrowski A. Prolonged 2-day esophageal pH-metry with impedance monitoring improves symptom-reflux association analysis. Dig Dis Sci. 2013;58(9):2556-63
101. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal Reflux, as Measured By 24-Hour pH Monitoring, in 509 Healthy Infants Screened for Risk of Sudden Infant Death Syndrome. Pediatrics. 1991;88(4):834-840
102. Da Dalt L, Mazzoleni S, Montini G, et al. Diagnostic accuracy of pH monitoring in gastro-oesophageal reflux. Arch Dis Child. 1989;64(10):1421-6

103. Skopnik H, Silny J, Heiber O, et al. Gastroesophageal reflux in infants: evaluation of a new intraluminal impedance technique. J Pediatr Gastroenterol Nutr. 1996;23(5):591-8
104. Mitchell DJ, McClure BG, Tubman TR. Simultaneous monitoring of gastric and oesophageal pH reveals limitations of conventional oesophageal pH monitoring in milk fed infants. Arch Dis Child. 2001;84(3):273-6
105. Smout A. Non-acid reflux as a cause of symptoms. J Pediatr Gastroenterol Nutr. 2011;53 Suppl 2:S3-4
106. Rosen R, Hart K, Nurko S. Does reflux monitoring with multichannel intraluminal impedance change clinical decision making? J Pediatr Gastroenterol Nutr. 2011;52(4):404-7
107. Rosen R, Johnston N, Hart K, et al. Higher rate of bronchoalveolar lavage culture positivity in children with nonacid reflux and respiratory disorders. J Pediatr. 2011;159(3):504-6
108. Van Wijk MP, Benninga MA, Omari TI. Role of the multichannel intraluminal impedance technique in infants and children. J Pediatr Gastroenterol Nutr. 2009;48(1):2-12
109. Orenstein SR. Crying in infant GERD: acid or volume? Heartburn or dyspepsia? Curr Gastroenterol Rep. 2008;10(5):433-6
110. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol. 2004;99(12):2452-8
111. Orlando LA, Orlando RC. Dilated intercellular spaces as a marker of GERD. Curr Gastroenterol Rep. 2009;11(3):190-4
112. Van der Pol RJ, Loots CM, Peeters L, et al. Outcomes of endoscopy and novel pH-impedance parameters in children: is there a correlation? J Pediatr Gastroenterol Nutr. 2013;56(2):196-200
113. Sifrim D, Holloway R, Silny J, et al. Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology. 2001;120(7):1588-98
114. Loots CM, van Wijk MP, Blondeau K, et al. Interobserver and intraobserver variability in pH-impedance analysis between 10 experts and automated analysis. J Pediatr. 2012;160(3):441-446.e1
115. Peter CS, Sprodowski N, Ahlborn V, et al. Inter- and intraobserver agreement for gastroesophageal reflux detection in infants using multiple intraluminal impedance. Biol Neonate. 2004;85(1):11-4
116. Zerbib F, Roman S, Bruley Des Varannes S, et al. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol. 2013;11(4):366-72
117. Barriga-Rivera A, Elena M, Moya MJ, Lopez-Alonso M. The binomial symptom index: toward an optimal method for the evaluation of symptom association in gastroesophageal reflux. Neurogastroenterol Motil. 2013;25(8):664-9
118. Bredenoord AJ, Smout AJPM. Association between reflux and symptoms during ambulatory reflux monitoring: pros and cons of existing methods. Neurogastroenterol Motil. 2013;25(8):633-7
119. Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol. 1988;83(4):358-61
120. Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol. 1991;86(2):160-4
121. Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology. 1994;107(6):1741-5
122. Omari TI, Schwarzer A, vanWijk MP, et al. Optimisation of the reflux-symptom association statistics for use in infants being investigated by 24-hour pH impedance. J Pediatr Gastroenterol Nutr. 2011;52(4):408-13
