

Gastroesophageal reflux in pediatrics; (patho)physiology and new insights in diagnostics and treatment

C. M. LOOTS¹, M. A. BENNINGA¹, T. I. OMARI²

GER is the passage of gastric contents into the esophagus and is referred to as GER disease (GERD) when GER causes troublesome symptoms and/or complications. GERD in infants and children is sometimes difficult to diagnose and even more difficult to treat. The diagnosis of GERD is hampered by the fact that GER symptoms such as irritability and crying, feed refusal and regurgitation are common problems in infants and these symptoms are not specific for GERD. Diagnostic criteria for the objective diagnosis of GERD with commonly used diagnostic tests such as pH-metry, pH-impedance monitoring and endoscopy are poorly or not defined. In this review the current understanding of (patho)physiology of GERD, clinical history in infants and children, new insights in diagnostic modalities and the role of non-pharmacological and pharmacological interventions are discussed.

Key words: Gastroesophageal reflux - Pediatrics - Esophagus.

The esophagus is protected by two sphincters, the upper esophageal sphincter and the lower esophageal sphincter (LES). Usually the LES is contracted preventing food from flowing back into the esophagus. The LES opens during every swallow to facilitate the passage of food into the stomach. When the LES opens without a

¹*Pediatric Gastroenterology and Nutrition
Emma Children Hospital/
Academy Medical Centre
Amsterdam, The Netherland*

²*University of Adelaide, Adelaide, Australia*

preceding swallow stomach contents may pass into the esophagus.¹ This is referred to as gastroesophageal reflux (GER), defined as the involuntary flow of stomach contents into the esophagus.

GER is a physiological phenomenon that occurs in infants, children and adults and allows depressurization of the stomach. Physiological regurgitation occurs regularly in up to 70% of the 4 month old infants.² In most infants GER does not cause symptoms. Regurgitation usually resolves in the first year of life and less than 5% of infants 12-14 months of age continue to experience GER.^{2,3} However, when GER causes troublesome symptoms or complications it is defined as GER disease (GERD).⁴ Using an administrative claims database, the incidence of the diagnosis of GERD in North America increased between 2000 and 2005 from 3.4% to 12.3% in infants and from 0.9% to 1.3% in older age groups.⁵ GER has a great impact on families and causes distress amongst parents.⁶ It is one of the most common problems for which parents consult first line health care. Undiagnosed

Corresponding author: C. M. Loots, Pediatric Gastroenterology and Nutrition Emma Children Hospital/Academic Medical Centre, Meibergdreef 9, Amsterdam, the Netherlands. E-mail: c.m.loots@amc.nl

GERD in infants increases the risk of developing feeding difficulties later in life³ and adult GERD has been associated with childhood GERD.⁷

Children with certain underlying disorders have a higher risk to develop severe GERD. Although this review does not focus on those subgroups, these patients are frequently seen in clinical practice and are therefore briefly mentioned. Patients with neurological impairment, particular cerebral palsy, anatomical disorders such as esophageal atresia and achalasia and chronic respiratory disorders such as cystic fibrosis are at high risk to develop GERD. Clinicians should be aware of the high incidence of GERD and complications of GERD in these patients.

Physiology of the esophagus and the esophago-gastric junction

Gastric contents are prevented from moving into the esophagus by a sphincter complex consisting of the lower esophageal sphincter (LES) and the crural diaphragm (CD), referred to as the esophago-gastric junction (EGJ). The basal pressure is maintained by tonic contraction of the LES and extrinsic pressure from the CD. The EGJ regulates the exchange of contents between the stomach and the esophagus, facilitating food progression into the stomach and gas venting, whilst minimizing liquid GER.

GER – mechanism and influencing factors

Sometimes the EGJ opens spontaneously without a preceding swallow when both the LES and the CD relax. This is referred to as a transient relaxation of the lower esophageal sphincter (TLESR). TLESR is a physiological mechanism to allow air to vent from the stomach and is the main underlying mechanism that allowing GER to occur in all infants, children and adults, in healthy controls and in patients with GERD.⁸⁻¹¹ TLESRs are mediated through a vago-vagal reflex.¹² Vagal afferents from the gastric cardia, pharynx an esophageal body synapse in the brainstem (nucleus

tractus solitarius) and activate motor neurons in the dorsal motor nucleus of the vagus nerve.¹²

Several factors are known to trigger TLESRs.¹³ The predominant trigger for TLESRs is activation of tension receptors located in the proximal stomach through gastric distension and gastric accommodation after a meal.^{14, 15} The presence of a nasogastric tube is also known to increase the rate of TLESRs. It has been suggested that this is due to pharyngeal stimulation and/or stimulation of the LES.¹⁶

Furthermore, cholecystokinin (CCK) decreases LES pressure and causes fundic relaxation.¹⁷ CCK is released when food enters the duodenum. It is unknown if this is the mechanism whereby CCK results in more TLESRs or alternatively if CCK interacts directly with the vagal afferent system.

Position has been shown to influence TLESRs as well, with TLESRs occurring less frequently in supine position in patients with GERD.¹⁸ In GERD patients and healthy adults, TLESRs and GER have been shown to occur more frequently in right lateral position (RLP) compared to left lateral position (LLP).¹⁹ Recently it was shown that TLESRs occurred more frequently in RLP and were more likely to cause liquid GER, despite more rapid gastric emptying in healthy premature infants.^{20, 21} Additionally, small volumes of a liquid meal caused a significantly faster onset of TLESR triggering after the start of a meal infusion in RLP compared to LLP.²²

Factors associated with GERD

Although the emphasis lies on TLESRs as the main underlying mechanism allowing GER, other mechanism may contribute to the occurrence of GER such as a hiatus hernia (HH), hypotonic LES, and delayed gastric emptying. HH refers to the condition in which the LES and CD are separated, allowing the proximal stomach to move into the thoracic cavity and preventing the CD from enforcing the LES. In adults HH is strongly associated with GERD with and without esophagitis. The prevalence in children of HH is unknown. Hiatus hernia may neverthe-

less play a role in children as patients who develop Barrett's esophagus more often have a HH and 39% of children receiving long term (median 3 years) anti reflux treatment had a HH.²³

