Gastroesophageal Reflux in Children

Yvan Vandenplas
Editor

Second Edition

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Introduction

Dear reader,

Thank you for reading this book on gastroesophageal reflux (disease) in children. This second edition was made possible thanks to the success of the first edition. The second edition was extensively revised but still provides a comprehensive overview of almost all aspects of Gastroesophageal Reflux (Disease) in children. There are chapters on the epidemiology and pathophysiology of the condition. Multiple diagnostic methods and treatment techniques are also covered. Profoundly revised chapters discuss several aspects associated with GER in defined patient populations. The chapters on diagnosis and management are also extensively updated. New chapters cover new knowledge on the microbiome, how nutrition can be key to treatment. Much attention is also given to adverse effects of medical treatment. Attention is also given to colic and new developments in eosinophilic esophagitis are also described. GER in preterm infants, neurologic patients, and children with cystic fibrosis is discussed as well. An important part of the book is dedicated to therapeutic approaches from medication to surgery and alternative approaches such as complementary medicine and hypnotherapy.

This Second Edition on Gastroesophageal Reflux in Children was made possible thanks to all co-authors who realized outstanding contributions. Without their tremendous work, this book would not have been possible. Thanks to their work, this book offers you an up-to-date overview of all aspects of Gastroesophageal Reflux disease in children. This book has the intention to be a critical resource for pediatricians, gastroenterologists to pulmonologists, otolaryngologists, and neurologists

Me and all co-authors do hope that you will enjoy the content of our book.

Yvan Vandenplas

Contents

Epidemiology of GER

1

Silvia Salvatore and Yvan Vandenplas

Abstract

The real prevalence of gastro-esophagel reflux (GER) and GER-disease (GERD) is difficult to estimate, particularly in infants and young children, because of caregiver's interpretation, lack of specific symptoms, proper investigation and a gold standard test, over-the-counter medications, and limited prospective studies. GER episodes may physiologically happen several times per day, especially in postprandial period, without causing any manifestations. In many reports, the terms GER and GERD, that is GER with troublesome symptoms or complications, are often erroneously interchangeably used, hampering the confusion about the real prevalence of these two different conditions. Regurgitation is a common manifestation of GER, occurring in at least 25% of infants, naturally disappearing before the first year of life and representing a functional disorder in the vast majority of cases. Despite it being neither sufficient nor specific, regurgitation is often considered a reliable symptom for the diagnosis of GERD. Conversely, heartburn shows an adequate specificity for GERD in older children and adolescents although sensitivity is poor particularly for extra-esophageal manifestations. Few studies assessed the prevalence of GERD performing upper endoscopy and esophageal pH-impedance and even in these studies, recruitment and diagnostic criteria are heterogeneous. Prospective data off and on GER treatment are also limited in pediatric ages and the rate of progression from GER to GERD is still unclear.

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Nevertheless, a number of studies demonstrated an increased prevalence of GERD in children with neurological impairment, cystic fibrosis, and esophageal atresia. However, individual sensitivity, esophageal clearance, and mucosal resistance determine the severity of symptoms and the presence of complications.

Keywords

Reflux · GER · GERD · Regurgitation · Natural history · Esophagitis · Infants Children

Introduction

The exact prevalence of gastroesophageal reflux (GER) and GER-disease (GERD) which is defined as GER causing troublesome symptoms or complications [1] is unclear in all pediatric ages. The caregiver's interpretation of symptoms, the lack of a specific manifestation of GERD, the complementary diagnostic role of upper endoscopy and esophageal pH-impedance (pH-MII) with no gold standard test, the limited investigations performed in young children, the high heterogeneity of the literature data and the over-the-counter medications determine the difficulty in the epidemiological estimation.

Epidemiological Pitfalls

GER, that is the return of gastric contents into the esophagus, physiologically occurs several times per day in every individual, particularly in postprandial periods and in the first months of life [1–3]. Most reflux episodes are brief and do not cause any manifestation. Regurgitation is the involuntary and effortless progression of GER into and eventually outside the oral cavity [1] and has a peak incidence at 3–4 months of life occurring in more than 25% of healthy infants. The spectrum of GERD presentation is wide and unspecific, including gastrointestinal (regurgitation, vomiting, heartburn, and epigastric pain), respiratory and general (feeding and sleeping problems, crying, irritability, failure to thrive) symptoms. Because these manifestations are age-related and overlap many other functional and organic conditions, the prevalence of GERD cannot accurately rely on a clinical diagnosis except in the case of heartburn that is considered a highly sensitive and specific symptom [1, 4]. Moreover, none of the above symptoms is predictive of esophagitis but only a minority of children are submitted to upper endoscopy and esophageal biopsies.

An impaired quality of life is sufficient to make the passage from GER to GERD in adults but is difficult to report in childhood because it is mainly related to parental perception.

The absence of a gold standard test for the diagnosis of GERD, the limited investigations in infants and children, the heterogeneity of diagnostic criteria used in different studies and the lack of large prospective trials hamper the difficulty to clarify the prevalence of GERD.

The natural history, evolution, and progression of GERD for an individual patient also depend on genetic, environmental, mucosal, and individual factors [5].

European and American guidelines on the diagnosis and management of GER have been published [1, 6, 7] clarifying the diagnostic approach in children. However, under and over-diagnosis of GERD as well as pharmacological overtreatment is still common, especially in infants and young children [8–10].

GER and Regurgitation in Infants

In healthy infants aged 3–4 month, 3–4 reflux episodes of GER are detectable during 5 min of intermittent fluoroscopic evaluation [11]. Esophageal pH-monitoring records a mean range of 31 ± 21 acid reflux episodes within a 24 h period in the first year of life [12] with less than 10% of infants have (acid) GERD [12]. In the last decades, pH-MII has demonstrated that up to 100 reflux episodes may be detected in symptomatic infants during 24 h, with symptoms related to GER only in selected cases [13–16].

In infancy, the most frequent manifestation of GER is regurgitation but is neither sensitive nor specific for GERD. All over the world, a number of studies confirmed that daily episodes of regurgitation are very common in infants, particularly in the first 6 months of age, with a peak incidence at 3–4 months, and resolution, in 90–95% of cases, by 1 year of age [17–36] (Fig. 1.1). Besides the geographical origin, the wide range of prevalence of regurgitation (from 3% to 87%) is mostly related to the different age of subjects, the episodes of regurgitation considered, the cross-sectional or prospective design and cumulative or detailed frequency.

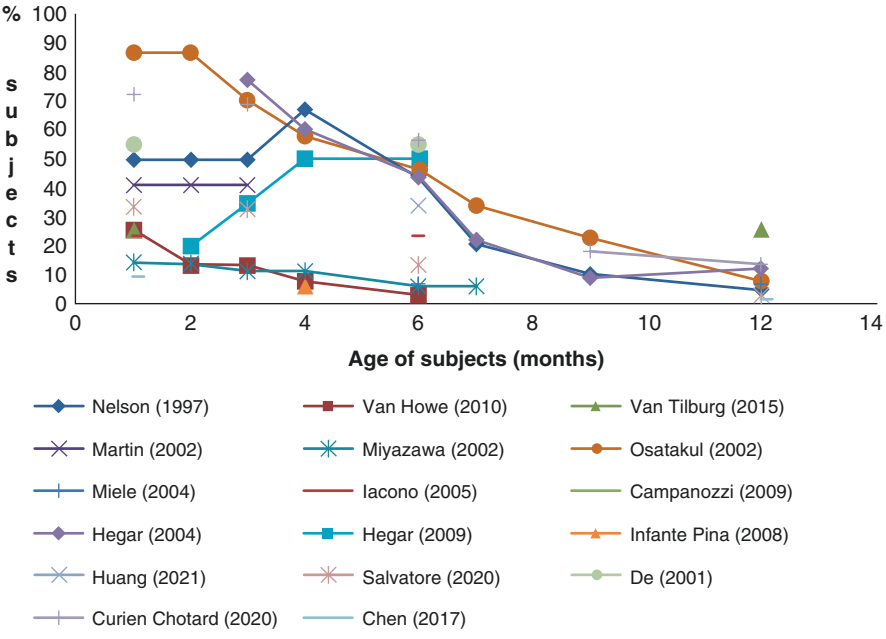

Fig. 1.1 Natural evolution of regurgitation according to the literature data

In 1992, a cross-sectional retrospective study from France [17] early showed that a diagnosis of GER, based on regurgitation, was made in 18% of an unselected population younger than 10 months of age [17].

In the US, at least one episode of regurgitation a day was reported in half infants aged 0–3 months [19], in two-thirds (67%) at 4 months, in one-fifth (21%) between 6 and 7 months of age, and only in 5% subjects aged 10–12 months [19].

In another prospective American cohort study, symptoms of GER were assessed using the Infant Gastroesophageal Reflux Questionnaire-Revised (I-GERQ-R) for 6 months in 128 maternal-infant pairs. Daily regurgitation was reported in 82%, 77%, 83%, and 67% of infants at the 1-month, 2-month, 4-month, and 6-month visits, respectively [30]. A quarter of infants at 1 month and 2.9% at 6 months had GERD based on positive cut-off of the I-GERQ-R [30]. Conversely, in 2017, Chen found reflux symptoms to decrease from 9.2% at the age of 1 month to 1.6% at the age of 12 months [32]. An overall prevalence of infantile regurgitation during the first year of life was 24% according to another parental recall [33].

In Australia, Martin et al. performed a prospective enrolling a large group of 836 neonates followed up for 2 years with a daily symptom diary [22]. The peak incidence of regurgitation was 41% between 3 and 4 months of age with a substantial decline to less than 5% between 13 and 14 months of age [22].

Another cohort in Japan showed that 47% of 1-month old infants had at least one regurgitation or vomiting per day [23], 29% of subjects at 4 months, and 6% at 7 months [23].

In India, 55% of the infants aged 1–6 months had daily regurgitation [20]. In Indonesia, 81% of neonates had daily regurgitation, 77% of infants younger than 3 months [24], 44% between 4–6 months of age, and 9% aged 7–9 months [24].

In Italy, 7% of infants had at least two episodes of regurgitation per day for 3 or more weeks, all improved after 3 months and none had symptoms at 1 year [25]. Among nearly 3000 infants followed by family paediatricians, regurgitation was the most common gastrointestinal complaint with a cumulative incidence of 23%, increased to 30% in infants with low birth weight [26].

Among another cohort of 2642 infants prospectively assessed with Rome II criteria, 300 infants reported infant regurgitation and only one of the 210 individuals who continued the follow-up period of 2 years had developed GERD with endoscopic and histological esophagitis, 9% had used antacids (alginate and/or aluminum hydroxide) and 3% prokinetics (domperidon) [29]. Unfortunately, the high dropout rate (33%) limits the strength of the conclusion on the natural history of GER in this population.

A worldwide survey and expert consensus reported an overall average prevalence of regurgitation of 30% (decreased to 23% when considering more than four episodes of regurgitation a day) [37]. In 2019, a systematic review on the prevalence of GER in infants and young children included 25 studies with a total population of 487,969 children. Among 8553 infants (0–18 months) enrolled in 11 studies, reflux symptoms were present in more than a quarter of infants (26.9%, range 23.1%–40.0%) on a daily basis and show a steady decline in frequency with almost complete disappearance of symptoms at the age of 12 months [38].

A recent Italian prospective study including a large cohort of infants born preterm, treated with antibiotics at birth and born from cesarean section reported 40% regurgitation, mostly occurring in the first 4 months and 60% combined FGIDs throughout the first year of life [39, 40]. A French cohort including 157 full-term neonates revealed the presence of daily regurgitation in 45.7% of subjects and in 72, 69, 56, 18, and 13% of infants at 1, 3, 6, 10, and 12 months of age. Among this group, GERD was estimated, as a positive score (≥16) at the Infant Gastresophageal Reflux Questionnaire-Revised (I-GERQ-R) in 19, 9, 5, 2, and 2% of subjects. Family history of GER and exposure to passive smoking were identified as risk factors. The authors reported that most cases spontaneously resolved but no investigations were performed [35].

In Chinese infants and young children, FGIDs occurred in 27.3% of 2604 total subjects: among the 0–6 months old group the most common disorder was infant regurgitation, reported in 33.9% of subjects [36].

Effect of Feeding

The influence of different feeding on GER has been investigated in a limited number of subjects and still need to be fully clarified. In two studies regurgitation was less present in the exclusive breastfed infants compared to partial breastfed subjects and exclusively formula-fed group [28, 32].

Nevertheless, other reports did not find any significant difference in the rate of regurgitation and vomiting when analyzing the type of feeding [21–23]. The possible reasons for a decreased prevalence of regurgitation in breastfed infants include both a more rapid gastric emptying compared to standard milk formula and less prevalence of cow's milk protein allergy. However, exclusively or partial breastfed infants could present an increased frequency of meals with possible overfeeding compared to the ones with a (more easily to quantify) formula intake.

GERD in Infancy

GERD is much less common in infants than in other age groups, although the real prevalence of this condition is uncertain because symptoms overlap several disorders, severity depends on caregiver interpretation, and most of subjects are not fully investigated [1, 10].

About 20–25% of parents consider a matter of concern and a troublesome symptom requiring medical advice the presence of more than three episodes of regurgitation a day [19, 28], particularly if of large volume or associated with crying or fussiness or back arching [19, 23]. However, only 5–9% of healthy infants showed pathological esophageal acid exposure at pH-monitoring and/or ongoing and troublesome GERD [12, 22]. Even when regurgitation was greater than five times per day the specificity of GERD was 70.9% with a positive predictive value of 22.2% [41]. In another study evaluating 100 infants through a detailed questionnaire (including many items about regurgitation), pH-monitoring was pathological in 21% and histology revealed esophagitis in 39% of subjects submitted to endoscopy,

with no significant correlation among the results of the three diagnostic tools [42]. Similarly, in the last years, no clear correlation between regurgitation or other symptoms and GERD was noted using pH-MII [1, 43].