123. Barriga-Rivera A, Elena M, Moya MJ, Lopez-Alonso M. Monte Carlo method for the evaluation of symptom association. Dis Esophagus. 2014;27:518-23
124. Wenzl TG, Benninga MA, Loots CM, et al. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. J Pediatr Gastroenterol Nutr. 2012;55(2):230-4
125. Roth-Cline M, Gerson J, Bright P, et al. Ethical considerations in conducting pediatric research. Handb Exp Pharmacol. 2011;205:219-44
126. Kessing BF, Govaert F, Masclee AAM, Conchillo JM. Impedance measurements and high-resolution manometry help to better define rumination episodes. Scand J Gastroenterol. 2011;46(11):1310-5
127. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900-20; quiz 1943
128. El-Serag HB, Bailey NR, Gilger M, Rabeneck L. Endoscopic manifestations of gastroesophageal reflux disease in patients between 18 months and 25 years without neurological deficits. Am J Gastroenterol. 2002;97(7):1635-9
129. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172-80
130. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology. 1988;95(4):903-12
131. Dahms BB. Reflux esophagitis: sequelae and differential diagnosis in infants and children including eosinophilic esophagitis. Pediatr Dev Pathol. 7(1):5-16
132. Volonaki E, Sebire NJ, Borrelli O, et al. Gastrointestinal endoscopy and mucosal biopsy in the first year of life: indications and outcome. J Pediatr Gastroenterol Nutr. 2012;55(1):62-5
133. Simanovsky N, Buonomo C, Nurko S. The infant with chronic vomiting: the value of the upper GI series. Pediatr Radiol. 2002;32(8):549-50; discussion 551
134. Tuncel M, Kıratlı PO, Aksoy T, Bozkurt MF. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. World J Pediatr. 2011;7(3):245-9
135. Meyers WF, Roberts CC, Johnson DG, Herbst JJ. Value of tests for evaluation of gastroesophageal reflux in children. J Pediatr Surg. 1985;20(5):515-20

136. Thompson JK, Koehler RE, Richter JE. Detection of gastroesophageal reflux: value of barium studies compared with 24-hr pH monitoring. Am J Roentgenol. 1994;162(3):621-6
137. Sigterman KE, van Pinxteren B, Bonis PA, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane database Syst Rev. 2013;5:CD002095
138. Benninga MA, Berger M, Venmans LMAJ, et al. Richtlijn "Gastro-oesofageale reflux(ziekte) bij kinderen van 0-18 jaar." Ned Tijdschr Geneeskd. 2014;158(A7190):0-4
139. Chafen JJS, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010;303(18):1848-56
140. Kelly KA. Gastric emptying of liquids and solids: roles of proximal and distal stomach. Am J Physiol. 1980;239(2):G71-6
141. Zangen S, Di Lorenzo C, Zangen T, et al. Rapid maturation of gastric relaxation in newborn infants. Pediatr Res. 2001;50(5):629-32
142. Jadcherla SR, Chan CY, Moore R, et al. Impact of feeding strategies on the frequency and clearance of acid and nonacid gastroesophageal reflux events in dysphagic neonates. J Parenter Enteral Nutr. 2012;36(4):449-55
143. Birch JL, Newell SJ. Gastrooesophageal reflux disease in preterm infants: current management and diagnostic dilemmas. Arch Dis Child Fetal Neonatal Ed. 2009;94(5):F379-83
144. Wenzl TG, Schneider S, Scheele F, et al. Effects of Thickened Feeding on Gastroesophageal Reflux in Infants: A Placebo-Controlled Crossover Study Using Intraluminal Impedance. Pediatrics. 2003;111(4):e355-e359
145. Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. Pediatrics. 2008;122(6):e1268-77
146. Corvaglia L, Spizzichino M, Aceti A, et al. A thickened formula does not reduce apneas related to gastroesophageal reflux in preterm infants. Neonatology. 2013;103(2):98-102