When the LES is continuously hypotonic the EGJ barrier function fails allowing GER to occur more frequently.⁹ This can be caused by several factors such as respiration, gastric activity, hormones, foods and medications. In children an hypotonic LES can be caused by multiple swallowing, a condition that is associated with an increase in GER.¹

During opening of the EGJ, a positive pressure gradient over the EGJ and distal longitudinal contraction with esophageal shortening is needed to allow GER to occur.²⁴ Obesity is a risk factor for GERD. Increased abdominal pressure, resulting in a greater positive pressure gradient over the EGJ, due to central obesity is likely to be the contributing factor.²⁵

Despite numerous studies, the role of gastric emptying in GER (disease) is still controversial.²⁶ It seems logical to relate more rapid gastric emptying to a decrease in GER as there is less distension of the stomach and less gastric content to flow back into the esophagus. Nevertheless, a convincing relation between delayed gastric emptying and GERD has not been proven. Proton pump inhibitors are widely prescribed to enhance gastric emptying, however they have not been proven to reduce bolus GER.²⁶ In the light of the controversies in the literature it can be stated that gastric emptying and the manipulation thereof is either not a major contributing factor to GER or it is more complex than we currently understand.

Esophageal factors in GERD

The esophagus is actively involved in the defense against GER through the rapid clearance of contents from the esophageal lumen.⁸ Esophageal motility fully functions in infants as young as 31 weeks of age.¹⁰ Delayed esophageal clearance has been observed in GERD patients and has

been identified as a risk factor for GERD in adults. However, it is unknown whether deteriorated motility is a cause or a consequence of acid exposure.

In adults a small proportion of patients experience symptoms of GER despite any evidence of GERD, suggesting esophageal hypersensitivity. It has been suggested that esophageal hypersensitivity plays an important role in patients without esophagitis, as patients with symptoms of GER but without esophagitis have shown to be more sensitive to acid perfusion than patients with esophagitis.²⁷ The cause of esophageal (hyper) sensitivity is unclear but a relation with impaired mucosal defense, visceral neural pathway dysfunction and sustained esophageal contractions has been suggested.

Difference between patients and healthy controls

Although TLESRs were originally described as inappropriate LES relaxations in early literature, current literature suggests that there is no clear difference in the number of TLESRs in GERD patients and healthy controls, in adults and in infants.^{11, 28, 29} The difference between GERD patients and healthy controls lies in the type of GER, which is more likely to be liquid and acidic in patients as opposed to gaseous and weakly acidic in healthy controls.²⁸ The underlying mechanism of this phenomenon is as yet unknown.

Several contributing factors have been suggested such as the acid pocket, the compliance of the EGJ and enhanced acid secretion. However none of these factors seem to solely provide the conclusive answer to the question of what causes the selectivity in type of GER in GERD patients *versus* healthy controls.

Diagnosis GER

Clinical history

Infants and children with suspected GERD may present with a wide range of symptoms. Esophagitis as assessed by en-

TABLE I.—Symptoms of GER (disease) and conditions associated with GER. Alarm symptoms requiring immediate intervention are marked with *. Conditions marked with ** are convincingly shown to be related to GER.

GER symptoms in infants	GER symptoms in children
Regurgitation	Heartburn (most specific symptom)
Vomiting	Epigastric pain (stomach ache above belly)
Excessive crying / irritability around feeds	
Associated conditions in infants and children	
Desaturation*	
Bradycardia*	
Failure to thrive*	
Hematemesis / melena*	
Anemia	
Apnea spells*	
ALTE*	
SIDS*	
Recurrent pneumonia	
Dysphagia	
Cough	
Hoarseness	
Wheezing	
Stridor	
Laryngitis	
Ear infection	
Foetor ex ore	
Dental erosions**	
Feed refusal	
Sandifer syndrome**	

doscopy confirms the diagnosis of GERD, however in most infants and children GERD is diagnosed based on clinical history. Symptoms suggestive of GER are different in infants and children and are therefore discussed separately.

INFANTS

In infants, symptoms most indicative of GERD are regurgitation, vomiting and irritability after feeds. However, these symptoms are not specific in infants and poorly correlate with GERD. Moreover, no combination of symptoms is conclusive for the diagnosis of GERD. For instance, the combination of regurgitation and irritability around feeds is also suggestive for cow's milk protein

(CMP) allergy (although CMP allergy usually presents with other symptoms such eczema or atopic dermatitis as well).³⁰ Other symptoms suggestive of GERD in infants are presented in Table I. GERD may cause complications such as hematemesis, failure to thrive, apneas or apparent life threatening events (ALTE). These complications require immediate adequate intervention.

An extensive differential diagnosis should be considered in infants presenting with regurgitation and vomiting. In the diagnostic process anatomical/obstructive, infectious, immunologic, neurologic, metabolic and pharmacological causes for vomiting should be ruled out. When warning signals are present (Table II) additional information should be acquired, GERD is less likely to

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TABLE II.—*Warning signals requiring further investigation in infants presenting with regurgitation and vomiting. Symptoms with an * may present in older children as well as infants. The second column is not a differential diagnosis, it indicates possible causes for the symptoms in the left column.*

Symptoms	Consider other underlying causes such as
Bilious vomiting*	Pancreas annulare Anorexia nervosa*
Gastrointestinal bleeding*	Gastric/duodenal ulcer
Consistent projectile vomiting	Pyloric hypertrophy/stenosis Duodenal web/stenosis Malrotation Achalasia (older children)
Onset of vomiting after 6 months of life*	Immunological cause (Celiac disease after introduction of gluten)
Failure to thrive*	Many causes possible – Insufficient intake?
Diarrhea*	Allergy, infections (gastroenteritis)
Constipation*	Hirschsprung's disease (infants) Severe functional constipation
Fever*	Infectious causes such as but not limited to meningitis, gastroenteritis, pneumonia
Lethargy*	Severely ill child, find underlying disease!
Hepatosplenomegaly*	Metabolic diseases
Bulging fontanel	Meningitis, central nervous system tumor
Macro/microcephaly	Syndrome
Seizures*	Cerebral process Epilepsy
Abdominal tenderness/swelling*	Abdominal infection Gastrointestinal atresia
Suspected genetic/ metabolic syndrome*	Genetic/ metabolic syndromes

be the underlying disease and alternative diagnoses should be considered.

