General introduction & Outline of the thesis

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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. 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.

**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-thoracic 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.

**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). 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. TLESRs, similar to those described in adults, are observed in prematurely born infants >28 weeks.

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. Multiple excitatory 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. 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. Another trigger is the stimulation of the superior laryngeal nerve in the pharynx. 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 or distension of the EGJ alone. 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.
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. 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. If abdominal pressure overcomes EGJ resting pressure, GER occurs more easily. This is especially relevant in cases of low LES resting pressures. 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. 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

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.
more likely to be liquid and acidic in patients with GERD.\textsuperscript{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.\textsuperscript{36} In GERD patients, this acid pocket is bigger and extends more proximal compared to healthy controls, especially in the presence of hiatal hernia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47,48}

**Epidemiology**

Daily regurgitation occurs in 70% of infants at 4 months of age.\textsuperscript{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.\textsuperscript{51,52} A recent national community survey revealed 25.9% of parents reported infant regurgitation matching Rome III criteria for functional gastrointestinal disorders.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 extraesophageal (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.\textsuperscript{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.\textsuperscript{51} 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. 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. 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). 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. For dental erosions and Sandifer’s syndrome (paroxysmal dystonic movement disorder), association with GER and hiatal hernia is confirmed. 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.

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. 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.

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<th>Symptoms of pediatric GER disease</th>
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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.\textsuperscript{75} Another disease with symptoms that can mimic GERD is eosinophilic esophagitis (EoE).\textsuperscript{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.\textsuperscript{77}

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<td>Celiac disease (after gluten introduction)</td>
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<td><strong>Children</strong></td>
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<td>Celiac disease</td>
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| **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                   |
| Supragastric belching                        |
| Rummation syndrome                           |
| Pediatric condition falsification            |
| 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.95,93,94,95

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
Continuous 24-hour esophageal ambulant intraluminal pH-metry is frequently used to diagnose acid GERD. 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 > 48 hr. 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. For older children an RI > 7% is considered abnormal, an RI < 3% is considered normal, and an RI between 3% and 7% is indeterminate. 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.

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). 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. 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.

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). In infants, baseline MII values are lower compared to older children. In older children, the association with esophagitis and low baselines is under debate.

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. 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. 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.
Several indices for symptom association on pH-MII have been developed. The three most used indices are: the symptom index (SI), the symptom sensitivity index (SSI) 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. However, for crying, a 5 minute window generates optimal symptom association. Recently, the influence of recording time on the association found was clearly shown, confirming the need for prolonged monitoring. Although current available association indices for GER related symptoms all have their limitations, it is indispensable to prove the presence of symptom association. 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. 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.
**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 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**

Esophagogastroduodenoscopy can be used to diagnose reflux esophagitis, a complication of GERD. Macroscopically visible mucosal breaks (erosions) are the most reliable evidence for GERD. These erosions are classified according to the Los Angeles classification and the Hetzel and Dent scale, similar to adult methods. 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).

**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. In gastroesophageal nuclear scintigraphy, patients consume a technetium labeled meal prior to start of a series of scans, and postprandial reflux becomes visible when labeled stomach contents move up in the esophagus. 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. Scintigraphy can provide information on gastric emptying time, however the correlation between delayed gastric emptying and GERD is under debate in children. 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. 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. 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{64} Overfeeding must be excluded, as distension of the stomach is able to increase the number of TLESRs and thus GER.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{144,145} Moreover, thickening of feeds does not reduce presumed GER-related apnea in preterm infants.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 treat-ment for uncomplicated GER symptoms in infants.\textsuperscript{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.\textsuperscript{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).\textsuperscript{151} Left lateral positioning significantly reduces liquid and acid GER in
healthy (pre)term infants as well as infants with GERD. 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. 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. 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.

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. 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. However, evidence is based on small trials and further research is needed to establish optimal conservative treatment for infants and children.

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. 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. Parental distress and desire for a medical intervention in case of pediatric GER symptoms might pressure physicians into prescribing acid inhibiting medication. The infant GER related healthcare burden seems to be influenced geographically: more urban infants are hospitalized for GER symptoms, compared to rural infants. 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. 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.
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 (CO₂), 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 CO₂ 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.⁴⁸,⁵⁸ More recent, gastric emptying rate of milk was found not significantly different between pediatric GERD patients and healthy children.⁵⁹ Nonetheless, prokinetics are frequently used in pediatric GERD aiming to accelerate gastric emptying. Not surprisingly, the three most commonly used agents (domperidone, metoclopramide and erythromycin) all lack convincing evidence for efficacy.⁴,¹⁷ ⁴,¹⁸²,¹⁸³ 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. 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. 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. Similar to adult findings, the few pediatric studies on this subject suggested that total and partial fundoplication produce equivalent GER control in children. 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. 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%). Overall complications during and after fundoplication in children occur in 0-54%, varying from post-operative dysphagia to wound infection and perforation. Post-operative dysphagia is the most common complication, occurring in 0-33% of patients in the first months after fundoplication. Dysphagia may occur less frequently in partial versus total fundoplication. 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.

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. 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 trans-nasally across the EGJ in the stomach allowing the measurement of intraluminal pressure of the esophageal body and LES, displayed in a line plot. Over the past years, more detailed assessment of esophageal function is possible due to the development of high resolution manometry (HRM). 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).

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. 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. 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

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<thead>
<tr>
<th>Category 1</th>
<th>Primary motor disorders</th>
<th>Classic achalasia</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Achalasia with esophageal pressurization</td>
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<tr>
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<td></td>
<td>Spastic achalasia</td>
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<tr>
<td>Category 2</td>
<td>Potential achalasia phenotype</td>
<td>EGJ outflow obstruction</td>
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<tr>
<td>Category 3</td>
<td>Disorders never observed in healthy (adult) individuals</td>
<td>Absent peristalsis</td>
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<td></td>
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<td>Diffuse esophageal spasm</td>
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<td>Hypercontractile esophagus</td>
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<tr>
<td>Category 4</td>
<td>Motor patterns outside the normal range (unclear clinical relevance)</td>
<td>Weak peristalsis</td>
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<td>Frequent failed peristalsis</td>
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<td>Hypertensive peristalsis</td>
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<td></td>
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<td>Rapid contraction</td>
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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.\textsuperscript{210,211} Moreover, the HRIM derived Dysphagia Risk Index seems to be able to predict postoperative dysphagia in both adults and children undergoing fundoplication.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{231–233} Especially in genetically susceptible individuals, aberrant immune response triggered by a viral infection might induce disease.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{238} Children with achalasia experience a lower quality of life compared to healthy children and children suffering from irritable bowel disease (IBD).\textsuperscript{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.\textsuperscript{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).\textsuperscript{240,243} Esophageal manometry, preferable high resolution manometry, is the gold standard to diagnose achalasia.\textsuperscript{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).\textsuperscript{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. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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.


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