The available epidemiological data demonstrate that regurgitation naturally and progressively disappear during the first year of life in almost all otherwise healthy infants [38, 44]. However, nutritional or pharmacological intervention is often reported in this age group [1, 8, 9, 17, 19].

Irritability may accompany regurgitation and vomiting but the duration of crying is not related to acid reflux, measured with pH-monitoring [41, 45] or pathological pH-MII [1, 43] or with response to acid inhibitors [46, 47]. Indeed, irritability and crying are common in healthy infants and may occur for many different reasons and conditions thus not been considered sufficient to diagnose GERD and to treat with acid inhibitors [1, 8, 9, 45].

A pH-MII based diagnosis of GERD has been reported in 21–83% of infants with persistent symptoms [42, 43, 48] with nearly 30% of increased rate of detection when non-acid reflux was considered compared to only acid episodes [1, 15, 43, 48, 49].

Histological evidence of reflux esophagitis was found in 23 out of 25 (92%) Indian infants investigated because of a positive score on a GER questionnaire [20]. In another cohort, histological esophagitis was identified in up to 83% of infants with reflux symptoms severe enough to perform endoscopy [50] but only in 39% of another report [42]. In a multicenter retrospective cross-sectional study in the United States using an Endoscopy Database System, emerged that 9.5% of 1 year aged children and 7.6% of 2 years aged had erosive esophagitis [51].

Data on the progression from GER in infancy to GERD later on in life is limited. A prospective follow-up study found the prevalence of feeding refusal, duration of meals, parental feeding-related distress, and impaired quality of life higher in individuals who had infantile regurgitation compared to those who never regurgitated [44]. Another report showed that 40% of children and adolescents (6–17 years) with GERD had GER symptoms in infancy and/or a family history of GERD [52]. Retrospective studies showed that adults with GERD symptoms were more frequently children with symptoms of reflux [53].

GER(D) in Children and Adolescents

A recent systematic review on GER prevalence in children older than 18 months, found that symptoms varied between 0% and 38% among studies, and were present in >10% and in 25% on a weekly or monthly basis [38].

Two studies [54, 55] included children aged 2–18 years and 7–16.9 years and reported weekly symptoms of GERD in a range varying from 2% to 32%, regurgitation 4–7.8%, and heartburn 3–8.5%.

Okimoto et al. reported an overall prevalence of weekly GERD symptoms in children younger than 10 years of 3.2% [56].

In 2000 an American study showed that parents reported approximately 2% of 3–9 years aged children suffer from regurgitation and heartburn [57]. In the group of adolescents (aged 10–17 years), heartburn is present in 3.5% and regurgitation is reported in 1.4%, respectively, with the medication needed in 0.5% of children and in 1.9% of teenagers. According to self-reports, adolescents complain about heartburn in 5.2% and regurgitation in up to 8.2%, while anti-acids are taken by 2.3% and histamine2 receptor antagonists by 1.3% [57].

The prevalence of GERD increases with age and, by adolescence, is considered similar to that in adults (20%) [34].

Based on eight studies enrolling adolescents pooled prevalence of weekly reflux symptoms was 10.1% (95% CI 5.1–15.1%, I2¼24.35) [38]. The lowest prevalence was 0.2% in an Israel study which considered frequent GERD symptoms (>3 times a week in three consecutive months) [58]. The highest prevalence was 18.8%, found in the USA using a purpose-designed symptom questionnaire among high school children [59]. Seven studies reported weekly heartburn or regurgitation, with a pooled prevalence of respectively 6.0% (95% CI 3.6–8.4% I2¼_63.14) and 6.1% (95% CI 4.2–7.9%, I2¼_62.60) [38].

GER symptoms are more frequently reported in children who had frequent regurgitations in infants [22] or persisting after 3 years of life [60] or in the ones who had constipation [61].

In older children, reflux symptoms are frequently relapsing, resistant to complete spontaneous resolution [62, 63]. A recall of 207 children and young adults with esophagitis and no other underlying disorders showed that 10 years after the diagnosis, 80% of the ones who completed the questionnaire reported at least monthly heartburn and/or acid regurgitation, 23% of them at least weekly symptoms, 30% were on acid suppressive agents, and 9% had fundoplication [60]. Assuming that the one who did not respond to the survey were free of symptoms, the incidence of GERD reduced to 31% with monthly symptoms and to 9% of subjects with weekly symptoms [60].

The prevalence of GERD in extraesophageal manifestations is not well established [1, 64, 65].

The accuracy of diagnostic tests (laryngoscopy, endoscopy, and pH- or pH-impedance monitoring) for patients with suspected extraesophageal manifestations of GERD is suboptimal and many patients do not undergo a complete investigation set. Moreover, the paucity of studies, small sample sizes and heterogeneity of GERD definitions, and patients recruitment do not allow to draw firm conclusions about this correlation [64, 65].

Children with GER symptoms present reflux esophagitis in a wide range of 2 up to 62%, with increasing rate with age Barrett's esophagus in 0.1–3% and refractory GERD requiring surgery in 6–13% [1, 51, 63, 66–68]. Esophageal strictures due to GERD with no other comorbidity are rare in children. In Belgrade 218 children, mean ages 6.7 years (range 0.06–18.0 years) were investigated because of reflux symptoms. GERD was diagnosed in 57% by pH-MII and in 34% of children by pH metry alone. Reflux esophagitis was identified in 26% of 119 children who

underwent endoscopy and logistic regression analysis showed that the best predictors of it were the longest acid reflux (≥ 18 min) and a positive reflux composite score [69].

A systematic review on the prevalence and outcome of Barrett's esophagus in the pediatric population revealed 18 articles and 130 patients for analysis with a mean age 10.6 years (0.8–17.2 years). Barrett's esophagus was diagnosed in 80 patients with confirmed GERD only; further 20 patients were neurologically impaired, 13 were born with esophageal atresia and the remaining 17 had other associated conditions. During the follow-up, adenocarcinoma was found in one 23-year-old patient [70]. According to a 15 years retrospective review of 564 Japanese children aged 5–18 years undergoing upper endoscopy for upper gastrointestinal symptoms or anemia, erosive esophagitis or endoscopic Barrett's esophagus increased significantly in the last years (9.8–18.1% for GERD and 2.5–9.6% for Barrett's esophagus) [71].

Patients' selection and criteria to perform endoscopy, definition of esophagitis, and previous treatment with PPI strongly influence these epidemiological data. Children with neurological impairment, cystic fibrosis (CF), and esophageal atresia are known to be children at risk for severe GERD reflux and esophageal complications [1]. However, differences in esophageal mucosal resistance and genetic factors may also impact esophageal complications and symptoms. Hence, the response to treatment, persistence of symptoms, and progression to complications is not accurately predictable for the individual patient. Moreover, the correlation between symptoms and esophageal lesions is poor in children [1, 42, 50, 66, 72].

Nevertheless, frequency, severity, and duration of reflux symptoms have long been significantly correlated to the development of esophageal complications in adults [73]. If early recognition and adequate treatment of GERD in childhood may decrease the rate of complications in adult life is still unknown.

Potential Risk Factors for GERD

Genetic Factors

A genetic influence on GER and GERD is supported by the high frequency of positive family history of GERD noted more than 20 years ago [74]. Moreover, the concordance for GER is higher in monozygotic than dizygotic twins [74]. A locus on chromosome 13q, between microsatellite D13S171 and D13S263, was linked with severe GER disease in five families with multigenerational histories [75], but the same abnormal locus was not found in other families with GERD [76]. Genetic and epigenetic factors are also implicated in the risk of developing esophageal adenocarcinoma and Barrett's esophagus [77] while ethnicity did not appear to be significantly related to GERD according to a recent systematic review [38].

Smoking and Alcohol

Smoking and alcohol abuse should always be avoided because of many severe complications, including increased GER and GERD in adult life [1, 38]. A few studies assessed the effect of passive smoking on GER symptoms or GERD in infancy and childhood with conflicting results [22, 29, 30].

Preterm Infants

Low birth weight was also associated to an increased prevalence of regurgitation [26, 40] and to a positive temporal association between GER episodes detected by pH-MII and cardiorespiratory events [78].

Reflux treatment is frequently administered to premature infants although the diagnosis of GERD is much more often based on symptoms (desaturation, crying, vomiting, feeding problems) supposed to be related to GER than on investigations. Natural history of GER in premature infants is uncertain. Esophageal adenocarcinoma was found to be highly associated (11-fold risk) to preterm and small-for-gestational age birth in one report [79], but not strongly related to birth weight in a subsequent nested case-control study [80].

Comorbidity

Esophageal atresia, diaphragmatic hernia, cystic fibrosis, specific genetic syndrome (i.e., Down syndrome), and severe neurological impairment are significantly associated to GERD that should be promptly recognized and adequately treated to avoid severe clinical and esophageal complications [1]. Noteworthy, young patients with cystic fibrosis show a high prevalence of acid and bile GER, even before respiratory symptoms developed [81]. According to a recent systematic review on these patients reported that approximately half of them had GERD, but published data are limited and heterogeneous in terms of GERD diagnosis and outcomes. In cases submitted to anti-reflux surgery a delay in the deterioration of lung function was noted [82].

The relation between obesity and GERD emerged in adult patients [3] but in pediatric ages has not been completely clarified [3] though a recent systematic review [38] reported that three out of four pediatric studies found a significant association between high BMI and waist circumference and GERD symptoms [54, 55, 58, 83]. In a recent Italian study, 113 obese children aged 4–17 years completed a questionnaire and a selected group underwent investigation. Nearly 40% reported reflux symptoms and gastric emptying time was significantly delayed in obese children with increased reflux events on pH-MII compared to matched asymptomatic no obese children [84]. Eosinophilic esophagitis may have similar presenting symptoms of GERD, may respond to PPI and may also be associated to pathological pH-MII [1, 15]. For these reasons, multiple esophageal biopsies and follow-up in a tertiary center with specific expertise are recommended.

Conclusion

The prevalence of GERD in infants and children is uncertain because there is a wide spectrum of unspecific symptoms of GERD, investigations are limited and empirical treatment is frequent. Regurgitation is the most common symptom of GER in the first months of life with progressive and spontaneous disappearance with increasing age in more than 90% of healthy infants. Except heartburn, no symptom or sign has been significantly related to GERD revealed by esophageal pH-MII and endoscopy. Esophageal mucosal lesions may occur in selected infants and their prevalence highly increase with age and in presence of at-risk conditions such as severe neurological disorders, cystic fibrosis, esophageal atresia, and diaphragmatic hernia.

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Pathophysiology of GER

2

Samuel Nurko

Abstract

The pathophysiology of gastroesophageal reflux disease (GERD) is multifactorial. It usually involves the function of the lower esophageal sphincter and esophageal peristalsis, as well as mucosal changes that result from the presence of the refluxate, and their consequences on pain perception. Transient lower esophageal sphincter relaxation is the most common event associated with reflux, and esophageal peristalsis is necessary to clear the esophagus from the refluxate. Abnormal permeability of the esophageal mucosa can result from reflux, and this may result in increased mucosal permeability that may lead to esophageal damage and pain sensitization. There are specific pathologic conditions that affect the mechanisms responsible for the prevention of GERD, so it is more common in certain populations.

Keywords

Gastroesophageal reflux disease · Transient lower esophageal sphincter relaxations (TLSERS) · Mucosal integrity · Intracellular spaces · Pain sensitization

Gastroesophageal reflux (GER) is a normal physiologic event that occurs multiple times a day, but that frequently evolves into a pathologic entity (gastroesophageal reflux disease (GERD)), when it becomes troublesome and symptomatic or is associated with esophageal damage or extraesophageal problems [1].

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GER is physiologic and more common in infants, and factors that contribute to the more frequent physiologic reflux in the infant include a combination of large fluid intake, a supine position that predisposes to a common immersion of the gastroesophageal junction, compounded by a small esophageal capacity to hold fluids [1–3].

The pathophysiology of GERD is multifactorial [4]. It is related on one hand to lower esophageal sphincter (LES) function and anatomy, and on the other to esophageal events that lead to reflux clearance, mucosal damage, and perception of the refluxate [4, 5]. The LES acts as a barrier to reflux, and the esophageal mechanisms include either (a) peristaltic waves that prevent the reflux from reaching very high toward the mouth and provide clearance of the refluxate toward the stomach and (b) esophageal mucosa and other physiologic events that prevent damage from the refluxate, and contribute to the perception and pain that is associated with reflux [2, 4–6].

In this chapter, we will review the different mechanisms that contribute to the pathophysiology of GERD in the pediatric population.

LES Function

An important part of study of the pathophysiology of GERD in children has focused on understanding the role that the LES plays [4, 7]. Conceptually reflux occurs when the LES pressure is lower than the intragastric pressure, which can occur either because the LES pressure is low, because of inappropriate relaxations or because the abdominal pressure is higher than the LES pressure.

The LES is primarily innervated by the parasympathetic system via the vagus nerve. At basal state, it remains "closed" in tonic contraction because of the excitatory cholinergic pathway. LES relaxation or "opening" occurs as a reflex response to swallowing, pharyngeal stimulation, esophageal distention (spontaneous or provoked), gastric distention, and abdominal strain via the inhibitory nitrergic pathway [6, 8]. It has now been shown in multiple studies that contrary to the initial hypothesis, in the vast majority of children, including premature infants, GER is not related to a decreased tone of the LES [2, 5–10]. The central motor control of the LES is fully developed during the intrauterine stage, although there may be some maturation that occurs in premature babies, until they become full term. All infants (PMA 33–38 weeks) had a high-pressure zone at the LES with a mean pressure of 20.5_1.7 mmHg and swallow-induced esophageal body motility showed a normal peristaltic progression [2, 8, 10].