It has become popular to give infants an empirical trial of PPI medication as a diagnostic trial; if parents report improvement on PPIs, the infant is deemed to have GERD and will be given PPIs for a long period of time. This approach may seem practical but has major drawbacks making this 'PPI test' unreliable. Firstly, PPIs have not been shown to reduce symptoms of GER in infants.^{31, 32} In a double blind placebo controlled trial in infants, 54% of the patients improved on lansoprazole, however 54% improved in the placebo group as well.³³ Moreover, side effects such as lower respiratory tract infections were significantly higher in the lansoprazole group. Lastly, a strong acid rebound effect occurs after the cessation of PPI, causing healthy adult volunteers to experience symptoms of GERD and dysphagia after ceasing PPI treatment.³⁴ This effect has

not been investigated in infants or children but they are likely to experience a rebound effect similar to adults. Due to the lack of efficacy for reducing GERD symptoms, the increased risk for adverse events, the high placebo effect and the acid rebound effect an empirical PPI trial cannot be advocated as a diagnostic test in children and infants.

When underlying pathology is ruled out it is important to reassure parents that symptoms of GERD usually disappear within the first year of life, with less than 5% of the 13 to 14 months old infants experiencing daily regurgitation.^{3, 35} Nevertheless, infants with GERD are a great burden for the family and every attempt to settle the infant and the family situation should be made.

OLDER CHILDREN

GERD in older children is different compared to infantile reflux in terms of type of

symptoms, incidence and prognosis. Typical GER symptoms in older children are heartburn, epigastric pain and regurgitation. Other, less specific symptoms of GER, are presented in Table I. As in infants, no cluster of symptoms has been shown to predict complication of GER or response to therapy. Furthermore, the severity of symptoms does not seem to correlate well with esophagitis found on endoscopy.³⁶

GER symptoms occur less frequently in older children compared to infants. In a community based study symptoms of heartburn, epigastric pain and regurgitation were reported up to 5.2%, 5.0%, and 8.2% of the time respectively, in children aged 3 to 17 years.³⁷ Although occurring less frequently, GERD is less likely to resolve spontaneously in children who develop GER after the age of three years.

In older children other conditions should be ruled out comparable to infants (marked with * in Table II). Furthermore lifestyle should be explored as heartburn has been associated with reported cigarette use in adolescents.³⁷ In the same cohort no relation between GER symptoms and use of alcohol, caffeine or passive smoking was observed. Although the percentage of self reported symptoms is up to 8.2% of time in the adolescent age group, the use of anti reflux medication was low.³⁷

In adults an empirical trial of PPIs as a diagnostic test is often performed. Evidence for the use of an empirical trial of PPIs in older children is lacking. One could argue that a "PPI test" in older children who can express their symptoms accurately may be useful although the poor specificity in adults should be kept in mind. If the "PPI test" is used, PPIs should be prescribed for a short starting period of 2-4 weeks and if effective continued for a maximum of three months. Thereafter the PPIs should be weaned and stopped for at least two weeks to assess if symptoms recur. If symptoms recur, further investigations may be considered. In younger children who are unable to express their symptoms accurately the 'PPI test' is likely to be unreliable.

Diagnostic tests

PH-MONITORING

24 hr pH-monitoring of the distal esophagus is the most widespread used diagnostic test in infants, children and adults because it is easy to perform, analysis is automated, it is relatively inexpensive and the results can be compared to available normative data. However, despite efforts to create normative values, there is no international consensus on the appropriate diagnostic criteria that should be applied in children and infants.³⁸ Furthermore, acid exposure poorly correlates with symptomatic or endoscopic findings in infants, children and adults.³⁶ This may not be so surprising knowing that the cut-off for acid GER pH<4 was based on the occurrence of heartburn in adults. Rather than an absolute value of acid exposure, the relation with symptoms may be more important in the assessment of the presence or severity of GERD. To this end, symptom association indices have been developed. However pH-monitoring is limited by the fact that non acid GER cannot be detected. This is particularly important in infants receiving frequent milk feedings. Milk is a potent buffer of stomach contents and it has been shown that stomach contents of milk-fed infants are non acidic for approximately 2 hours after a meal. Most GERD episodes occur postprandial and pH-monitoring will fail to detect these non acidic episodes.

PH-IMPEDANCE MONITORING

Combined pH multichannel intraluminal impedance (pH-impedance) monitoring is a method to measure bolus flow in a lumen in addition to recording pH in the distal esophagus and was first described in children by Skopnik *et al.* in 1996.³⁹

Impedance is defined as the resistance against an alternating current between two electrode pairs. Impedance values, representing changes in conductivity, drop in the presence of highly conductive contents, such as saliva or gastric fluids indicating a liquid swallow or GER. Less con-