147. Lasekan JB, Linke HK, Oliver JS, et al. Milk protein-based infant formula containing rice starch and low lactose reduces common regurgitation in healthy term infants: a randomized, blinded, and prospective trial. J Am Coll Nutr. 2014;33(2):136-46
148. Meunier L, Garthoff JA, Schaafsma A, et al. Locust bean gum safety in neonates and young infants An integrated review of the toxicological database and clinical evidence. Regul Toxicol Pharmacol. 2014;70(1):155-69
149. Meyers WF, Herbst JJ. Effectiveness of positioning therapy for gastroesophageal reflux. Pediatrics. 1982;69(6):768-72
150. Orenstein SR, Whitington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. N Engl J Med. 1983;309(13):760-3
151. Oyen N, Markestad T, Skaerven R, et al. Combined effects of sleeping position and prenatal risk factors in sudden infant death syndrome: the Nordic Epidemiological SIDS Study. Pediatrics. 1997;100(4):613-21
152. Omari T. Gastroesophageal reflux in infants: can a simple left side positioning strategy help this diagnostic and therapeutic conundrum? Minerva Pediatr. 2008;60(2):193-200
153. Loots C, Kritas S, van Wijk M, et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. J Pediatr Gastroenterol Nutr. 2014;59(2):237-43
154. Alaswad B, Toubas PL, Grunow JE. Environmental tobacco smoke exposure and gastroesophageal reflux in infants with apparent life-threatening events. J Okla State Med Assoc. 1996;89(7):233-7
155. Gaffney KF. Infant exposure to environmental tobacco smoke. J Nurs Scholarsh. 2001;33(4):343-7
156. Shabib SM, Cutz E, Sherman PM. Passive smoking is a risk factor for esophagitis in children. J Pediatr. 1995;127(3):435-7
157. Orenstein SR, McGowan JD. Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux. J Pediatr. 2008;152(3):310-4
158. Shalaby TM, Orenstein SR. Efficacy of telephone teaching of conservative therapy for infants with symptomatic gastroesophageal reflux referred by pediatricians to pediatric gastroenterologists. J Pediatr. 2003;142(1):57-61
159. Van der Pol R, Smite M, Benninga MA, van Wijk MP. Non-pharmacological therapies for GERD in infants and children. J Pediatr Gastroenterol Nutr. 2011;53 Suppl 2:S6-8
160. Chen I-L, Gao W-Y, Johnson AP, et al. Proton pump inhibitor use in infants: FDA reviewer experience. J Pediatr Gastroenterol Nutr. 2012;54(1):8-14
161. De Bruyne P, Christiaens T, Vander Stichele R, Van Winckel M. Changes in prescription patterns of Acid-suppressant medications by belgian pediatricians: analysis of the national database, [1997-2009]. J Pediatr Gastroenterol Nutr. 2014;58(2):222-7
162. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. Pharmacoepidemiol Drug Saf. 2010;19(10):1019-24
163. Ray KN, Lorch SA. Hospitalization of rural and urban infants during the first year of life. Pediatrics. 2012;130(6):1084-93
164. Laheij RJF, Sturkenboom MCJM, Hassing R-J, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292(16):1955-60
165. Trikha A, Baillargeon JG, Kuo Y, et al. Development of food allergies in patients with gastroesophageal reflux disease treated with gastric acid suppressive medications. Pediatr Allergy Immunol. 2013;24(6):582-8
166. Hampson FC, Farndale A, Strugala V, et al. Alginate rafts and their characterisation. Int J Pharm. 2005;294(1-2):137-47
167. Dettmar PW, Sykes J, Little SL, Bryan J. Rapid onset of effect of sodium alginate on gastro-oesophageal reflux compared with ranitidine and omeprazole, and relationship between symptoms and reflux episodes. Int J Clin Pract. 2006;60(3):275-83