Gastroesophageal reflux can occur via four main mechanisms. Transient Lower Esophageal Sphincter Relaxations (TLSERs), low LES pressure, swallow-associated LES relaxations, and straining during periods with low LES pressure [4, 8]. It is now known that the predominant mechanism through TLSERs (Fig. 2.1) [2, 4–8] which are relaxations of the LES that are not preceded by swallowing, and they facilitate the retrograde passage of gastric contents into the esophagus [8]. High-resolution manometry is the new gold standard to detect TLSERs. Using HRM,

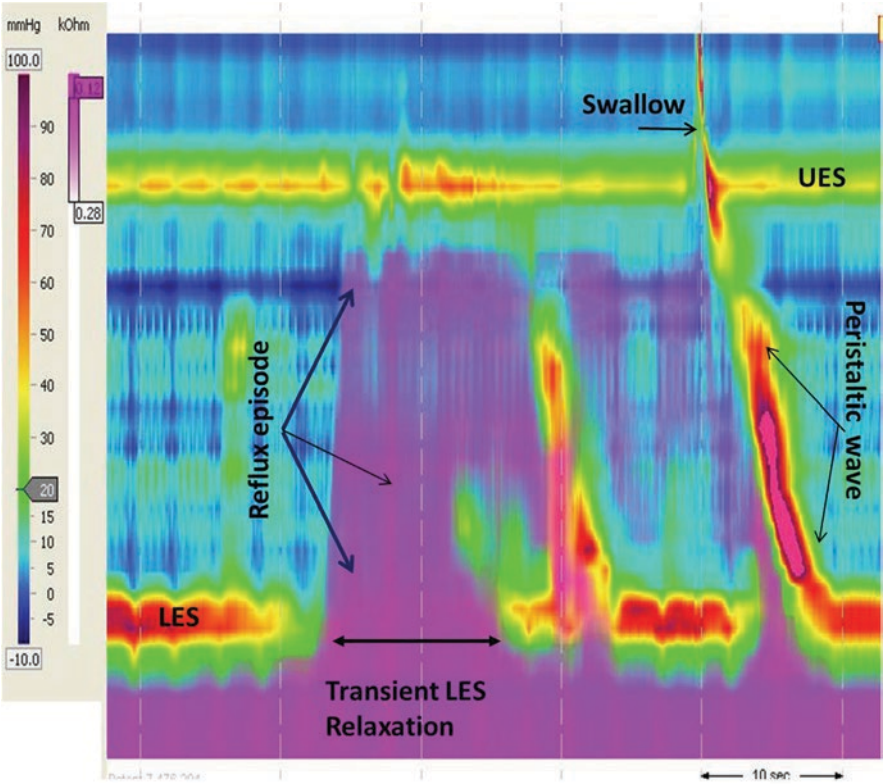

Fig. 2.1 Transient lower esophageal sphincter relaxation (TLSER) with a reflux event. The figure shows a tracing from a high-resolution esophageal manometry with impedance during an episode of gastroesophageal reflux (pink color). The episode is occurring after there is a relaxation of the lower esophageal sphincter that is not associated with swallowing. The reflux episode is followed by a normal swallow that clears the refluxate

TLESR might be defined as LES relaxation occurring in absence of swallowing, lasting more than 10 s and associated with inhibition of the crural diaphragm [11, 12] (Fig. 2.1). Gastric distension is a potent stimulus for TLESR, via vago-vagal pathways [13]. In infants, more TLESRs were triggered when feedings are administered in the right lower position, as compared with the left lateral position [8, 13].

Not all TLSERs are associated with reflux events, and when comparing controls with patients with gastroesophageal reflux disease (GERD) TLESRs do not occur more often in patients with GERD [4, 8, 14, 15]. However, in patients with GERD the TLSERs are more likely to be associated with reflux as compared to healthy controls [16, 17]. The mechanism behind this phenomenon remains largely unknown. The frequency TLSERs that are associated with more reflux is higher when the osmolarity and volume of the meals increases [15]. Most reflux occurs in the postprandial period, although nocturnal reflux has been associated with an increased severity.

An interesting observation has been that even though TLSERs explain why reflux is more frequent in the postprandial period they do not explain why the refluxate is more acidic. The paradox of acid reflux occurring at a time when the intragastric environment is least acidic due to the buffering effect of the meal was unraveled by the discovery of the acid pocket [18]. The acid pocket forms due to the buffering effect of food within the stomach. The acidity falls within the main stomach body where the mixing of food and gastric juice is at its greatest. The proximal stomach relaxes after a meal and acts as a reservoir for food. Acid in this area will therefore escape the buffering effect of the meal [18]. The lack of mixing will also allow gastric juice to pool and form a layer of acid on top of the gastric contents. Therefore, increase reflux during a TLSER may be related to the acid pocket, that reaches more proximally in patients with GERD than in healthy people thereby providing a reservoir of unbuffered acid and gastric contents that will probably reflux whenever the LES fails [18, 19].

The esophageal wall stiffness and the distensibility of the GEJ have been recently measured with the functional luminal imaging probe (FLIP), and studies have shown that there is no correlation between the measurements obtained with the FLIP and reflux monitoring [20].

Delayed gastric emptying has been suggested as another factor that can increase TLSERs and reflux [21], although the evidence that there is an association is controversial and most studies in children do not show a correlation [2, 22].

Exercise has been associated with an increase in the percentage of transient lower esophageal sphincter relaxations (TLESRs) that resulted in reflux significantly increased during exercise and all but one reflux episode occurred during TLESRs [23]. Ingestion of medications or other substances (nonsteroidals, antibtiotics, alcohol), and ingested nutrients (fatty and spicy foods, tomato-based sauces), can also lead to increased TLSERs.

Other LES related mechanisms that have been postulated include a failure in young children of the LES to respond to a sudden increase in intra-abdominal pressure, such as during crying, as well as reductions in intrathoracic pressures, as in bronchopulmonary disease [24], and in a very small percentage of patients that usually have underlying conditions that affect the tone of the smooth muscle, like scleroderma, congenital malformations or other smooth muscle myopathies the basal tone of the LES is low [25].

Other Structural Abnormalities

The antireflux barrier is not only comprised of the LES [4, 5]. The esophagogastric junction (EGJ) functions as an antireflux barrier and consists of the smooth muscle of the LES which is surrounded by oblique gastric fibers. These are anchored to the striated muscle of the crural diaphragm by the phrenoesophageal ligament [4]. The lower esophageal sphincter and the crural diaphragm form a high-pressure zone that functions as an antireflux barrier. Their synergistic function is supported by the angle of His and gastroesophageal flap valve [5]. Therefore, there are other structural and physiologic antireflux mechanisms at the gastroesophageal junction, like

the diaphragm and the phrenoesophageal ligament. In children with reflux disease, the morphology of the LES and cardia may be distorted and demonstrate shortening of the intra-abdominal part of the esophagus, a rounded gastroesophageal junction, and obliteration of the angle of His when assessed by ultrasonography [4, 5, 26]. In patients with a hiatal hernia, the antireflux barrier is compromised as there is dissociation of the internal LES sphincter from the external diaphragmatic crura which leads to sphincter weakening [5, 27]. There is also an increased number of TLSERs [28]. However, in limited pediatric studies it has been shown there was no difference in the prevalence of GER comparing children with or without a hiatal hernia [5, 9].

The body position has an effect on reflux events [5, 8, 29]. Prone and left lateral position resulted in lower acid and nonacid reflux indexes. In addition, studies using esophageal manometry techniques showed an increased number of TLESRs and GER episodes in infants lying in the right-side lateral position [8]. In healthy preterm infants, the right lateral position shows the highest number of liquid reflux events but as it promotes gastric emptying. Therefore, it is still recommended to place infants in the right lateral position for the first postprandial hour and thereafter in the left later to enhance gastric venting and obliterate reflux events [29].

Esophageal Mechanisms

Esophageal Peristalsis

There are some esophageal mechanisms that also participate in the pathophysiology of GERD. These include insufficient clearance, buffering of the refluxate, mucosal abnormalities, and impaired neural protective aerodigestive reflexes [2, 4, 5, 8].

Esophageal clearance of refluxate is directly related to the presence of normal esophageal motility [4, 8, 30]. A normal motility is needed to avoid the possibility of the reflux going high toward the mouth, and to provide a rapid clearance once the refluxate is present [5, 6, 8, 30]. Swallow-induced peristalsis is fully developed at the gestational age of 26 weeks while secondary peristalsis has been described as early as 32 weeks gestation [8]. Postnatal maturation of the peristaltic propagation leads to improved bolus propulsion and transit velocity and continues throughout the infant/toddlers years till childhood [5, 8].

There has been some controversy about whether impaired esophageal motility in patients with severe reflux disease is a primary problem directly contributing to the pathophysiology of the disease or a consequence of the reflux [8, 9, 30, 31]. Theoretically, esophageal mucosal inflammation may affect nerves and muscles that alter LES function and esophageal body motility. A vicious cycle of inflammation and impaired motility may cause progressive disease [9, 31]. It has been shown that in patients with GERD there may be subtle alterations in esophageal peristalsis [9, 30], although most patients have normal esophageal motility. These mild abnormalities have been found in some studies not to be related to the presence of esophagitis, suggesting there may be an underlying motility disturbance in children with GER [9, 31].

In children with GERD, there is a higher incidence of nonspecific esophageal motility defects during primary peristalsis and their prevalence increases with disease severity [5]. Children with erosive disease present with a 30–50% decrease in pressure wave amplitude indicating impairment of the esophageal contractile vigor [32]. Clearing efficacy is achieved with primary peristalsis in 70.86% of pediatric nonerosive reflux disease (NERD) versus 52.08% of pediatric GERD and with secondary peristalsis in 45.45% of pediatric NERD and 20% of pediatric [32]. Similar abnormalities in secondary peristalsis in GERD patients have been described in adults [30]. These abnormalities are increasingly recognized as important in the genesis of delayed refluxate clearance [30], as they contribute to the maintenance of an empty esophagus by clearing refluxed gastric contents or residual food bolus after a failed primary peristalsis or after a reflux event.

In patients with severe motility dysfunction, as is observed in children with esophageal atresia [33] or patients with scleroderma [25], the abnormal motility predisposes to delayed clearance and more esophagitis.

Esophageal chemical clearance is aided by saliva. Saliva contains bicarbonate, which buffers acid, and growth factors, such as epidermal growth factor, which promotes mucosal repair and defenses [4]. Esophageal clearance with saliva has recently been measured indirectly with Impedance monitoring by using the postreflux swallow-induced peristaltic wave (PSPW) [34], which is a clearing wave originating in the upper esophagus that reaches the lower esophagus, and occurs within 30 s after the end of a reflux episode. It has been suggested that it reflects salivary clearance of a reflux episode. The PSPW has been shown to separate erosive reflux disease patients, from nonerosive reflux patients, and non-GERD patients including functional heartburn [34, 35]. These suggest that abnormal chemical esophageal clearance may play a role in the pathogenesis of GERD.

Esophageal Mucosa Defense

The esophageal mucosa has defense mechanisms that are designed to protect it from excessive acid exposure. The esophageal lumen is protected from transient acid exposure by the buffering action of bicarbonate coming from saliva and esophageal submucosal glands, as well as the clearing action of gravity and esophageal peristalsis [4, 5]. Mucosal defense mechanisms may be overcome by prolonged exposure of the esophageal mucosa to a pH <4 that may lead to severe and complicated esophagitis. Acid is not the only component of the refluxate, as gastric contents also include pepsin, and even bile, or pancreatic and duodenal enzymes.

It has been shown that the combination of acid and proteolytic enzymes causes more esophageal damage than acid alone. Decades-old experiments performed on cats showed pouring hydrochloric acid with a pH 1.3–2.0 into the esophagus for 1 h did not cause acute esophagitis. However, solutions of the same pH that also contained pepsin led to the development of esophageal erosions. However, studies show that the levels of pepsin in gastric juice and the maximum output of pepsin are not different in patients with or without esophagitis [36]. Generally, the intact

epithelium is protected from pepsin-mediated damage if the refluxing pH is greater than 5. The role that bile plays is also controversial. The presence of duodenogastroesophageal reflux alone as measured by bilirubin content did not produce esophagitis in partial gastrectomy patients. Patients with both acid and duodenal content in the esophagus had a high frequency (67%) of esophagitis and duodenogastric reflux is more common in GERD patients with stricture or Barrett's esophagus. Therefore, as with pepsin, the presence of acid in the gastroesophageal refluxate is required for the duodenal content to have its potential deleterious effect on the production of esophagitis. Recent experimental evidence suggests that bile may indeed have a role [37, 38]. Recent animal studies have shown that bile produces dilatation of the intracellular spaces in esophageal epithelium [37–39].

Mucosal Integrity

Problems in mucosal integrity have been identified histologically by measuring intercellular space [40], in vitro [41] by measuring permeability and electrical resistance, and by using baseline esophageal impedance values in vivo [5, 42].