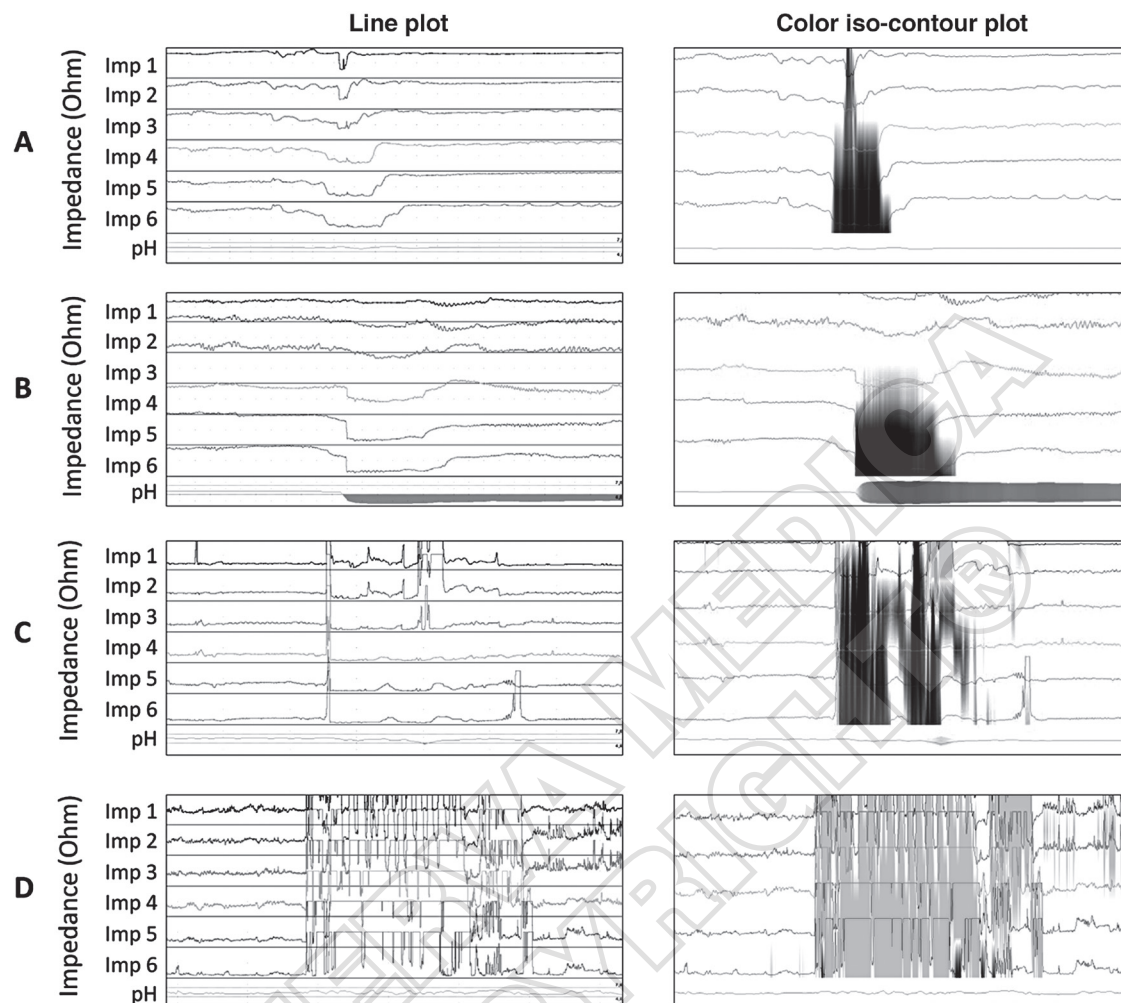


Figure 1.—Different types of GER.

ductive bolus, such as air during a burp, cause an increase in the impedance signal. When the bolus moves through the esophagus the bolus is in contact with multiple electrode pairs, allowing assessment of antegrade (swallowed) or retrograde (regurgitated) movement. In combination with the pH, different types of GER can be detected; acid or weakly acid, liquid, gas or mixed GER (Figure 1). From studies using pH-impedance it has become clear that a substantial proportion of GER in infants and children is weakly acidic and that weakly acidic GER causes symptoms as well.⁴⁰

It is now recommended to use pH-

impedance monitoring in children rather than pH-monitoring alone for the detection of GERD by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).⁴¹ Furthermore, impedance has been shown to yield important additional diagnostic information in children and infants.⁴²

pH-impedance analyses.—Guidelines for the analysis of 24 hr pH-impedance tracings in adults have been developed. Although these guidelines are rather arbitrary,

it is generally accepted to mark liquid GER when a retrograde drop in impedance to 50% from baseline in ≥ 2 channels occurs. Gas GER is defined as a simultaneous or retrograde rise in impedance to >3000 Ohm in ≥ 2 channels,⁴³ although most software packages use an impedance rise to >5000 Ohm as cut off value.⁴⁴ Mixed GER is defined as a GER episode meeting both liquid and gas criteria. GER episodes with a drop to $\text{pH}<4$ and no change in impedance, pH-only GER, have been described although their clinical relevance is as yet unclear.

Symptom associations.—To assess the relation between GER and symptoms, three symptom association indices have been developed, the Symptom Index (SI),⁴⁵ the Symptoms Sensitivity Index (SSI)⁴⁶ and the symptom association probability (SAP).⁴⁷ The SAP is least influenced by the total number of GER or the total number of symptoms and is the symptom association index of choice.

Traditionally the time window for GER – symptom associations is two minutes. Intuitively a 2 minute relation between GER and the onset of symptoms is logical and good day to day reproducibility has been shown for symptoms of regurgitation and cough.⁴⁸ However, for the evaluation of crying in infants a 5 minute time window increases day to day reproducibility.⁴⁸ Furthermore, a minimum of 20 crying episodes should be recorded during a 24hr study to ensure reproducibility.⁴⁸

Symptom association is a useful tool to evaluate the temporal relation between symptoms such as cough, regurgitation, irritability and GER. However, the relation of other symptoms without a clear temporal relation to GER, such as asthma, cannot be assessed. Furthermore, symptoms association is highly dependent on the diligence of children and their parent to record symptoms accurately during the 24hr pH-impedance study. This is a drawback potentially limiting the diagnostic power of pH-impedance symptoms association.

Other limitations of pH-impedance in children and infants include the lack of

normative data, the relatively higher cost of consumables and more time consuming analysis compared to pH-metry.

The analysis of pH-impedance recordings is based on pattern recognition, the investigator analyses a line or color plot and judges whether a specific pattern represents GER. In a recent study, ten pediatric 24-hr pH-impedance tracings were analyzed by ten observers from seven world groups and with automated analysis.⁴⁹ The difference in analysis between experts in the world was large, and this difference is likely to be even greater amongst non experts in pediatric gastroenterology. Compared to majority consensus automated analysis had a 94% sensitivity rate and 74% specificity rate. Considering the poor inter observer outcomes, automated analysis seems favorable over manual analysis due to its reproducibility. However, the relatively low specificity suggests the need for refinement of automated analysis before widespread use can be advocated.