168. Strugala V, Dettmar PW, Sarratt K, et al. A Randomized, controlled, crossover trial to investigate times to onset of the perception of soothing and cooling by over-the-counter heartburn treatments. J Int Med Res. 38(2):449-57
169. Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000;14(6):669-90
170. Tytgat GN, Simoneau G. Clinical and laboratory studies of the antacid and raft-forming properties of Rennie alginate suspension. Aliment Pharmacol Ther. 2006;23(6):759-65
171. Sweis R, Kaufman E, Anggiansah A, et al. Post-prandial reflux suppression by a raft-forming alginate (Gaviscon Advance) compared to a simple antacid documented by magnetic resonance imaging and pH-impedance monitoring: mechanistic assessment in healthy volunteers and randomised, controlled, doub. Aliment Pharmacol Ther. 2013;37(11):1093-102
172. Rohof WO, Bennink RJ, Smout AJPM, et al. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2013;11(12):1585-91; quiz e90
173. Kwiatek MA, Roman S, Fareeduddin A, et al. An alginate-antacid formulation (Gaviscon Double Action Liquid) can eliminate or displace the postprandial "acid pocket" in symptomatic GERD patients. Aliment Pharmacol Ther. 2011;34(1):59-66
174. Tighe MP, Afzal NA, Bevan A, Beattie RM. Current pharmacological management of gastro-esophageal reflux in children: an evidence-based systematic review. Paediatr Drugs. 2009;11(3):185-202
175. Carroccio A, Iacono G, Montalto G, et al. Domperidone plus magnesium hydroxide and aluminum hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus placebo. Scand J Gastroenterol. 1994;29(4):300-4
176. Cucchiara S, Staiano A, Romaniello G, et al. Antacids and cimetidine treatment for gastro-oesophageal reflux and peptic oesophagitis. Arch Dis Child. 1984;59(9):842-7
177. Del Buono R, Wenzl TG, Ball G, et al. Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. Arch Dis Child. 2005;90(5):460-3
178. Forbes D, Hodgson M, Hill R. The effects of gaviscon and metoclopramide in gastroesophageal reflux in children. J Pediatr Gastroenterol Nutr. 5(4):556-9
179. Miller S. Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. Curr Med Res Opin. 1999;15(3):160-8
180. Buts JP, Barudi C, Otte JB. Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. Eur J Pediatr. 1987;146(2):156-8
181. Omari TI, Rommel N, Staunton E, et al. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr. 2004;145(2):194-200
182. Patole S, Rao S, Doherty D. Erythromycin as a prokinetic agent in preterm neonates: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2005;90(4):F301-6
183. Craig WR, Hanlon-Dearman A, Sinclair C, et al. Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years. Cochrane Database Syst Rev. 2004;(4):CD003502
184. Maclennan S, Augood C, Cash-Gibson L, et al. Cisapride treatment for gastro-oesophageal reflux in children. Cochrane database Syst Rev. 2010;(4):CD002300
185. Vieira MC, Miyague NI, Van Steen K, et al. Effects of domperidone on QTc interval in infants. Acta Paediatr. 2012;101(5):494-6
186. Gomez R, Fernandez S, Aspirot A, et al. Effect of amoxicillin/clavulanate on gastrointestinal motility in children. J Pediatr Gastroenterol Nutr. 2012;54(6):780-4
187. Welage LS. Overview of pharmacologic agents for acid suppression in critically ill patients. Am J Health Syst Pharm. 2005;62(10 Suppl 2):S4-S10
188. Kothari S, Nelson SP, Wu EQ, et al. Healthcare costs of GERD and acid-related conditions in pediatric patients, with comparison between histamine-2 receptor antagonists and proton pump inhibitors. Curr Med Res Opin. 2009;25(11):2703-9
189. Van der Pol R, Langendam M, Benninga M, et al. Efficacy and Safety of Histamine-2 Receptor Antagonists. JAMA. 2014;168(10):947-54