The impaired mucosal integrity was initially suggested by histological findings that showed dilated esophageal intercellular spaces (ISD) in patients with GERD [5]. Increased ISD have been shown to represent an early morphological marker of reflux injury in the esophageal epithelium [40, 41, 43, 44]. Changes have been shown to be independent of visible erosions, and have been shown both in erosive (ERD) and nonerosive reflux disease (NERD) [40–44]. Experimental models initially showed that DIS dilation occurred as a consequence of acid peptic injury to the esophageal epithelial cells [37]. Recently it has been shown that continuous exposure of the esophageal mucosa to both acidic and weakly acidic solutions can impair mucosal integrity inducing identical morphological changes to those observed after perfusion with acid solutions [37]. Abnormal DIS in patients with erosive esophagitis has been shown to normalize following antisecretory therapy [41].

In vitro measurements of mucosal integrity using different methodologies have shown abnormalities in animal models, and patients with GERD [5, 41]. With the use of *Ussing chambers, to evaluate* transepithelial mucosal resistance and permeability it has been shown there is increased permeability and decreased mucosal resistance in patients with GERD. Those abnormalities correlate to the degree of acid exposure and exposure to other gastric contents [37, 39], and are reversible with successful therapy [41].

Baseline esophageal impedance values have been correlated with in vitro measurement of mucosal integrity using a Ussing Chamber, so they provide a validated tool [42]. Studies in experimental animals have shown that in vivo esophageal perfusion with an acid solution decreased the transepithelial resistance and increased the paracellular permeability in vitro, which were in turn associated with dilated ISD, supporting the hypothesis that measurement of esophageal transepithelial epithelial resistance in vitro might provide useful information on the esophageal

mucosal integrity. Baseline impedance values in patients with GERD are low, while they are high in normal healthy volunteers [45, 46]. Baseline impedance values correlate with esophageal acid exposure time, and low impedance values have been shown in patients with severe esophagitis, Barrett's, and patients with nonerosive reflux disease [5, 42, 44–46]. More importantly previous findings have shown that the baseline impedance levels increase in response to PPI treatment [40, 41, 43, 44]. Adult patients with NERD have lower baseline mucosal impedance than controls and patients with functional heartburn (FH) while greater sensitivity to acid is observed in patients with lower baseline impedance [5]. In pediatrics, baseline impedance shows a negative association with acid exposure and is predictive of erosive esophagitis [45, 46].

The relationship between mucosal impedance and DIS is not so clear, and recent pediatric studies have shown that the distal baseline impedance in children with GERD did not correlate with the degree of ISD [44], suggesting they may be measuring different aspects of esophageal function.

Sensation

Not all patients with GERD have symptoms, and many patients with GERD symptoms do not have excessive acid exposure [4, 5]. The mechanisms that lead to the perception of the refluxate or to symptoms are not well understood, but multiple factors may influence them. In neonates the strongest stimulus for symptom generation was volume and this was independent of GERD severity as expressed by means of esophageal acid exposure time. Water and apple juice, stimulating osmoreceptors and chemoreceptors, respectively, produced more cardiorespiratory symptoms compared with air, stimulating mechanoreceptors [47]. No similar studies are available in older children.

Sensory abnormalities have become more important in recent years with the recognition of reflux-related entities that are mostly sensory in nature, like functional heartburn, or reflux hypersensitivity [4, 5, 41, 44, 48–50]. It has become evident that an important underlying mechanism in patients with esophageal symptoms is the presence of esophageal hypersensitivity [4, 5, 41, 44, 48, 50].

Esophageal sensitivity is determined by both peripheral and central mechanisms [4, 5]. It has been hypothesized that this enhanced esophageal sensitivity for reflux in GERD patients is caused by the impaired mucosal integrity that has been described in GERD [41, 43, 44]. It is important to note that in recent studies both in children [40, 42] and adults [41] it was shown that there is no correlation between reflux severity or the reversal of the mucosal changes after therapy, and the perception of symptoms, suggesting that the enhanced sensitivity to reflux episodes is not only explained by increased mucosal permeability [41]. It has been hypothesized that this impaired mucosal integrity enables the refluxed material to reach the sensory nerve endings through dilated intracellular spacing, activating chemosensitive nociceptors which in turn transmit signals via the spinal cord to the brain resulting in symptom perception, and pain sensitization [40–42]. Therefore, pain sensitization can occur both at peripheral and central levels.

Peripheral sensitization can occur after excessive stimulation of the peripheral receptors of the afferent nerve endings can lead to an upregulation of these receptors through the release of intracellular inflammatory mediators and thus lead to a reduced threshold of transduction [48, 50]. For example, the infusion of acid reduced the esophageal pain threshold in patients with noncardiac chest pain, and after acid infusion into the distal esophagus, pain thresholds in both acid-exposed distal esophagus and nonexposed proximal esophagus were reduced in patients and healthy controls [51].

Furthermore, the decreased pain threshold in patients with GERD-related noncardiac chest pain was increased after proton pump inhibitor (PPI) treatment [51].

It is also not clear if the distribution of mucosal nerve fibers differs when comparing patients with NERD or GERD. In a study of adults it was shown that proximal and distal esophageal mucosa of patients with NERD have more superficial afferent nerves compared with controls or patients with GERD, suggesting that acid hypersensitivity in patients with NERD might therefore be partially explained by the increased proximity of their afferent nerves to the esophageal lumen [52]. However, a recent study in children demonstrated that the mucosal innervation in children with NERD is similar to controls, with deep-lying nerve fibers both in the proximal and distal esophagus [53].

Various receptors have been found to be involved in peripheral sensitization, including the transient receptor vanilloid 1 (TRPV1) receptor, the TRPV4- and the TRPA1-receptor, the acid-sensitivity ion channels, and the purinergic (P2X) receptors [4, 5, 52, 54]. TRPV1-receptor expression is higher in the inflamed esophageal mucosa. It has been proposed that TRPV1 activation due to acid-induced inflammation results in the synthesis and release of substance P and calcitonin gene-related peptide from submucosal neurons and of platelet-activating factor by the epithelial cells [54], which are pro-inflammatory mediators thus promoting further inflammation which could lead to increased mucosal permeability and further peripheral sensitization [4, 5, 50].

Central mechanisms, attributed to altered processing of afferent signals from the esophagus, have also been implicated. Recent studies suggest that esophageal pain and heartburn perception in some patients with functional heartburn, or esophageal hypersensitivity may also be due to *central sensitization* [55]. Acid stimulation of the esophagus can sensitize the insula and cingulate cortex to subliminal and liminal non-painful mechanical stimulations [50, 55]. The suggested mechanism is that enhanced nociceptor input results in repetitive signaling cascades in the spinal dorsal horn neurons which subsequently lead to facilitated excitatory synaptic responses and depressed inhibition, resulting in amplified responses to both noxious and innocuous inputs [50, 55]. Interestingly, using fMRI it was found that the same stimulus was perceived more intensely during a negative emotional context and was associated with increased cortical activity in the anterior insula and the dorsal anterior cingulate gyri than during a neutral emotional context [56]. Moreover, it has been demonstrated that acid exposure in GERD patients leads to a more rapid and greater cerebral activity than in healthy controls [4, 5, 50].

This sensitization effect can be modulated by drug manipulation. In a controlled study of healthy subjects, citalopram, a selective serotonin reuptake inhibitor (SSRI) given intravenously, significantly increased sensory thresholds and prolonged the time for the perception of heartburn after acid infusion. In randomized trials, SSRIs were shown to be effective in the treatment of patients with hypersensitive esophagus [57].

Special Patient Groups

There are certain patient groups at increased risk of GERD and its complications, and they will be discussed in detail in their respective chapters. Overall, neurologic impairment, and cerebral palsy, in particular, are one of the most common conditions that predispose patients to severe GERD [4, 5, 8, 58, 59]. Several studies confirmed the high prevalence of reflux esophagitis and pathological pH monitoring in NI children [9, 58, 59]. Some chromosomal abnormalities, like Cornelia de Lange [60], are associated with severe GERD. Patients with certain congenital esophageal abnormalities, such as repaired esophageal atresia or congenital diaphragmatic hernia are also associated with an increased risk of GERD [5, 8, 61]. An increased prevalence of GERD and its complications has also been reported in patients with chronic pulmonary disease, including cystic fibrosis [62].

The association between GERD and obesity has also been reported and total and abdominal obesity are risk factors for the development of GERD in children. Large epidemiological studies have demonstrated that obesity is an important risk factor of GERD [63, 64]. Pathophysiological mechanism in obesity includes lower esophageal sphincter abnormalities, increased risk of hiatal hernia, and increased intragastric pressure [64].

Conclusion

The pathophysiology of gastroesophageal reflux disease (GERD) is multifactorial. It usually involves the function of the lower esophageal sphincter and esophageal peristalsis, as well as mucosal changes that result from the presence of the refluxate, and their consequences on pain perception. A better understanding of the different mechanisms will lead to better and more specific therapies.

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Symptoms of GER

3

Paolo Quitadamo and Annamaria Staiano

Abstract

Gastroesophageal reflux (GER) is defined by the passage of gastric contents into the esophagus. GER is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals last <3 min, occur in the postprandial period, and cause few or no symptoms. Conversely, gastroesophageal reflux disease (GERD) is present when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications. Distinguishing physiologic GER from GERD may often be tricky, especially in infants. Indeed, in the first months of life, GER usually underlies recurrent regurgitation and vomiting, mainly due to anatomic features and liquid feeding. These symptoms, along with persisting crying and irritability, are often a source of anxiety for parents. Clinicians should be aware that the vast majority of these spitting infants does not deserve diagnostic test, and GERD should be suspected only when alarm signs arise.

Unlike infants, children and adolescents do not usually experience any relevant symptom related to physiologic GER. Therefore, in these age groups symptoms such as vomiting, heartburn, and chest pain should not be overlooked, and a diagnostic work-up is advisable. Only in older children and adolescents, an empiric acid-suppressive trial may be recommended. Respiratory symptoms,

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such as cough, wheezing, and hoarseness, may also be associated with GERD, being sometimes the only "atypical" presentation of the disease.

Keywords

Gastroesophageal reflux · Gastroesophageal reflux disease · Regurgitation Vomiting · Irritability · Heartburn · Chest pain · Typical GERD presentation Atypical GERD presentation · Respiratory symptoms

Introduction

Gastroesophageal reflux (GER) is a normal physiologic process occurring several times per day in healthy infants, children, and adults. It is defined as the passage of gastric contents into the esophagus, with most episodes lasting <3 min, occurring in the postprandial period, and causing few or no symptoms [1]. Conversely, gastroesophageal reflux disease (GERD) is diagnosed when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications [2].

A proper diagnosis of these two conditions, besides other possible conditions mimicking GER, is crucial in order to target the treatment, avoiding the overuse of acid-suppressive drugs which currently represents a major source of concern. Reflux symptoms may vary widely according to age and distinguishing physiologic GER from GERD may often be tricky. The clinical picture alone is frequently nonspecific and does not allow, except in older children and adolescents, to settle the actual need for acid-suppressive medications. Therefore, instrumental diagnostic tests, such as combined esophageal multiple intraluminal impedance and pH monitoring and upper gastrointestinal endoscopy, are often requested.

The typical presentation of GERD includes the following symptoms: recurrent regurgitation, vomiting, weight loss or poor weight gain, excessive crying and irritability in infants, ruminative behavior, heartburn or chest pain, hematemesis, and dysphagia. Besides these esophageal symptoms, there is a set of extra-esophageal symptoms, mainly respiratory, which may occur along with typical symptoms or may represent the only clinical picture of GERD: odynophagia, wheezing, stridor, cough, hoarseness, dental erosions and apnea/apparent life-threatening events. Moreover, GERD may underlie other signs or conditions, such as impaired quality of life, food refusal, persisting hiccups, abnormal posturing/Sandifer's syndrome, anemia, and bradycardia. Finally, esophagitis, Barrett's esophagus, and esophageal adenocarcinoma are possible acknowledged and worrisome long-term outcomes, especially when GERD is undiagnosed or untreated.

As already reported, all the abovementioned signs and symptoms are variously prevalent and relevant in the different pediatric age groups. Therefore, GERD clinical pictures of infants, children, and adolescents will be treated in separate paragraphs.

Clinical Picture of Physiologic GER and GERD in Infants

Physiologic GER is very common in infants, especially during the first 6 months of life. About 70% of healthy infants show regurgitation, vomiting, and irritability several times per day, and in about 95% of them these symptoms disappear without intervention by 12–14 months of age [3, 4]. The term "happy spitter" has been used to identify these subjects, in order to emphasize the benignity of such condition. Regurgitation occurs more frequently in infants than in adults because of the large liquid volume intake, the limited capacity of the stomach and esophagus, and the prolonged horizontal position of infants [5, 6]. Reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response, causing forceful expulsion of gastric contents through the mouth. Vomiting associated with reflux is probably a result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents.

Unlike physiologic GER, GERD is very rare in infants and should be suspected only in the presence of warning signals (Table 3.1). A proper diagnosis of GERD should rely on instrumental testing, such as combined esophageal multiple intraluminal impedance and pH monitoring and upper gastrointestinal endoscopy. Indeed, no symptom or cluster of symptoms has been shown to reliably predict complications of reflux or to predict those infants likely to respond to therapy. Therefore, the major role of history and physical examination in the evaluation of purported GERD is to rule out other more worrisome disorders that present with similar symptoms

Table 3.1 Warning signals requiring investigation in infants with regurgitation or vomiting

Bilious vomiting
Gastrointestinal bleeding
Hematemesis
Hematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Macro-/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

(especially vomiting) and to identify possible complications of GERD. Parent-reported questionnaires based on clusters of symptoms have been developed in the last decades. *Orenstein* et al. developed a diagnostic questionnaire for GERD in infants, in which a score >7 (of possible 25) demonstrated a sensitivity of 0.74 and a specificity of 0.94 during primary validation [7]. The questionnaire has undergone several revisions [8]. The questionnaire has been shown to be reliable for documentation and monitoring of reported symptoms. However, when applied to a population in India, it had a sensitivity and specificity of only 43% and 79%, respectively, compared with pH monitoring results [9]. In another study of infants referred for symptoms of reflux disease and controls, the questionnaire had a sensitivity and specificity of 47 and 81% for a RI >10% and 65 and 63% for a reflux index >5%. The questionnaire score failed to identify 26% of the infants with GERD. The score was positive in 17 of 22 infants with normal biopsies and pH studies and in 14 of 47 infants with normal pH studies. No single symptom was significantly associated with esophagitis [10]. In another study, the questionnaire was unable to identify a group of infants responsive to proton pump inhibitor (PPI) therapy [2].