BASELINE IMPEDANCE

Until recently, pH-impedance has been used for the detection of GsER only whereas the intrinsic characteristics of impedance measurement to measure resistance against an alternating current may allow assessment of the conductivity of the esophageal wall. When the esophagus is at rest and no swallows or GER occur, the impedance signal, is measured through the esophageal mucosa. This is referred to as the impedance baseline.^{50, 51} Low baselines have been observed in patients with esophagitis⁵¹ and esophageal motility abnormalities.⁵² Recently Farré et al demonstrated *in vitro* and *in vivo* that impedance is a useful tool for the evaluation of mucosal integrity and that patients with GERD and non-erosive reflux disease (NERD) have lower baselines compared to healthy volunteers.⁵⁰ The authors reported that the changes in baseline are not only related to macroscopic changes and secretion of inflammatory fluids, as seen in esophagitis, but to more subtle changes in the esophageal mucosa such as dilated intra-

cellular spaces (DIS). This was confirmed by a study from Kessing et al in which the authors observed a higher impedance baseline in healthy controls compared to patient with physiological and pathological acid exposure.⁵³ Furthermore, a relation between impedance baselines and esophageal acid exposure was observed.

This new way of interpreting impedance baselines have great potential in infants and children in whom endoscopy is infrequently performed due to low diagnostic yield and the risk for complications. The first study to assess the impact of proton pump inhibitor (PPI) therapy in infants was recently published.⁵⁴ Impedance baseline values were reanalyzed in infants before and after PPI treatment. This study was performed in 21 infants with symptoms of GER disease before and after a week of PPI (esomeprazole) therapy. In infants with a low baseline (<1250 Ohm) before therapy (n=15) the baseline increased significantly during treatment. In patients with normal baselines (n=6), no change in baseline was observed. In addition, patients with the lowest baseline before treatment had the greatest increase on PPI therapy. The data from this study suggest that low impedance baselines may be a new marker of esophageal mucosal integrity. Similar findings in adults have been published

MANOMETRY

Esophageal manometry measures upper and lower esophageal sphincter pressures and esophageal peristalsis. As in pH-impedance monitoring, data on motility patterns in healthy infants and children are scarce as it is unethical to introduce a nasogastric catheter for research purposes in healthy children. Motility studies in otherwise healthy preterm tube fed children are an exception as manometry catheters that allow tube feeding through a central lumen have been developed. These studies have provided important insights in the pathophysiology of GERD such as identification of TLESRs, the underlying mechanism of GER.^{1, 10, 11} Manometry, however cannot

detect bolus flow and clearance, and no manometric abnormalities have been identified that indicate patients with esophagitis or increased acid exposure.⁵⁵ Therefore, GERD cannot be diagnosed by manometry alone. Nevertheless, manometry is part of the diagnostic workup in children with suspected esophageal motility disorders as it can confirm those disorders that may present with GERD-like symptoms such as achalasia, hypotensive peristalsis and diffuse esophageal spasm.

High resolution manometry (HRM) is now becoming standard in adults. An HRM catheter has an array of closely spaced pressure sensors, usually 22 – 36 sensors spaced 1-3 cm apart, in the esophagus. It can be appreciated that this yields more information, which has enabled sub categorization of motility disorders such as achalasia, esophageal spasm and nutcracker's esophagus in adults.⁵⁶ The use of HRM in infants and children has been hampered by the size and stiffness of HRM catheters. Only recently HRM catheters for pediatric use have become available and research with HRM in infants and children is promising but has only just started.

The concurrent assessment of manometry with pH-impedance has been used successfully to investigate the cough – GER relationship objectively.⁵⁷ Furthermore, combining manometry and impedance provides a means to assess esophageal function. This additional information is important as it has been demonstrated that abnormal motility patterns are not always predictive of symptoms of GER and vice versa, patients with severe symptoms may have normal motility. Furthermore, up to one third of adult patients with manometric abnormalities have normal bolus transit.⁵⁸ Therefore, combined manometry and impedance testing is a esophageal function test with great potential.

Recently the analysis of concurrent manometry and impedance has been taken to a next level in terms of an automated impedance manometry analysis (AIM). AIM analysis is an objective, reliable and reproducible method to assess pharyngeal

and esophageal function in relation to ineffective pharyngeal swallowing, deglutitive aspiration and potentially dysphagia. AIM analysis was initially developed for evaluation of pharyngeal swallowing, where early evidence suggests that it may enhance the clinical utility of impedance-manometry.⁵⁹⁻⁶¹ Using pharyngeal AIM, deglutitive function was assessed using the swallow risk index (SRI). The SRI is a global measure of swallow effectiveness and aspiration risk derived through the combination of AIM variables associated with the occurrence of deglutitive aspiration on videofluoroscopy. The SRI has been shown to detecting the presence of aspiration during swallows with an almost perfect agreement with expert scoring of videofluoroscopy.⁶⁰ This novel method has not to date been applied to esophageal motor disorders such as non-obstructive dysphagia.

ENDOSCOPY

Upper gastrointestinal endoscopy allows macroscopic evaluation of the esophageal mucosa and is the diagnostic test of choice to confirm the presence of esophagitis. Mucosal biopsies can be taken to detect histological and cytological changes. Although the finding of esophagitis on endoscopy supports the diagnosis of GERD, the absence of mucosal abnormalities does not exclude GERD. In addition, esophagitis can be caused by other disorders than GERD such as eosinophilic esophagitis, Crohn disease and infections.⁶² Because there is insufficient data to support the use of histology for the diagnosis of GERD, the primary use of histology is to exclude other conditions.

One of the complications of GERD that can be diagnosed on endoscopy is Barrett's esophagus (metaplasia of the squamous epithelium in the distal esophagus, a precursor of esophageal cancer). In a recent study in 157 children who underwent endoscopy for various clinical purposes, only 3 children had a Barrett's esophagus.⁵⁵ The children that developed Barrett's esophagus all had psychomotor retardation. Other children at

risk of developing severe GERD, esophagitis and Barrett's esophagus are children with congenital esophageal abnormalities such as esophageal atresia (EA); those with chronic lung diseases such as cystic fibrosis; with hiatal hernia; with obesity; and those with a strong family history of GERD, Barrett's esophagus or adenocarcinoma of the esophagus. These groups of children are more likely to require long-term treatment for healing and endoscopic screening in these children is advisable.

In summary, endoscopy is neither specific nor sensitive enough to be the diagnostic test of choice for detecting GERD in children, whereas it does play an important role in the diagnosis of esophagitis. Endoscopy may have a more important role in children with neurological impairment in whom GERD, esophagitis and Barrett's esophagus are more prominent than in normal children. Endoscopy should be considered if esophagitis is suspected or when GER related symptoms persist despite adequate therapy.