190. McDermott CM, Abrahams TP, Partosoedarso E, et al. Site of action of GABA(B) receptor for vagal motor control of the lower esophageal sphincter in ferrets and rats. Gastroenterology. 2001;120(7):1749-62
191. Lidums I, Lehmann A, Checklin H, et al. Control of transient lower esophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in normal subjects. Gastroenterology. 2000;118(1):7-13
192. Van Herwaarden MA, Samsom M, Rydholm H, Smout AJPM. The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. Aliment Pharmacol Ther. 2002;16(9):1655-62
193. Zhang Q, Lehmann A, Rigda R, et al. of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. Gut. 2002;50(1):19-24
194. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA B agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. Gut. 2003;52(4):464-70
195. Kawai M, Kawahara H, Hirayama S, et al. Effect of baclofen on emesis and 24-hour esophageal pH in neurologically impaired children with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2004;38(3):317-23
196. Omari TI, Benninga MA, Sansom L, et al. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. J Pediatr. 2006;149(4):468-74
197. Vadlamudi NB, Hitch MC, Dimmitt RA, Thame KA. Baclofen for the treatment of pediatric GERD. J Pediatr Gastroenterol Nutr. 2013;57(6):808-12

198. Blondeau K. Treatment of gastro-esophageal reflux disease: the new kids to block. Neurogastroenterol Motil. 2010;22(8):836-40
199. Vakil NB, Huff FJ, Cundy KC. Randomised clinical trial: arbaclofen placarbil in gastro-oesophageal reflux disease--insights into study design for transient lower sphincter relaxation inhibitors. Aliment Pharmacol Ther. 2013;38(2):107-17
200. Boeckxstaens GE, Beaumont H, Hatlebakk JG, et al. A novel reflux inhibitor lesogaberan (AZD3355) as add-on treatment in patients with GORD with persistent reflux symptoms despite proton pump inhibitor therapy: a randomised placebo-controlled trial. Gut. 2011;60(9):1182-8
201. Boeckxstaens GE, Denison H, Jensen JM, et al. Translational gastrointestinal pharmacology in the 21st century: "the lesogaberan story". Curr Opin Pharmacol. 2011;11(6):630-3
202. Stylopoulos N, Rattner DW. The history of hiatal hernia surgery: from Bowditch to laparoscopy. Ann Surg. 2005;241(1):185-93
203. Mauritz FA, van Herwaarden-Lindeboom MYA, Stomp W, et al. The effects and efficacy of antireflux surgery in children with gastroesophageal reflux disease: a systematic review. J Gastrointest Surg. 2011;15(10):1872-8
204. Rhee D, Zhang Y, Chang DC, et al. Population-based comparison of open vs laparoscopic esophagogastric fundoplication in children: application of the Agency for Healthcare Research and Quality pediatric quality indicators. J Pediatr Surg. 2011;46(4):648-54
205. Billingham MJ, Basterfield SJ. Pediatric surgical technique: laparoscopic or open approach? A systematic review and meta-analysis. Eur J Pediatr Surg. 2010;20(2):73-7
206. Schneider A, Gottrand F, Sfeir R, et al. Postoperative lower esophageal dilation in children following the performance of Nissen fundoplication. Eur J Pediatr Surg. 2012;22(5):399-403
207. Broeders JAJL, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg. 2010;97(9):1318-30
208. Weber TR. Toupét fundoplication for gastroesophageal reflux in childhood. Arch Surg. 1999;134(7):717-20; discussion 720-1
209. Capito C, Leclair M-D, Piloquet H, et al. Long-term outcome of laparoscopic Nissen-Rossetti fundoplication for neurologically impaired and normal children. Surg Endosc. 2008;22(4):875-80