The concept that infant irritability and sleep disturbances are manifestations of reflux is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy [11–14]. Although one study in infants showed a correlation between infant grimacing and episodes of reflux [15], multiple other studies have shown no relationship between crying and GERD determined by esophageal pH testing [16–19] or the presence of esophagitis [17, 20]. Therefore, neither regurgitation and vomiting nor irritability and excessive crying, regardless of their extent and their severity, are sufficient to diagnose GERD. GERD should be suspected in infants with these symptoms but none of the symptoms are specific to GERD alone.

Although reflux does occur physiologically in most infants, clinicians should be aware that there is a continuum between physiologic GER and GERD leading to significant symptoms, signs and complications. The vast majority of these spitting and crying infants suffer from physiologic GER (also called infant regurgitation), a benign condition with a good prognosis, needing no other intervention than parental education and anticipatory guidance, and possible changes in feeding composition. Overfeeding exacerbates recurrent regurgitation [5]. Thickened or anti-regurgitation formulas decrease overt regurgitation [21]. Only a small proportion of symptomatic infants may deserve an instrumental diagnostic assessment for GERD or other GERD-mimicking diseases.

Clinical Picture of GERD in Young Children

Whether of new onset or persisting from infancy, physiologic regurgitation, episodic vomiting, or regurgitation followed by swallowing of refluxate in the mouth is less common in children older than 18 months of age and deserves an instrumental evaluation to diagnose possible GERD and to rule out alternative diagnosis [2]. Besides regurgitation and vomiting, GERD may present in children with many other signs or

symptoms, the most frequent of which are heartburn, food refusal, dysphagia, persisting hiccups, feeding or sleeping disturbances, impaired quality of life, failure to thrive and dental erosions. Respiratory symptoms, such as chronic cough, wheezing, hoarseness, laryngitis, ear problems, aspiration pneumonia, chronic asthma, and sinusitis, are atypical symptoms possibly associated with GERD. Nevertheless, the paucity of clinical studies, small sample sizes, and varying disease definitions do not allow firm conclusions about their association with reflux to be drawn [22].

According to the latest NASPGHAN-ESPGHAN pediatric GER guidelines, subjective symptom descriptions are unreliable in children younger than 8–12 years of age, and many of the purported symptoms of GERD in children are nonspecific. A five-item questionnaire developed for children showed a sensitivity of 75% and a specificity of 96% compared with pH monitoring during primary validation [23]. No subsequent independent confirmatory validation has been performed. Other diagnostic questionnaires, such as the GERD symptom questionnaire [24], have not been compared with objective standards like endoscopy, pH monitoring, or esophageal multiple intraluminal impedance monitoring. Some researchers have used questionnaires to monitor symptoms of children during GERD therapy [16]. Whether this method is preferable to monitoring, individual symptoms are uncertain. Although daily symptom diaries are frequently used in adults to monitor the effects of therapy, these have not been validated in children.

Therefore, a clinical diagnosis based on a history of heartburn cannot be used because these individuals cannot reliably communicate the quality and quantity of their symptoms. According to expert opinions, although the verbal child can communicate pain, the description of quality, intensity, location, and severity is generally unreliable until at least 8 and possibly 12 years of age [25–29]. GERD testing may include upper GI endoscopy and/or esophageal pH/MII and/or barium upper GI series. The diagnosis of GERD should be inferred when tests show excessive frequency or duration of reflux events, esophagitis or a clear association of symptoms and signs with reflux events in the absence of alternative diagnoses (Table 3.2).

Clinical Picture of GERD in Older Children and Adolescents

In older children and adolescents heartburn, chest pain, and regurgitation are the typical symptoms of GERD. According to expert opinion, the description and localization of these symptoms are a reliable indicator of GERD in this age group, and an empiric acid-suppressive trial may be indicated regardless of an objective assessment of reflux. This approach is mainly driven by adult studies. One study found that dominant heartburn had a positive predictive value of 81% for GERD determined by pH study [30], even if other studies have not confirmed this close association between history and test results [31]. Esophageal pH probe results are normal in one-third of adults with chronic heartburn, even those whose heartburn is reproduced by esophageal acid perfusion and those who respond favorably to antacids. Nevertheless, some adults with heartburn and normal pH studies have endoscopically proven esophagitis [31].

Table 3.2 Differential diagnosis of vomiting in infants and children

Gastrointestinal obstruction
Pyloric stenosis
Malrotation with intermittent volvulus
Intestinal duplication
Hirschsprung disease
Antral/duodenal web
Foreign body
Incarcerated hernia
Other gastrointestinal disorders
Achalasia
Gastroparesis
Gastroenteritis
Peptic ulcer
Eosinophilic esophagitis/gastroenteritis
Food allergy
Inflammatory bowel disease
Pancreatitis
Appendicitis
Infectious
Sepsis
Meningitis
Urinary tract infection
Pneumonia
Otitis media
Hepatitis
Metabolic/endocrine
Galactosemia
Hereditary fructose intolerance
Urea cycle defects
Amino and organic acidemias
Congenital adrenal hyperplasia
Renal
Obstructive uropathy
Renal insufficiency
Toxic
Lead
Iron
Vitamins A and D
Medications—Ipecac, digoxin, theophylline, etc.
Cardiac
Congestive heart failure
Vascular ring
Others
Pediatric falsification disorder (Munchausen syndrome by proxy)
Child neglect or abuse
Self-induced vomiting
Cyclic vomiting syndrome
Autonomic dysfunction

Along with heartburn and chest pain, many other signs and symptoms may occur in older children and adolescents, such as epigastric pain, regurgitation, dysphagia, impaired quality of life, food refusal, anorexia, sleeping disturbances, and dental erosions. Moreover, likewise, infants and younger children, even older children**,** and adolescents may experience respiratory symptoms as the only manifestation of GERD. Among these, the most relevant symptoms complained are chronic cough, wheezing, and hoarseness.

Several studies indicate a significant degree of overlap between GERD and functional dyspepsia (FD) [32, 33]. According to the latest Rome diagnostic criteria for pediatric functional gastrointestinal disorders, FD is defined as "a feeling of persistent or recurrent pain or discomfort in the upper abdomen, most often aggravated by meal ingestion, not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome) when no physical or organic cause for the symptom is identified with conventional testing" [34]. A defective accommodation reflex leading to a reduced postprandial relaxation of the fundus has been suggested as an underlying mechanism for FD in adults [35]. In FD, there is an abnormal intragastric distribution of food, with preferential accumulation in the distal stomach 6–8. It is unclear whether the symptoms are generated by distension-induced activation of the mechanoreceptors in the fundus or in the antrum.

However, clinicians should carefully approach upper GI symptoms, being aware that the current scientific literature on the overlap between GERD and FD is affected by considerable heterogeneity in terms of the criteria and diagnostic procedures used to assess both conditions. To exclude GERD, patients must undergo upper digestive endoscopy and/or pH monitoring and/or an empiric acid-suppressive trial. A lack of correspondence between symptoms and reflux episodes, together with normal acid exposure in the distal esophagus, would suggest a diagnosis of FD.

Finally, clinicians should be aware that other causes of heartburn-like chest pain including cardiac, respiratory, musculoskeletal, medication-induced, or infectious etiologies should be considered besides GERD.

Overview on GERD and Respiratory Symptoms

As abovementioned, GERD may also underlie respiratory symptoms, such as chronic cough, odynophagia, wheezing, stridor, and hoarseness. Although the role of GERD in the pathogenesis of respiratory symptoms in adults is widely accepted [36], in children there is less evidence to support this relationship [37, 38]. Several pathogenetic mechanisms have been proposed to explain the link between GERD and respiratory symptoms, including aspiration of acid gastric contents into the upper airways, vagal reflex induced by the presence of acid in the esophageal lumen, and sensitization of the central cough reflex [2, 39].

Recent advances in the pathogenesis of reflux-induced respiratory symptoms have followed the introduction in clinical practice of MII-pH, which is available for pediatric use since 2002 [40]. Combined esophageal pH and impedance

monitoring offers several advantages over a standard pH assessment, such as the ability of detecting nonacid reflux events, recognizing swallows from authentic reflux episodes, determining the height and composition of the refluxate (liquid, gas, or mixed), assessing the bolus clearance time, and measuring symptom association with reflux (symptoms association probability, SAP) even while the patient is taking acid-suppressive medication [41]. Thanks to pH-impedance studies, several authors have recently emphasized the role of nonacid and weakly acid reflux [42–49]. Furthermore, a recent systematic review by Chang et al. showed that a significant number of patients with GERD-related respiratory symptoms do not report improvement despite aggressive acid-suppressive therapy [50] thus supporting the hypothesis that respiratory symptoms are less related to acidity than GI symptoms.

In conclusion, the analysis of the medical literature concerning the relationship between GERD and respiratory symptoms highlights a large body of evidence often discordant and conflicting, which almost never allows to draw firm conclusions to be used in clinical practice. The reason for this variability of the study results is probably linked to the poor methodological quality of the clinical trials that often lack a perspective design, a rigorous sampling, a comparison group, and accurate diagnostic criteria of the different analyzed conditions. In addition, the use of relatively recent diagnostic methods, such as esophageal impedance, allowed to investigate for the first time the alkaline or weakly acid reflux, downsizing the role of acidity in the genesis of lung problems and contradicting the results of numerous studies solely based on the finding of acid reflux pH-metric.

Over the next years the use of pH-impedance, combined with manometry or with cardiorespiratory monitoring, in longitudinal, double-blind, placebo-controlled, clinical trials will help clarify the main pathophysiological aspects that link, with currently still little know modalities, GER and respiratory system, providing the clinician with a fundamental scientific basis for diagnostic and therapeutic choices.

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Dysphagia and GER

4

Valeria Dipasquale and Claudio Romano

Abstract

Dysphagia, or oropharyngeal dysfunction, refers to problems in swallowing that may involve one of the phases of swallowing, such as the preparatory, oral, pharyngeal, or esophageal phase. It is an increasingly common disorder in chronically ill children and in cases of gastroesophageal reflux disease (GERD). The pathogenesis of dysphagia is often multifactorial. Clinical evaluation should be the first diagnostic step. Among instrumentals, high-resolution impedance manometry (HRIM) is increasingly used. A multidisciplinary evaluation can facilitate early diagnosis and adequate treatment.

Keywords

Dysphagia · GERD · Manometry · Oropharyngeal dysfunction · Swallowing

Introduction

Gastroesophageal reflux disease (GERD) is prevalent worldwide, with an incidence among young patients that has been rising [1, 2]. Although the most frequently reported symptoms are heartburn and regurgitation, other symptoms, including dysphagia, odynophagia, globus sensation, chest pain, belching, and hoarseness, may be present [2, 3]. Dysphagia or oropharyngeal dysfunction refers to problems in swallowing that may involve the preparatory, oral, pharyngeal, or esophageal phases of swallowing [4]. The incidence of pediatric dysphagia is estimated to be 0.9% but

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is thought to be even higher in at-risk populations [5–7]. Indeed, in the pediatric population, at-risk groups are represented by children with a history of prematurity, neurological impairment, cardiopulmonary disorders, anatomic anomalies of the upper aerodigestive tract, and gastrointestinal disorders, including GERD [2, 5]. Since the ability to care for patients with extreme prematurity and complex medical conditions such as cerebral palsy, bronchopulmonary dysplasia, and cardiac anomalies improves, the incidence of conditions related to oropharyngeal dysfunction increases [6, 7]. GERD is the most reported cause of esophageal dysphagia and the major cause in younger patients [2, 8]. A study in adults reported that GERD was observed in about 24% of the patients who needed to be treated for dysphagia [8]. Symptoms frequently mimic GERD and can be related to Eosinophilic esophagitis (EoE) which is a clinicopathologic entity distinguished clinically by a pattern of symptoms related to esophageal dysfunction and histologically by intraepithelial eosinophilia on biopsy. EoE predominantly presents with dysphagia and esophageal food impaction, along with persistent heartburn and regurgitation in adults.

The consequences of dysphagia can be debilitating as it may lead to feeding difficulties, failure to thrive, respiratory complications, and a compromised quality of life. Therefore, early diagnosis and management by a multidisciplinary team are essential [9].

Pathophysiology of Swallowing

The act of swallowing includes four phases: the preparatory phase, when food is taken into the oral cavity, moistened with saliva, chewed, and prepared into a bolus; the oral phase, when the food bolus is transported towards the pharynx (swallow reflex); the pharyngeal phase, when the bolus is transported through the pharynx to the upper esophageal sphincter (UES); and the last esophageal phase, which includes transportation of the bolus through the esophagus to the stomach. In infants, all four phases are under involuntary reflex control. In children and adults, the preparatory and oral phases are under voluntary control, and the pharyngeal and esophageal phases remain involuntary [5].