BARIUM CONTRAST

A barium contrast study, for the evaluation of GERD in children is neither specific nor sensitive. The short duration of the barium contrast study yields many false negative results, whereas the occurrence of physiological GER gives false positive results. Therefore, the use of barium contrast studies is not justified for the diagnosis of GERD.⁶³ It is however an appropriate test to assess esophageal strictures, malrotation or other anatomical abnormalities.

Nuclear scintigraphy

In gastroesophageal scintigraphy, ⁹⁹Tc-labeled food is introduced into the stomach. During the scanning period the labeled food is visualized on scans, providing information on the position of food which may be digested (through gastric emptying), regurgitated and possibly aspirated. Sensitivity and specificity of a 1-hr scintigraphy scan for the diagnosis of GERD range

from 15% - 59% and 83% - 100%, respectively when compared to pH monitoring.⁴¹ Nuclear scintigraphy may be used to assess gastric emptying although this test is compromised by the absence of normative data. Scintigraphy is not recommended for the diagnosis of GERD in children.⁴¹

Overall, different diagnostic modalities like clinical symptoms, endoscopic and pH findings poorly correlate. Various studies have shown different outcomes when comparing endoscopy (macroscopy), biopsies (histology), pH-metry and gastroesophageal reflux symptoms in infants and children.^{36,64} This compromises the ability to diagnose GERD accurately in infants and children.

Treating GERD

The management of GERD in infants and children consists of *non pharmacological interventions* such as parental reassurance, different feedings regimes and positioning, *pharmacological interventions* with acid or TLESR suppressive therapies and *surgery* as a last option.

Non pharmacological interventions

Parental education and reassurance is the first step in the conservative treatment of mild infant GERD. Conservative therapy with parental reassurance, feeding advice and tobacco avoidance in the environment is effective over a 2 week period with a significant decrease in GER symptoms in 59% of infants with GERD based on a validated infant questionnaire.⁶⁵

TOBACCO SMOKE AVOIDANCE IN INFANTS AND CHILDREN

Tobacco smoke exposure increases esophagitis and heartburn in children and GER episodes are increased in infants in a tobacco smoke environment.³⁷ For this reason, and many others, it is recommended to avoid tobacco smoke.

POSITIONING STRATEGIES IN INFANTS

Prone and upright positioning.—Positioning of the body has an impact on the incidence of GER episodes. Positioning in the upright, sitting, position (60°) exacerbates GER, while the prone 30° anti-Trendelenburg position tends to decrease reflux.^{66, 67} However, the prone position is associated with a tenfold increased risk of sudden infant death (SID). Therefore this treatment option cannot be justified, unless the infants cardio-respiratory status is monitored continuously or when the child outgrows the age of increased risk of SID (>6 months) in unguarded infants.

Recently an infant bed has been designed to reduce GER. In this bed infants are positioned in a 40° - 50° angle and maintain their position with a special diaper-like construction. In a preliminary report it was observed that this position decreased regurgitation in a statistical and clinical significant way in 22/30 infants presenting with frequent regurgitation and reflux-associated symptoms with therapy resistant GERD symptoms, furthermore acid exposure was decreased.⁶⁸ This study was however uncontrolled, regurgitation was based on parental diaries and there was a high dropout rate of infants who did not seem to like the position. The outcomes should therefore be interpreted with caution. Nevertheless, this position may be promising and well designed, controlled studies are awaited.

Side positioning.—Left lateral positioning (LLP) significantly reduces liquid and acid GER in both healthy and GERD preterm and term infants, while right lateral positioning (RLP) enhances GER.^{20, 69} In a recent study, a strategy of right side positioning for the first postprandial hour with a position change to LLP thereafter is effective in reducing GER.²¹ Lateral positioning is associated with an increased risk for SIDS⁷⁰ so LLP and RLP can only be advocated in well controlled settings including stabilization with custom made cushions and cardio respiratory monitoring. Until large randomized controlled trials are performed to assess reduction of GER and symptoms of GER with

side positioning, LLP positioning therapy cannot be advised.

FEEDING STRATEGIES

Overfeeding.—Although exact numbers are unknown, overfeeding is thought to be a prominent cause of GER because the ingested volume is relatively large compared to the size of the stomach in infants. Frequent smaller volume feeds decrease acid exposure and might reduce symptoms as a subgroup of GERD patients suffer from acid GER.⁷¹ This study was however performed before pH-impedance measurements were introduced and the influence of more frequent, smaller feeds on weakly acid GER is unknown. Older children with GERD symptoms may benefit from smaller, more frequent meals as well. Furthermore, avoidance of spicy foods and late night meals has been reported to reduce symptoms.⁴¹

Thickening feeds.—Feed thickeners decrease the frequency and volume of regurgitation, but they do not reduce acid exposure nor affect the height and frequency of reflux episodes.⁷² Some thickening agents have potential side effects (increased coughing, abdominal pain, diarrhea, decreased intestinal absorption of nutrients) and there is a lack of data on nutritional and allergic safety. Nevertheless thickening of feeds is considered a valuable first-line therapy to relieve excessive infant regurgitation most likely because the reduction in regurgitation reassuring has a reassuring effect on parents.

Cow's Milk allergy.—Symptoms of cow's milk allergy (CMA) closely resemble symptoms of GERD.⁷³ CMA occurs in 2-3% of unselected children < 1yr of age, and some studies suggest an association between GER and CMA in up to half of infants presenting with GERD.⁷⁴ This association is a logic consequence of the fact that symptoms may be identical in both entities, rigid diagnostic criteria are lacking and both GERD and CMA tend to disappear around 12 months of age. Unifying mechanisms have been suggested such as altered motility in CMA resulting in more GER, however the dis-

ussion on underlying mechanisms is still ongoing. Particularly in infants with atopic families, with a higher risk for developing CMA, eliminating cow's milk and replacing it with hypoallergenic formula, is a potentially successful therapy.⁷³

Pharmacological therapy

When conservative therapy fails, pharmacological interventions may be considered. Most commonly used pharmacological therapies are discussed below.