210. Nguyen NQ, Holloway RH, Smout AJ, Omari TI. Automated impedance-manometry analysis detects esophageal motor dysfunction in patients who have non-obstructive dysphagia with normal manometry. Neurogastroenterol Motil. 2013;25(3):238-45, e164
211. Omari TI, Dejaeger E, van Beckevoort D, et al. A method to objectively assess swallow function in adults with suspected aspiration. Gastroenterology. 2011;140(5):1454-63
212. Loots C, van Herwaarden MY, Benninga MA, et al. Gastroesophageal reflux, esophageal function, gastric emptying, and the relationship to dysphagia before and after antireflux surgery in children. J Pediatr. 2013;162(3):566-573.e2
213. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut. 2001;49(1):145-51
214. Pandolfino JE, Fox MR, Bredenoord AJ, Kahrilas PJ. High-resolution manometry in clinical practice: utilizing pressure topography to classify oesophageal motility abnormalities. Neurogastroenterol Motil. 2009;21(8):796-806
215. Bredenoord AJ, Hebbard GS. Technical aspects of clinical high-resolution manometry studies. Neurogastroenterol Motil. 2012;24 Suppl 1:5-10
216. Srinivas M, Balakumaran TA, Palaniappan S, et al. High resolution esophageal manometry-The switch from "intuitive" visual interpretation to Chicago classification. Indian J Gastroenterol. 2014;33(2):157-60
217. Kessing BF, Smout AJPM, Bredenoord AJ. Clinical applications of esophageal impedance monitoring and high-resolution manometry. Curr Gastroenterol Rep. 2012;14(3):197-205
218. Carlson D a, Pandolfino JE. The Chicago criteria for esophageal motility disorders: what has changed in the past 5 years? Curr Opin Gastroenterol. 2012;28(4):395-402
219. Bredenoord AJ, Fox M, Kahrilas PJ, et al. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. Neurogastroenterol Motil. 2012;24 Suppl 1:57-65
220. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015 Feb;27(2):160-74
221. Singendonk MMJ, Kritas S, Cock C, et al. Applying the Chicago Classification criteria of esophageal motility to a pediatric cohort: effects of patient age and size. Neurogastroenterol Motil. 2014 Sep;26(9):1333-41
222. Roman S, Damon H, Pellissier PE, Mion F. Does body position modify the results of oesophageal high resolution manometry? Neurogastroenterol Motil. 2010;22(3):271-5
223. Xiang X, Tu L, Zhang X, et al. Influence of the catheter diameter on the investigation of the esophageal motility through solid-state high-resolution manometry. Dis Esophagus. 2013;26(7):661-7
224. Sweis R, Anggiansah A, Wong T, et al. Normative values and inter-observer agreement for liquid and solid bolus swallows in upright and supine positions as assessed by esophageal high-resolution manometry. Neurogastroenterol Motil. 2011;23(6):509-e198
225. Goldani HAS, Staiano A, Borrelli O, et al. Pediatric esophageal high-resolution manometry: utility of a standardized protocol and size-adjusted pressure topography parameters. Am J Gastroenterol. 2010;105(2):460-7
226. Staiano a, Boccia G, Miele E, Clouse RE. Segmental characteristics of oesophageal peristalsis in paediatric patients. Neurogastroenterol Motil. 2008;20(1):19-26
227. Kessing BF, Bredenoord AJ, Smout AJPM. The Pathophysiology, Diagnosis and Treatment of Excessive Belching Symptoms. Am J Gastroenterol. 2014 Aug;109(8):1196-203

228. Rommel N, Van Oudenhove L, Tack J, Omari TI. Automated impedance manometry analysis as a method to assess esophageal function. Neurogastroenterol Motil. 2014;26(5):636-45
229. Walzer N, Hirano I. Achalasia. Gastroenterol Clin North Am. 2008;37(4):807-25, viii
230. Goldblum JR, Rice TW, Richter JE. Histopathologic features in esophagomyotomy specimens from patients with achalasia. Gastroenterology. 1996;111(3):648-54