A physiologic swallow is the result of the complex integration of more than 30 nerves and muscles and must progress with the child as their anatomy matures [5]. Dysphagia is defined as difficulty in one of the four phases of swallowing and can be further categorized depending on the impaired phase (oral, pharyngeal, or esophageal dysphagia) [4]. In particular, esophageal dysphagia results from obstruction of passage of the food bolus through the esophagus or from poor coordination of esophageal muscle contractions.

Genesis of Dysphagia in Patients with GERD

The presence of dysphagia in patients with GERD may be explained by the following mechanisms, which have been mainly explored in adults [10]:

1. UES dysfunction: gastroesophageal reflux (GER) can have an impact on UES function. Patients with GERD have a longer UES opening during deglutition, which means a longer time for the bolus to pass through the sphincter [11]. Other UES changes include short and hypotonic sphincter and increased UES pressure associated with transient lower esophageal sphincter relaxation [12, 13].
2. Hypersensitivity: some patients with heartburn may have abnormal esophageal sensitivity to acid (reflux hypersensitivity), which is characteristic of a functional esophageal disorder [14]. Such hypersensitivity seems to be related to esophageal innervations and may increase the perception of esophageal bolus transit during swallowing; stress, anxiety, and hypervigilance may have a role in the development of esophageal hypersensitivity [14]. Moreover, calcitonin gene-related positive nerves, markers of nociceptive sensory innervation, are more superficial in the proximal and distal esophagus of patients with GERD, which may contribute to symptoms during swallowing [15].
3. Esophageal motility abnormalities: GERD may be the cause or the consequence of esophageal motility abnormalities [16]. The frequency and intensity of esophageal dysmotility increase with the severity of GERD [16]. Transient lower esophageal sphincter relaxation followed by GER, hypotensive lower esophageal sphincter, ineffective esophageal peristalsis, and bolus transit abnormalities are strongly implicated in GERD [17]. High-resolution esophageal manometry (HRM) during solid swallows demonstrated motility abnormalities in patients with nonerosive GERD, including ineffective swallows, large breaks, and decreased distal contractile integral, leading to a delay in acid clearance [17]. Another condition associated to esophageal dysmotility is EoE, an inflammatory condition of the gastrointestinal tract that can affect swallowing in children and may coexist with GERD [9].

Clinical Presentation

The clinical presentation of dysphagia in children may vary based on the cause of the dysphagia [9]. For instance, oral dysphagia usually presents with absent oral reflexes, weak and/or uncoordinated suck, disordered biting and/or chewing, poor bolus propulsion and/or containment. Pharyngeal dysphagia may appear as laryngeal penetration, aspiration, or choking. Laryngeal penetration and aspiration can be present without classic feeding symptoms [9]. Silent aspiration is an aspiration that occurs without coughing or attempting to clear the food bolus from the airway. Silent aspiration is thought to be related to decreased laryngopharyngeal sensation, neurologic weakness or incoordination of the pharyngeal musculature, or weak cough [18]. Aspiration can lead to acute and chronic respiratory diseases in children, including pneumonia and bronchiectasis [18]. Children with recurrent respiratory tract infections without other overt signs of swallowing dysfunction should undergo a diagnostic workup for dysphagia [9].

Diagnosis

Techniques used for diagnosing and monitoring pediatric dysphagia include clinical evaluation tools and a range of instrumental evaluation tools [9]. A bedside swallow examination is one of the first tools used by a speech-language pathologist in the evaluation of a child with potential dysphagia [19]. A food bolus or just water is introduced to the patient and swallowing is observed, so that the clinician may be able to determine whether the dysfunction lies in the preparatory phase, the oral phase, the pharyngeal phase, or a combination. The test can also reveal whether the child is able to participate and whether it is safe to proceed with additional swallowing examinations. The bedside swallow is a sufficient screening test for aspiration, but it cannot detect silent aspiration [19]. The videofluoroscopic swallow study (VFSS) and fiberoptic endoscopic evaluation of swallow (FEES) are the most used instrumental tools in pediatric dysphagia [9]. The upper gastrointestinal series (UGI), a series of radiographic images of the esophagus, stomach, and duodenum, can be helpful in identifying anatomic and functional abnormalities [9]. Esophagogastroduodenoscopy allows macroscopic and histologic assessment for GERD and/or eosinophilic esophagitis [2, 9]. Recent attention for the assessment of dysphagia in pediatrics has gained the high-resolution impedance manometry (HRIM), which is becoming the standard investigation for the diagnosis of esophageal dysmotility [20, 21]. HRM is the primary method to evaluate esophageal motility and sphincter function in patients with nonobstructive dysphagia, i.e., dysphagia in the absence of mechanical obstruction on esophagogastroduodenoscopy. The incorporation of multichannel intraluminal esophageal impedance sensors into the HRM catheter (HRIM) has empowered the evaluation of esophageal function by allowing the assessment of the interplay between esophageal motility and bolus transit [20].

Treatment

Children with dysphagia benefit from the care of a multidisciplinary team that may be made up of pediatricians, otolaryngologists, speech-language pathologists, pulmonologists, gastroenterologists, and dieticians [5, 9]. Feeding therapy is often the first-line treatment for children with dysphagia. This type of therapy consists of changing the means of food delivery and/or the feeding position and implementing sensory and motor exercises aimed at improving the strength and coordination of the lips, tongue, jaw, soft palate, and pharyngeal muscles [5, 9]. Notably, feeding therapy should be attempted only if oral intake has been considered safe. Other strategies include the use of different formulas, thickeners, and/or an increase in daily caloric intake. Thickened feeds may help to reduce or resolve laryngeal penetration, aspiration, and GERD [22]. A variety of thickeners are on the market, including rice cereals, carob beans, and xanthan gum, and must be chosen carefully based on the patient's age and comorbidities [22]. Anti-acid drugs are often prescribed based on clinical symptoms of GERD [2]. With time and conservative

management, many infants with aspiration will improve within 1–2 years [23]. In case of EoE diagnosis, the management consists of dietary modification and anti-acid therapy. Three diet forms are commonly used: an elemental diet that is a liquid formula based on amino acids and free of all allergens; a 6-food elimination diet; or a targeted elimination diet. Swallowed corticosteroids are effective in acute exacerbations of EoE, but the disease often relapses after discontinuation [24].

Surgical management of dysphagia in children is indicated when an anatomic abnormality is identified as the cause of the dysphagia (i.e., ankyloglossia, laryngomalacia, laryngeal cleft, etc) [9].

Conclusion

Dysphagia is an increasingly common disorder in pediatric patients, especially in chronically ill children and in the case of GERD. The underlying mechanisms of dysphagia are different and often multifactorial. Clinical evaluation should be the first diagnostic step. Among instrumentals, HRIM is increasingly used. A multidisciplinary evaluation can facilitate early diagnosis and adequate treatment.

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Duodeno-GER

5

Ilse Hoffman

Abstract

Gastroesophageal reflux disease is a multifactorial disorder in children and adults and results from reflux of gastric contents into the esophagus. Animal studies suggest the possibility of synergism between acid and pepsin and conjugated bile acids with a damaging potential for the esophageal mucosa. Human studies show an interaction between acid and duodenogastroesophageal reflux in inducing symptoms and lesions.

Gastroesophageal reflux symptoms are more related to acid reflux events than to nonacid reflux events. The role of duodenogastroesophageal reflux has been evaluated by endoscopy with biopsies, scintigraphy, aspiration studies, esophageal pH monitoring/impedance, and bilirubin monitoring. Therapeutic options are reducing the secretion of gastric acid, prokinetics, baclofen, mucosal protective agents, and surgery.

Keywords

Bile reflux · Nonacid reflux · Alkaline reflux · Duodenogastroesophageal reflux Gastroesophageal reflux · Gastroesophageal reflux disease · Reflux esophagitis Children · Bilitec · Reference value bilitec · Bilirubin monitoring · pH monitoring/impedance · Barrett's mucosa · Bile salt · Bile acids

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Abbreviations

DGER	Duodenogastroesophageal reflux
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HIDA	Hepatobiliary iminodiacetic acid scan
PPI	Proton pump inhibitor
ROS	Reactive oxygen species
Tc-99 m	Technetium-99 m
TEER	Transepithelial resistance

Introduction

Gastroesophageal reflux disease (GERD) is defined as the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the esophagus. Although incompletely understood, it is clear that the pathophysiology of GERD is multifactorial both in children and adults. The pressure of the lower esophageal sphincter, the motility of the esophageal body and stomach, the composition of the reflux material, and the sensitivity of the esophageal mucosa to the refluxate are important factors involved in the pathogenesis of GERD-related symptoms or lesions [1].

The reflux material is not only composed of gastric acid and pepsin but may also contain food and regurgitated duodenal contents. Reflux of duodenal contents into the stomach is a physiological event, both postprandial and at night. Regurgitation of duodenal contents through the pylorus into the stomach, with following reflux into the esophagus is called duodenogastroesophageal reflux (DGER). The term bile reflux is usually synonymously used with DGER, since bile or bilirubin are the constituents used most often as markers of the reflux [1–8].

Mechanism of Bile Injury

The interaction of gastric acid, bile acids, and the development of mucosal damage have been studied extensively in vivo and in vitro. The mechanism of esophageal mucosal damage by pepsin and trypsin is related to the proteolytic characteristics of these enzymes. They promote detachment of the surface cells from the epithelium by digesting the intercellular substances and surface structures. Each agent causes the most damage at its optimal pH activity range: pH 2–3 for pepsin and pH 5–8 for trypsin [9, 10].

In humans, the normal liver converts a daily average of 0.78–1.29 mmol of cholesterol into bile acids. These primary bile acids, cholate, and chenodeoxycholate are synthesized from cholesterol by the hepatocytes. Secondary bile acids are formed as metabolic products of intestinal bacteria. These include deoxycholic and lithocholic acid. Before secretion into the biliary tract, 98% of the bile acids are conjugated with taurine or glycine in a ratio of 3:1. Conjugation, especially with taurine, increases the solubility of bile acids by lowering their pK_a [10, 11].

Bile acids damage mucosal cells by their detergent property and solubilization of the mucosal lipid membranes. This is supported by studies in gastric mucosa in which bile acid-induced mucosal injury was correlated with the release of phospholipids and cholesterol in the lumen. However, studies with rabbit esophageal mucosa show significant mucosal barrier disruption occurring at the bile acid concentrations below the level at which phospholipids are solubilized [11]. Therefore, this mechanism is less likely to explain the esophageal disruption caused by bile acids. The second hypothesis suggests that bile acids gain entrance across the mucosa because of their lipophilic state, causing intramucosal damage primarily by disorganizing membrane structure or interfering with cellular function. Bile acids, once penetrating the mucosal barrier, are trapped inside the cells by intracellular ionization, explaining the increase in intracellular concentrations of bile acids [12]. Studies by Schweitzer have correlated bile acid entry and mucosal accumulation with bile acid-mediated mucosal damage [11]. In vivo studies show that bile acid accumulation in mucosal cells is driven by the pH gradient between the acidic lumen and the neutral cytosol. The intracellular bile acid concentration can reach levels as high as eight times the luminal concentration. This results in increased mucosal permeability and eventually induces cell death. This effect is not only related to the concentration of luminal bile acids but also to the time the mucosa is exposed to bile acids. Depending on their conjugation status, bile acids precipitate at an acidic pH. Precipitation occurs at a pH below 3–4 for the unconjugated bile acids and conjugated bile acids precipitate only at a pH below 1.5. This explains the increased mucosal injury by conjugated bile acids at pH 2 and unconjugated bile acids at pH 7. So in conclusion, the potentially injurious effect of bile reflux is not only related to the concentration of bile acids but also dependent on the pH [10–12] (Fig. 5.1).

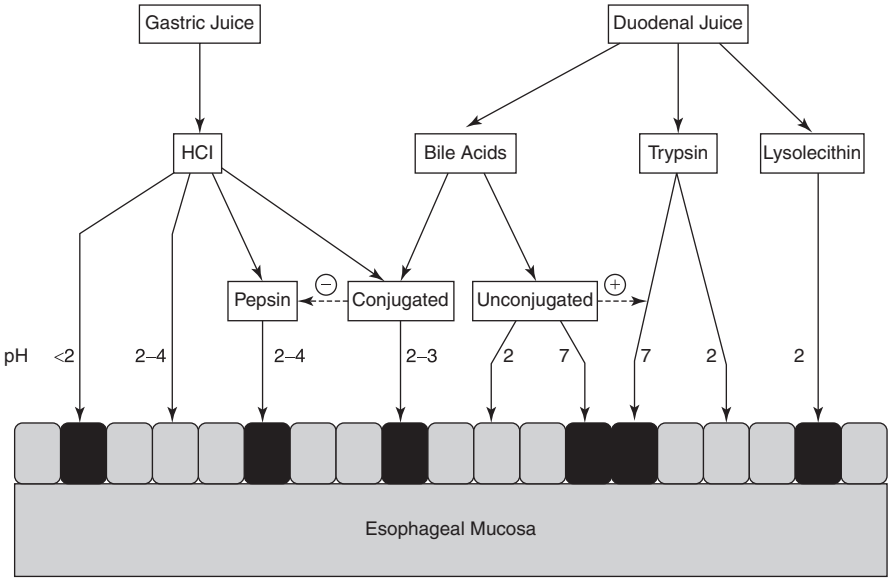

Fig. 5.1 Proposed agents responsible for esophageal mucosal inury. HCl = hydrochoric acid. Vaezi M, Richter J. Duodenogastroesophageal reflux and methods to monitor nonacidic reflux. The American Journal of medicine 2001; 111(8A): 160S–168S

Luminal Factors Responsible of Impaired Mucosal Integrity

Cell-to-cell adhesions proteins are in charge to maintain the integrity of the esophageal epithelium. Compared to other parts of the gastrointestinal tract, the esophageal mucosa is not composed of a simple epithelium, except for a short segment in the distal esophagus. The normal esophageal epithelium is a non-keratinizing and stratified squamous epithelium divided into different cell layers based on their morphology and function: basal cell layer, intermediate or prickle cell layer, and superficial layer. There are three different types of attachments, from apical to basal: zonula occludens or tight junctions, adherence junction, and macula adherens or desmosomes [7, 13–16] (Fig. 5.2).