ANTACIDS AND ALGINATES

Antacids neutralize gastric acid are over-the-counter available and are broadly used in the treatment of GERD in adults. Antacids have effect on the short term relief of heartburn. Alginates and antacids components are frequently combined in one product, of which Gaviscon preparations are the most well-known. In contact with the acid environment of the stomach alginates form a viscous gel. The antacid usually contain a bicarbonate that reacts with the acid gastric contents and generates carbon dioxide. The carbon dioxide bubbles up and becomes entrapped in the viscous gel making the raft float. A special alginate for children, Gaviscon-Infant, has been developed. This preparation does not contain bicarbonate, hence a "raft" is not formed and it acts as a feed thickener instead.⁷⁵ Strictly speaking, Gaviscon-Infant is therefore an alginate only preparation.

There is little evidence for the use of antacids in infants and children. Two randomized controlled trials have been performed, one of them suggesting efficacy of antacids⁷⁶ and one of them failed to show a treatment effect.⁷⁷

The effect of alginates in infants and children has been studied to a greater extent. A randomized, placebo controlled, double blind study using combined pH and impedance measurement in 20 infants and children with gastro-esophageal reflux showed no differences in the number of (acid) GER episodes, distal or proximal pH and acid

clearance between Gaviscon Infant (alginate only preparation) and placebo. A minimal but significant difference in average reflux height was found.⁷⁸

Another, double-blind, randomized, parallel-group study in 90 infants with GERD showed that alginate was superior to placebo in terms of reducing the number of vomiting/regurgitation episodes.⁷⁹ The safety profile of alginate was similar to that of placebo.⁷⁹ Long-standing utilization of antacids should not be advised due to the risk of possible adverse effects such as increased serum levels of aluminum, magnesium or calcium.

HISTAMINE-2 RECEPTOR ANTAGONISTS

Histamine stimulates the H₂ receptors, located in parietal cells in the stomach wall. The histamine-2 receptor antagonists (H₂RAs) have affinity for the H₂ receptors and inhibit the interaction of histamine in the parietal cell and thus decrease gastric acid production. Although most data in pediatric patients is based on small studies, ranitidine and cimetidine are well characterized.

Two recent review articles^{41, 75} described the use of ranitidine for GERD in children. In these reviews, ranitidine is reported to be a safe and effective therapy (for 8-12 weeks) for infant GERD. No double blind randomized, placebo controlled trials to assess the effectiveness of ranitidine have been performed. Therefore these results should be interpreted with caution. Cimetidine is rarely used in pediatric patients.

Recently, it has been suggested that gastric acid inhibitors (H₂RA as well as proton pump inhibitors, see below) raise the risk of acute gastroenteritis and community acquired pneumonia in children.⁸⁰ This increased risk of infection is attributed to the interference of these agents with the first line defense mechanism by changing the acidic environment of the stomach.

PROTON PUMP INHIBITORS

The use of proton pump inhibitors (PPIs) in infants has increased exponentially over

the last decade. PPIs prevent the release of acid into the stomach by blocking the H⁺/K⁺ ATPase pump and thereby increase the pH of the stomach. In North America, five PPIs have been approved for use in children, omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. None of these have been approved by the Food and Drug Association (FDA) in infants <12 months of age, moreover the FDA has now concluded that PPIs should not be administered to treat the symptoms of GERD in the otherwise healthy infant without evidence of acid induced disease.³² PPIs have been shown to reduce acid secretion in infants and children⁸¹⁻⁸³ and promote esophageal healing in patients with esophagitis.⁸⁴ Efficacy and safety have been shown for maintenance of remission of chronic, relapsing erosive esophagitis retrospectively up to 11 years.²³ Therefore a PPI is the first choice medication in children with proven GERD with esophagitis. However, side effects include headaches, dizziness, nausea, diarrhea and constipation and PPIs have been associated with an increased risk for gastroenteritis and lower respiratory tract infections.³³

Although PPIs effectively reduce esophagitis, they have not been shown to reduce GER symptoms in infants. This was convincingly shown in a recently published systematic review showing that PPI treatment is not effective for the reduction of GER symptoms in infants³¹ and confirmed by a working group from the FDA.³² Efficacy data on reduction of GER symptoms on PPI treatment in older children is less convincing.

In conclusion, PPIs are the best available acid blocking medication for infants and children. PPIs cause a reduction in esophageal acid exposure and promote healing of the esophageal mucosa, however the use of PPI to reduce symptom of GER in infants or children is not recommended.

PROKINETICS

As discussed above, the role of gastric emptying in GER (disease) is still contro-

versial. A convincing relation between delayed gastric emptying and GERD has never been found. The most well known prokinetic agent is Cisapride, a prokinetic that was regarded as the “drug of choice in chronic and persistent GER in infants and children” by the ESPGHAN until 2000 when it was withdrawn due to cardiac toxicity (prolonged QT interval). Although Cisapride reduces esophageal acid exposure, it has not been shown to be superior to placebo in terms of a reduction in bolus GER.⁸⁵ Currently, other prokinetics such as domperidone and metoclopramide are still commonly prescribed, although a systematic review and the ESPGHAN working group on GERD has concluded that available data do not support its use for GERD in infants and children.⁸⁶ Furthermore, recent data suggest that domperidone, especially in high doses, is associated with an increased risk of sudden cardiac death in adults.⁸⁷

Moreover, recent positioning studies have shown a decrease in GER episodes in the presence of delayed gastric emptying in left side position, a paradoxical finding that contradicts the hypothesis that more rapid gastric emptying will result in a decrease in GER.²⁰

INHIBITORS OF REFLUX TRIGGERING

The above mentioned medical interventions do not alter the underlying mechanism of GER, TLESRs. Over the last decades many efforts have been made to create drugs that reduce the number of TLESRs. One type of TLESR inhibiting agent that has been tested in infants is Baclofen, a GABA_B agonist. GABA plays an inhibitory role in the TLESR reflex-mediated via GABA(B) receptors both at sites of gastric mechanoreceptor transduction and within the central nervous system.