231. Storch WB, Eckardt VF, Wienbeck M, et al. Autoantibodies to Auerbach's plexus in achalasia. Cell Mol Biol (Noisy-le-grand). 1995;41(8):1033-8
232. Moses PL, Ellis LM, Anees MR, et al. Antineuronal antibodies in idiopathic achalasia and gastro-oesophageal reflux disease. Gut. 2003;52(5):629-36
233. Facco M, Brun P, Baesso I, et al. T cells in the myenteric plexus of achalasia patients show a skewed TCR repertoire and react to HSV-1 antigens. Am J Gastroenterol. 2008;103(7):1598-609
234. Ruiz-de-León A, Mendoza J, Sevilla-Mantilla C, et al. Myenteric antiplexus antibodies and class II HLA in achalasia. Dig Dis Sci. 2002;47(1):15-9
235. Gennaro N, Portale G, Gallo C, et al. Esophageal achalasia in the Veneto region: epidemiology and treatment. Epidemiology and treatment of achalasia. J Gastrointest Surg. 2011;15(3):423-8
236. Podas T, Eaden J, Mayberry M, Mayberry J. Achalasia: a critical review of epidemiological studies. Am J Gastroenterol. 1998;93(12):2345-7
237. Marlais M, Fishman JR, Fell JME, et al. UK incidence of achalasia: an 11-year national epidemiological study. Arch Dis Child. 2011;96(2):192-4
238. Frankhuisen R, van Herwaarden MA, Heijkoop R, et al. Persisting symptoms and decreased health-related quality-of-life in a cross-sectional study of treated achalasia patients. Aliment Pharmacol Ther. 2007;26(6):899-904
239. Marlais M, Fishman JR, Fell JM, et al. Health-related quality of life in children with achalasia. J Paediatr Child Health. 2011;47(1-2):18-21
240. Hallal C, Kieling CO, Nunes DL, et al. Diagnosis, misdiagnosis, and associated diseases of achalasia in children and adolescents: a twelve-year single center experience. Pediatr Surg Int. 2012;28(12):1211-7
241. Chumpitazi B, Nurko S. Pediatric gastrointestinal motility disorders: challenges and a clinical update. Gastroenterol Hepatol (N Y). 2008;4(2): 140–48
242. Hussain SZ, Thomas R, Tolia V. A review of achalasia in 33 children. Dig Dis Sci. 2002;47(11):2538-43
243. Iwanczak F, Smigiel R, Blitek A, Huebner A. The triple "a" syndrome confirmed by molecular analysis: a case report of 7-year-old boy. J Pediatr Gastroenterol Nutr. 2005;40(1):87-9
244. Kahrilas PJ. Esophageal motor disorders in terms of high-resolution esophageal pressure topography: what has changed? Am J Gastroenterol. 2010;105(5):981-7
245. Pandolfino JE, Kwiatek MA, Nealis T, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology. 2008;135(5):1526-33
246. Fisichella PM, Raz D, Palazzo F, et al. Clinical, radiological, and manometric profile in 145 patients with untreated achalasia. World J Surg. 2008;32(9):1974-9
247. Howard PJ, Maher L, Pryde A, et al. Five year prospective study of the incidence, clinical features, and diagnosis of achalasia in Edinburgh. Gut. 1992;33(8):1011-5
248. Hurwitz M, Bahar RJ, Ament ME, et al. Evaluation of the use of botulinum toxin in children with achalasia. J Pediatr Gastroenterol Nutr. 2000;30(5):509-14
249. Maksimak M, Perlmutter DH, Winter HS. The use of nifedipine for the treatment of achalasia in children. J Pediatr Gastroenterol Nutr. 5(6):883-6
250. O'Neill OM, Johnston BT, Coleman HG. Achalasia: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2013;19(35):5806-12
251. Boeckxstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. N Engl J Med. 2011;364(19):1807-16
252. Vela MF, Richter JE, Khandwala F, et al. The Long-term Efficacy of Pneumatic Dilatation and Heller Myotomy for the Treatment of Achalasia. Clin Gastroenterol Hepatol. 2006;4(5):580-587
253. Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment for achalasia depend on manometric subtype. Gastroenterology. 2013;144(4):718-25; quiz e13-4
254. Franklin AL, Petrosyan M, Kane TD. Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management. World J Gastrointest Endosc. 2014;6(4):105-111
255. Di Nardo G, Rossi P, Oliva S, et al. Pneumatic balloon dilation in pediatric achalasia: efficacy and factors predicting outcome at a single tertiary pediatric gastroenterology center. Gastrointest Endosc. 2012;76(5):927-32
256. Mehra M, Bahar RJ, Ament ME, et al. Laparoscopic and thoracoscopic esophagomyotomy for children with achalasia. J Pediatr Gastroenterol Nutr. 2001;33(4):466-71
257. Lee CW, Kays DW, Chen MK, Islam S. Outcomes of treatment of childhood achalasia. J Pediatr Surg. 2010;45(6):1173-7
258. Corda L, Pacilli M, Clarke S, et al. Laparoscopic oesophageal cardiomyotomy without fundoplication in children with achalasia: a 10-year experience: a retrospective review of the results of laparoscopic oesophageal cardiomyotomy without an anti-reflux procedure in children with achalasia. Surg Endosc. 2010;24(1):40-4
259. Pescarus R, Shlomovitz E, Swanstrom LL. Per-oral endoscopic myotomy (POEM) for esophageal achalasia. Curr Gastroenterol Rep. 2014;16(1):369
260. Swanstrom LL, Kurian A, Dunst CM, et al. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. Ann Surg. 2012;256(4):659-67
261. Maselli R, Inoue H, Misawa M, et al. Peroral endoscopic myotomy (POEM) in a 3-year-old girl with severe growth retardation, achalasia, and Down syndrome. Endoscopy. 2012;44 Suppl 2:E285-7
262. Familiari P, Marchese M, Gigante G, et al. Peroral endoscopic myotomy for the treatment of achalasia in children. J Pediatr Gastroenterol Nutr. 2013;57(6):794-7
263. Wang L, Li Y-M, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. Dig Dis Sci. 2009;54(11):2303-11
264. Singh S, Wakhlu A, Pandey A, et al. Retrospective analysis of paediatric achalasia in India: single centre experience. Afr J Paediatr Surg. 2012;9(2):117-21

265. Wei MT, He YZ, Deng XB, et al. Is Dor fundoplication optimum after laparoscopic Heller myotomy for achalasia? A meta-analysis. World J Gastroenterol. 2013;19(43):7804-12
266. Mayo D, Griffiths EA, Khan OA, et al. Does the addition of a fundoplication improve outcomes for patients undergoing laparoscopic Heller's cardiomyotomy? Int J Surg. 2012;10(6):301-4
267. Zurita Macías Valadez LC, Pescarus R, Hsieh T, et al. Laparoscopic limited Heller myotomy without anti-reflux procedure does not induce significant long-term gastroesophageal reflux. Surg Endosc. 2014 Aug 27. [Epub ahead of print]
268. Canani R, Cirillo P, Roggero P. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006;117(5):e817-20
269. Mertens V, Blondeau K, van Oudenhove L, et al. Bile acids aspiration reduces survival in lung transplant recipients with BOS despite azithromycin. Am J Transplant. 2011;11(2):329-35
270. Pauwels A, Verleden S, Farre R, et al. The effect of gastric juice on interleukin-8 production by cystic fibrosis primary bronchial epithelial cells. J Cyst Fibros. 2013;12(6):700-5
271. Bredenoord AJ, Weusten BLAM, Timmer R, et al. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. Am J Gastroenterol. 2006;101(3):453-9
272. Peter CS, Wiechers C, Bohnhorst B, et al. Detection of small bolus volumes using multiple intraluminal impedance in preterm infants. J Pediatr Gastroenterol Nutr. 2003;36(3):381-4
273. Boeckxstaens GE, Jonge W De, van den Wijngaard RM, Benninga MA. Achalasia: from new insights in pathophysiology to treatment. J Pediatr Gastroenterol Nutr. 2005;41 Suppl 1:S36-7