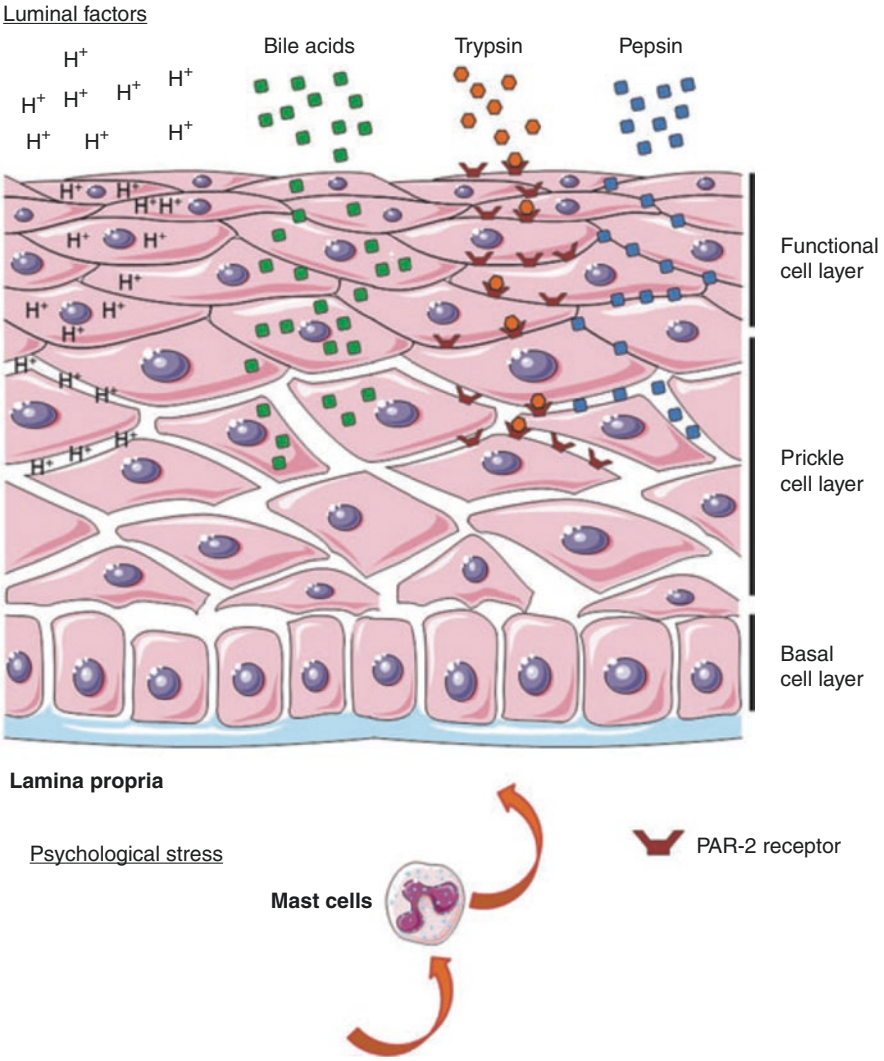

Fig. 5.2 Summary of the luminal and endogenous factors that can impaire esophageal mucosa integrity. Farré R. Pathophysiology of gastro-esophageal reflux disease: arole for mucosa integrity? Neurogastroenterol Motil (2013) 25, 783–799

Studies aspirating the reflux content from the esophagus of patients with GERD showed a higher concentration of both conjugated and unconjugated bile acids compared with aspirated material from healthy volunteers. The effects of bile acids on esophageal mucosa were tested for the first time at the beginning of the 1980s in rabbit tissue. Authors observed that high concentrations of bile acids impair mucosal integrity as it decreases transepithelial resistance (TEER) and increases permeability to hydrophilic molecules. Esophageal injury in the deeper layers (prickle and basal cell layer) was shown by margination of nuclear chromatin in the basal cells, intracellular vacuolization, complete necrosis, and separation of the overlying layers. Incubation of human esophageal biopsies up to 15 min with bile acids and human duodenal juice can mimic these observations in animals. Chen showed that the conjugated bile acids glycocholic and taurocholic in acidic conditions downregulate the tight junction proteins Claudin-1 and 4. At weekly acidic pH, deoxycholic acid provokes downregulation of the same tight junction proteins [16]. Ghatak studied the influence of bile salts at low pH and concluded that bile salts at pH 5 disrupt different junctional complexes and cause increased permeability of the stratified esophageal epithelium. These changes approximate the appearance of dilated intercellular space similar to that found in GERD patients [17].

It is established for almost 20 years that acute and chronic stress in rats increases mucosa permeability and reduces TEER. Farré showed in a rat model that the combination of stress and acid increases the passage of larger molecules. This could not be blocked by omeprazole and seems to be mediated by corticotrophin-releasing factor 2 receptors. As it occurs in other parts of the GI tract and the skin, the effect of stress on esophageal epithelial integrity may be mediated by mast cells as is indicated by the slight increase of these immune cells in the lamina propria [13]. Bile acids may also induce the release of intracellular mediators and induce mast cell degranulation and release of histamine and prostaglandins [7, 13–18] (Fig. 5.2).

Measurement of Duodenogastroesophageal Reflux

The intermittent nature of DGER poses a challenge in the development of an optimal investigation. Methodologies employed for measuring DGER include pH monitoring/impedance, Bilitec, endoscopy, aspiration studies (both gastric and esophageal), and scintigraphy. A more complete DGER profile requires prolonged monitoring. Unfortunately, none of the current techniques are ideal. (Table 5.1).

Esophageal pH Monitoring/Impedance

Measurement of esophageal pH > 7 as a marker of DGER is confounded by several problems. Precautions must be taken to use only glass electrodes and dietary restriction of foods with pH > 7. Studies reported that increased saliva production or

Table 5.1 Summary of recommendations. *HIDA* hepatobiliary iminodiacetic acid, *MII-pH* multichannel intraluminal impedance-pH, *EGD* esophagogastroduodenoscopy [25]

Test	Duration	Cost[a]	Limitations	When to use
HIDA scintigraphy	3 h	$210	– Short monitoring period – No information on concentration, duration, or composition of reflux	– For diagnosis of bile reflux without the requirement for characterization of refluxate or reflux profile
MII-pH	24 h	$190	– Poor patient tolerability – Not specific for bile reflux – Requires skilled staff for data interpretation	– Reflux symptoms refractory to medical therapy – Characterization of reflux profile
Bilitec	24 h	$230	– Poor patient tolerability – Non-clearance of probe tip – No quantifiable data on bile acid concentrations	– Estimation of duration of bile exposure
EGD + aspiration	~ 6 h	$240	– Significant infrastructure requirements – Invasive test requiring sedation – Risk of complications	– Persistent reflux symptoms. – Dysphagia/odynophagia – Need for tissue visualization and biopsy

[a]Costs, shown in $AUD, include consumables and government rebates but are not inclusive of staff labor, medications (if required), and reusable equipment items

bicarbonate production by the esophageal submucosal glands were the most common causes of esophageal pH > 7. Gotley found no relation between alkaline exposure time and esophageal bile acids or trypsin [19]. The intraluminal esophageal impedance technique detects gastroesophageal reflux events based on changes in resistance to electrical current flow between pairs of electrodes. The method allows the detection of several types of reflux events, regardless of whether they are liquid (drop in impedance) or gas (increase in impedance) or mixed. It is often assumed that DGER and nonacid reflux detected by impedance monitoring represent the same event, but studies have shown that the DGER component usually accompanies acid reflux events and that the nonacid component is not equivalent to bile reflux. The pH monitoring/impedance certainly lacks in determining the composition of the refluxate [3–6, 9, 20–25].

Bilirubin Monitoring

The Bilitec 2000 (Synectics Medical, Stockholm, Sweden) device is a fiberoptic spectrophotometric, transnasally passed probe, developed to quantify DGER. Bilirubin, present in bile, has a characteristic absorption band at 450 mm. In vitro validation studies confirmed a good correlation between the total bilirubin concentration and pancreatic enzymes of aspirated samples in the esophagus and the fiberoptic reading of the bilirubin concentration. Based on these studies, bilirubin seems to be an accurate tracer for DGER. Vaezi and Richter published normal values in adults [26]. A patient is considered to have pathologic DGER if the fraction of time that the esophageal mucosa is exposed to a refluxate with a bilirubin absorbance of >0.14 exceeds 4.2% of the total study time. It is a semi-quantitative technique of detecting DGER because of limitations inherent in the Bilitec probe. Studies have shown that this device underestimates bile reflux at least by 30% in an acidic medium (pH < 3.5). In solutions with pH < 3.5 bilirubin undergoes monomer to dimer isomerization, which is reflected by the shift in the absorption wave length from 453 to 400 nm. Because Bilitec readings are more based on the detection of absorption at 470 nm, this shift results in the underestimation of the DGER. Therefore, Bilitec measurements are always accompanied by the simultaneous measurement of esophageal acid exposure. A second limitation is the recording of any other substance around 470 nm. This necessitates the use of a modified diet to avoid interference. Interference of Bilitec absorbance readings by solid and liquid meals was evaluated in 211 patients and 40 healthy subjects [13]. Major meal artifacts occurred in 19% of patients consuming solid meals and non-consuming liquid meals. Tack has shown that a liquid meal (Nutridrink 200 ml, 300 kcal) does not interfere with the measurements [27]. Ambulatory Bilitec monitoring therefore requires adherence to a white, liquid diet, which can impact the normal gastrointestinal condition during which reflux occurs. Thirdly, Bilitec measures reflux of bilirubin, and not bile acids presuming that the presence of bilirubin in the refluxate is accompanied by other duodenal contents. Bilitec does not quantify bile acid concentration, and absorbance readings are affected both by the pH and dilution of the refluxate so that whether a bile reflux event is significant is unknown [2–5, 26–36].

HIDA Scintigraphy

Hepatobiliary Iminodiacetic Acid (HIDA) scintigraphy is a nuclear medicine diagnostic investigation. Iminodiacetic acid, combined with technetium-99 m (Tc-99 m), is injected intravenously as a radioactive tracer and detected by an external gamma camera. Tc-99 m circulates to the liver and is secreted in bile, allowing visualization of bile drainage through the biliary tree, into the duodenum, and, in cases of DGER, passing into the stomach and/or esophagus. Patients are instructed to fast for 4 h and positioned supine in front of the gamma camera for 1.5–2 h. Pharmacologic agents may enhance the diagnostic value of the examination, through gallbladder contraction and relaxation of the sphincter of Oddi.

Despite these advantages, scintigraphy lacks anatomical resolution due to the overlap of organs/structures in a two-dimensional image. The interpretation of the images during small volume DGER can be especially difficult due to the proximity of the gastric antrum to the left lobe of the liver and the duodenal-jejunal flexure. Scintigraphy does not accurately quantify volume, concentration, or the composition of the refluxate and the intermittent nature of bile reflux and the availability of longer term monitoring techniques limits its utility [25].

Aspiration Study

The observation of bile in the esophagus or stomach is a poor indicator of DGER with poor sensitivity (37%), specificity (70%), and positive predictive value (55%) for endoscopy in diagnosing excessive DGER. Gastroesophageal fluid aspiration allows chemical analysis of the concentration and composition of the fluid and determination of the presence of bile acids. Aspiration can be performed either endoscopically under vision during EGD or via a nasogastric tube, then liquid chromatography-tandem mass spectrometry can give quantitative bile acid analysis. Collection of fluid during EGD has the advantage of direct visualization of the fluid and allows an assessment of the esophageal and gastric mucosa with the further advantage of tissue biopsy. Important endoscopic features include the following: presence of a gastric bile lake, acute gastritis with erythema, thickening of the gastric folds, or mucosal erosions. Histological findings include foveolar hypertrophy, intestinal metaplasia, and acute or chronic inflammation. Obviously, these findings are not specific for bile reflux thus limiting the diagnostic value of endoscopic visualization and histological analysis when used in isolation. The intermittent nature of bile reflux also limits the utility of isolated gastric and esophageal fluid aspirates [25–36].

Other

Sodium ion concentration is a marker for duodenal reflux, as the Na + concentration in duodenal, pancreatic, and biliary fluid is fairly constant at ~150 mmol/L in contrast to gastric fluid Na + concentration which varies significantly. A British group developed a sodium ion-selective electrode which can be used to detect duodenal reflux events. This technique showed very positive results but study conditions were highly controlled and artificial and non-representative of usual bile reflux conditions. Readings in vivo are again likely to be significantly affected by acidic environments (pH < 3) and food intake. Further research is necessary.

High-resolution color Doppler ultrasonography of the pylorus allows for real-time detection of DGER events and quantification of reflux volume. First described by King et al. in 1984, the technique was evaluated further by Hausken. A probe placed over the epigastrium records the retrograde flow of enteric contents through the pylorus into the stomach by applying Doppler principles. The frequency of

reflux events and the distance of the color signal from the pylorus determine the severity of the DGER. However, movement of the pylorus during respiration disrupts continuous visualization and proximal extent of reflux and duration of exposure cannot be determined [25].