Two randomized trials have been performed in children.^{88, 89} Baclofen significantly reduced the numbers of TLESR and acid GER. Baclofen had no effect on the swallowing rate, pattern of esophageal peristalsis, or lower esophageal sphincter pressure.⁸⁸ Despite these encouraging results,

Baclofen is seldom used for the treatment of GERD in children due to the unfavorable side effects such as but not limited to drowsiness, nausea, respiratory depression and muscle weakness. Baclofen is a centrally active GABA_B agonist and it was thought that peripherally active GABA_B agonists would have less adverse effects. Nevertheless, these agents have been withdrawn from the market to due side effects as well.

Surgery

When patients continue to experience severe symptoms and/or esophagitis despite treatment with high doses of PPI, management is a major clinical challenge. In these patients anti-reflux surgery may be a treatment of last resort. The most commonly performed intervention, fundoplication, is the surgery of choice in most centers. However, the indications for fundoplication are poorly defined in children^{41, 90, 91} and there is no uniformity between hospitals in the approach to infants and children with persisting GERD despite medical treatment with PPI.⁹² Nevertheless, fundoplication is among the most commonly performed pediatric surgeries.

The primary goal of anti-reflux surgery is to reduce GER without inhibiting passage into the stomach of swallowed substances. Different types of fundoplication have been developed according to Nissen (360° fundic wrap around the esophagus), Thal and Toupet (both partial wraps). Traditionally these procedures were performed open, however with advancing technology laparoscopic fundoplications are now more common. Most fundoplication research has been performed in adults because fundoplications are less common in children, patient populations are often heterogeneous and ethical restrictions apply in terms of measurements for research purposes. In adults it has been established that laparoscopic partial fundoplication is effective in terms of reducing GERD and causes less dysphagia, gas bloating and redo surgeries compared to laparoscopic Nissen fundoplication.⁹³

In children, fundoplication has been sub-

ject to discussion. This discussion is ongoing as prospective studies with enough power have not been performed. Laparoscopic partial fundoplication has been suggested to have a lower incidence of post operative complications compared to open or Nissen fundoplication.⁹⁴ In a recently published systematic review on the effects and efficacy of anti-reflux surgery in children with GERD, the authors conclude that fundoplication in children shows a good success rate in terms of complete relief of symptoms and that post operative dysphagia may occur less in partial fundoplications.⁹⁵ However, other authors have made a case for more reluctance in the use of fundoplications.⁹⁰,⁹¹ Di Lorenzo and Orenstein underline the complications inherent to fundoplication and advise careful selection of patients and thorough explanation of possible adverse outcomes to the families.⁹⁰ Hassall has suggested that many children undergo surgery without a firm diagnosis of GERD and without having failed a thorough trial of optimized medical therapy.⁹¹

The applicability of fundoplication has been hampered by the inability to predict which patient may benefit from surgery and which patients are more likely to develop complications such as dysphagia. Several adult studies have evaluated esophageal manometry and esophago-gastric junction characteristics to determine if pressure variables allow prediction of complications,⁹⁶⁻⁹⁸ none of these studies have been conclusive. Rosen et al used impedance to predict fundoplication outcome in children and did not observe any predictive variables.⁹⁹

The latest international guidelines on the treatment of GERD in the pediatric population state that "Antireflux surgery may be of benefit in children with confirmed GERD who have failed optimal medical therapy, or who are dependent on medical therapy over a long period of time, or who are significantly nonadherent with medical therapy, or who have life-threatening complications of GERD. Before surgery it is essential to rule out non-GERD causes of symptoms, and ensure that the diagnosis of chronic-relapsing GERD is firmly established."⁴¹

Conclusions

The definition of GERD in infants, GER with troublesome symptoms or complications is not objective enough to ensure correct identification of patients with GERD. Symptoms that are most indicative for GERD are irritability, crying and regurgitation around feeds. These symptoms are non specific to and poorly correlate with GERD. The introduction of pH-impedance has contributed to a better understanding of GER in infants, GER – symptom associations and it allows assessment of weakly acid GER as well, an important entity in the pediatric population. Nevertheless, the use of pH-impedance is hampered by the fact that there are no normative data, analysis is time consuming and inter observer variability is high. The development of a validated automated analysis will be the first step to solve these issues and will allow availability to a wider public. The new paradigm of impedance baselines being a marker of esophageal mucosal integrity is interesting and future research should determine whether impedance baselines have the potential to select patients who are at risk for having esophagitis and should undergo endoscopy. Another highly novel and interesting development is automated impedance manometry analysis as this is the first esophageal test to assess esophageal function by combining pressure and bolus flow parameters. The AIM analysis may provide more insight in esophageal function and diseases of the esophagus such as dysphagia in the future.

Treatment of uncomplicated infant GERD is becoming more challenging because PPIs have been shown not to be effective for the reduction of symptoms. Indeed, PPIs are still the drug of choice for proven esophagitis, however uncomplicated GERD is best treated with non pharmacological interventions and parental guidance. TLESR inhibitors seem to be promising agents, although the adverse event profiles of the currently available agents, prevent widespread use in infants and children. Surgery may be considered as a treatment of last resort although indications for surgery are not defined and

none of the esophageal function tests has the ability to predict which patients may experience complications after surgery.

Riassunto

Reflusso gastroesofageo in pediatria; fisiopatologia e nuovi elementi di conoscenza per la diagnosi e il trattamento

Il RGE è il passaggio di contenuti gastrici nell'esofago e viene denominato come malattia da reflusso gastroesofageo (MRGE) quando il RGE è fonte di sintomi e/o complicanze fastidiose. La MRGE nei lattanti e nei bambini è spesso difficile da diagnosticare e ancor più difficile da curare. La diagnosi di MRGE è ostacolata dal fatto che i sintomi del RGE come l'irritabilità e il pianto, il rifiuto del cibo e il rigurgito sono problemi comuni nei lattanti. Inoltre, tali sintomi non sono esclusivi della MRGE. I criteri diagnostici per la diagnosi obiettiva di MRGE con i test diagnostici comunemente utilizzati quali la pH-metria, la pH-impedenziometria e l'endoscopia sono scarsamente o per nulla definiti. Nella presente rassegna discuteremo dell'attuale comprensione della fisiopatologia della MRGE, dell'anamnesi nei lattanti e nei bambini, dei nuovi elementi di conoscenza nelle modalità diagnostiche e del ruolo degli interventi farmacologici e non-farmacologici.

Parole chiave: Reflusso gastroesofageo - Pediatria - Esofago.

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