The intermittent nature of DGER poses a challenge in the development of an optimal investigation. Of the available techniques, HIDA scintigraphy is the least invasive but only provides a short window for the capture of DGER events. A more complete DGER profile requires prolonged monitoring. Unfortunately, none of the current ambulatory techniques are ideal. Bilitec ambulatory monitoring was specifically developed for the detection of bile reflux but is prone to errors, particularly false-positive readings, while ambulatory pH and MII-pH monitoring do not directly detect bile reflux.

Role of Duodenogastroesophageal Reflux in Esophageal Lesions

Despite its limitations, Bilitec has been an important advancement in the assessment of DGER in the clinical area. Although reflux of duodenal contents into the stomach is a natural phenomenon, excessive bile reflux can be responsible for a clinical syndrome [36–43].

In partial gastrectomy patients, excessive DGER is present in the majority, but esophagitis seems confined to a subset with excessive gastroesophageal acid reflux. Several studies in non-operated GERD patients suggest increasing amounts of acid reflux and DGER with increasing severity of esophageal lesions, especially in patients with Barrett's esophagus and complicated Barrett's esophagus. In a study by Koek, the presence of esophagitis was associated with DGER exposure and the severity of esophagitis with esophageal acid exposure [43]. Male, sex, acid exposure, and DGER exposure are all independent risk factors for the presence of Barrett's esophagus. It has also been reported that total gastrectomy patients may still develop severe esophagitis. In critically ill patients receiving stress ulcer prophylaxis with ranitidine, the presence of esophagitis was significantly correlated with the presence of pathological DGER [41]. These data support the role of DGER even in the absence of an acidic component. So the amount of DGER increases with the degree of esophageal damage, the highest levels found in patients with Barrett's esophagus.

The same results were reported in children by Orel, Hoffman, and Jiang with both bile and acid reflux increased stepwise with the severity of esophagitis. Isolated acid or bile reflux was present in mild or moderate esophagitis. [37–40] In the study by Hoffman, it was demonstrated that DGER might play a role in the pathophysiology of PPI refractory GERD and esophagitis [37]. The results of these studies are supportive of synergistic activity of acid and bile in inducing esophageal lesions. The existence of a bile pocket at the gastroesophageal junction needs further investigation and could be a reservoir of bile reflux [36–43].

Role of Duodenogastroesophageal Reflux in Symptoms

The relationship between acid reflux episodes and symptoms has been extensively studied. Acid perfusion studies established that hydrochloric acid at pH 2 or lower is able to induce symptoms in adults, but it was demonstrated that the perfusion of bile acids in the esophagus is also able to induce symptoms. In a study by Koek using the combination of acid and DGER reflux monitoring, they found that most symptom episodes were associated with acid reflux alone or mixed reflux, while <10% were associated with bile reflux alone [43].

When symptomatic patients are studied while on PPI therapy, a high proportion of symptomatic episodes are related to nonacid reflux, as measured with the esophageal impedance meting. The prevalence of a positive symptom index for nonacid reflux (defined as weakly acidic (pH > 7) or alkaline reflux is 25–27% in adults, nonacidic reflux seems to trigger refractory GERD. So, DGER without excessive acid reflux can cause symptoms but not usually produce esophagitis [43, 44] (Fig. 5.3).

Bronchopulmonary dysplasia (BPD) is the most common respiratory disorder, affecting 40% of extremely low birth weight infants. Many studies have suggested that neonatal GER is associated with respiratory diseases such as asphyxia, aspiration pneumonia, and apnea. Infants with BPD may have an increased risk of GER due to the respiratory effort and transient increases in intra-abdominal pressure related to coughing, crying, and airflow obstruction. Currently, the most recommended method for detecting GER is pH-multichannel intraluminal impedance (pH-MII). However, its resolution for GER in preterm infants is uncertain because there is a weaker acidic secretion in preterm infants than in older infants and adults. Preterm infants are fed frequently, and therefore their gastric reflux may be less acidic or alkaline. In the presence of duodenogastroesophageal reflux (DGER), the limitations of pH-MII are even more pronounced. Neonatal jaundice, which increases the amount of detectable bilirubin in the esophagus, can overturn the results of testing. Assessing levels of gastric sodium ions (Na^+) has been considered a novel tool for this condition.

Infants with BPD and DGER were more prone to late complications compared with those with acid GER or no reflux. There are several potential underlying reasons for this. First, pancreatic enzymes and bile salts in the duodenal contents cause more damage to the respiratory system compared with general acid reflux.

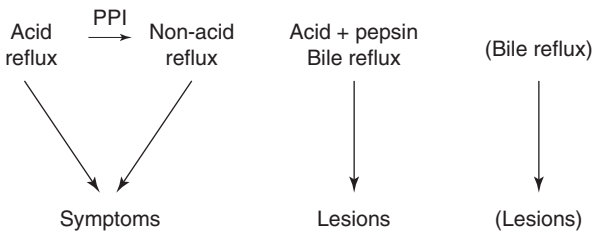

Fig. 5.3 Animal studies and human studies suggest that a synergism between acid, pepsin and bile is involved in the pathogenesis of GERD-related lesions. Under specific, more rare circumstances, non-acid reflux alone seems to underlie the pathogenesis of oesophageal lesions. J Tack. Review article: the role of bile and pepsin in the pathophysiology and treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006; 24 (Suppl.2), 10–16

Second, GER and BPD are indicators of developmental prematurity of the upper digestive and respiratory systems because they both originate from the embryonic foregut under the regulation of the same signaling pathways. DGER represents dysfunction of both the pylorus and cardia, meaning that the extent of prematurity may be associated with the degree of reflux. Finally, DGER may be triggered or aggravated by BPD. In infants with BPD, coughing and wheezing increase abdominal pressure and aggravate reflux. Thus, a vicious cycle between reflux and respiratory disease is established. GER/DGER poses a risk factor for late symptoms associated with BPD [45].

Cholecystectomy—the standard of care for symptomatic cholelithiasis—alters the dynamics of bile storage and release. Bile is normally stored in the gallbladder in the fasting inter-digestive period and is propelled into the duodenum in response to meals under the influence of cholecystokinin (CCK)-mediated gallbladder contraction. After cholecystectomy, the facility for bile storage is lost, and bile is continuously released into the duodenum, even during fasting.

The continuous presence of bile in the duodenum permits its overflow across the pylorus and into the stomach. A significantly greater concentration of bile acids has been confirmed in nasogastric aspirates from patients with gallstones compared with those without, and this increases further after cholecystectomy. Cholecystectomy also results in elevated serum levels of CCK. Cholecystokinin is an enteric hormone that is normally inhibited by the negative feedback of the CCK-mediated bile bolus in the duodenum, but after cholecystectomy, this switch-off mechanism is lost, resulting in persistent elevation of CCK levels. Gastric ulceration and gastritis have been shown to attenuate CCK-mediated increases in pyloric muscle tone, which may explain the observation of a bilious refluxate through an open pylorus on gastroscopy of patients with gastritis. The increase in circulating CCK results in the reduction of lower esophageal sphincter pressure and increases the frequency of transient lower esophageal sphincter relaxation episodes, potentially further exposing the lower esophageal mucosa to refluxed bile [46].

The Role of Duodenogastroesophageal Reflux in Neoplasia

The incidence rates for adenocarcinoma of the esophagus and gastric cardia have risen rapidly. Nicotine, alcohol abuse, nutritional factors, high body mass index acidic gastric reflux, and Barrett's esophagus are believed to be critical factors of carcinogenesis. In most patients, the reflux-damaged mucosa heals through regeneration of the squamous epithelium. In some alternative healing processes and in the development of a Barrett's esophagus, intestinal-type epithelium replaces the reflux-damaged squamous epithelium. Although the mechanisms of the development of Barrett's esophagus are not clear, bile acids may play a role. The study by Wolfgarten confirms that patients with Barrett's esophagus have significantly more frequent DGER in the esophagus compared with age and sex-matched healthy controls [7–49].

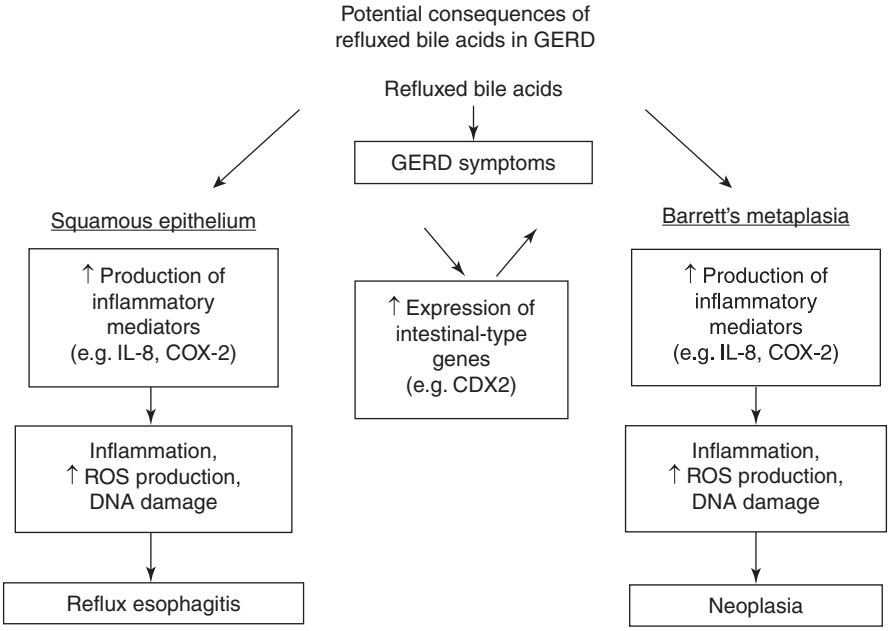

Fig. 5.4 Potential consequences of refluxed bile acids in GERD. McQuaid K, Laine L et al. Systematic review: the role of bile acids in the pathogenesis of gastro-oesophageal reflux disease and related neoplasia. Aliment Pharmacol Ther 2011; 34: 146–165

Bile acids cause esophageal squamous cells to express CDX2, (a gene with a key role in the development of intestinal epithelia), BMP4 (growth factor that promotes squamous to columnar metaplasia and MUC2 (mucin normally found in intestinal global cells). In esophageal cell cultures, the level of p63 protein (marker for esophageal squamous progenitor cells) declines when the cells are exposed to bile acids, suggesting that bile acids may affect the progenitor cells responsible for maintaining normal epithelium.

Bile acids cause Barrett's cells to increase the production of reactive oxygen species (ROS), which is known to cause oxidative DNA damage. Bile acids cause also a decrease in the activity of MnSOD, an enzyme that protects against oxidative injury. Bile acid-induced DNA damage that activates oncogenes or disable tumor suppressor genes in Barrett's metaplasia could contribute to carcinogenesis in Barrett's esophagus. [47–50] (Fig. 5.4).

Therapeutic Implications

PPIs are the cornerstone of GERD treatment. Studies have shown that PPI treatment dramatically decreases both acid and DGER measured by the Bilitec [50–56]. Acid suppressant therapy prevents esophageal exposure to duodenal contents by reducing intragastric volume as a consequence of the suppression of gastric acid secretion.

Symptoms relief during acid suppression does not equate to normalization of esophageal pH. Studies have shown that PPIs not only reduced acid but remarkably also bile reflux by reducing the bile exposure time from 29% to 3% [51–56]. In recent studies, this reduction is less pronounced from 22% to 12% [50]. Important is that 60% of the patients had still pathological bile exposure time. Studies evaluating DGER before and after long-term use of acid suppression therapy are absent. There is even a deleterious effect on the esophagus with the acid suppressant therapy allowing gastric and small bowel bacterial overgrowth leading to deconjugation of bile acids. At the present time, there are no drugs in clinical practice that can be used specifically to target bile reduction [51–53].

It seems logical that prokinetics may improve DGER, by accelerating esophageal clearance and gastric emptying. Oral macrolide antibiotics are a promising treatment option because they possess both anti-infective and antireflux properties that enhance GI motility. Transient lower esophageal sphincter relaxations are the main pathophysiological mechanism underlying in GERD events. GABA-B agonist baclofen was shown to decrease these relaxations. In a study by Koek adding baclofen 20 mg to PPI in PPI refractory patients improved DGER exposure and symptoms. This can be used as add-on therapy, but due to adverse effect the development and evaluation of newer GABA-B agonist is driven [56].

In view of the involvement of toxic radicals and cellular membrane degeneration, there is a role for locally acting mucosal protective therapy. Alginates decrease gastroesophageal reflux by forming a pH-neutral raft localized near the gastroesophageal junction, at the site of the postprandial acid pocket on top of the ingested food [54]. Antireflux surgery was shown to adequately reverse DGER, but not all patients are suitable candidates for surgical therapy and should be guided by a rigorous patient evaluation. Further research is necessary to evaluate the minimally invasive antireflux approaches. Studies in adults are ongoing to treat esophageal sensitivity [49–57].

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GER in Preterm Infants

6

Francesco Cresi, Domenico Umberto De Rose, and Elena Maggiora

Abstract

Gastroesophageal reflux (GER) typically occurs in preterm infants, mostly due to the immaturity of the lower esophageal sphincter and the still impaired esophageal motility. Only in a minority of cases, GER is pathological and known as gastroesophageal reflux disease (GERD).

In symptomatic infants with less than 34 weeks of corrected age, the degree of immaturity is such that any manifestation of GERD should be considered above all an expression of "feeding intolerance" before starting specific treatment. Afterward, food allergies and dysmotility patterns should be ruled out, given the overlapping symptoms. Symptoms usually resolve spontaneously with the growth and maturation of the neonate.

A clinical score could be useful to objectively evaluate symptoms and monitor therapeutic response, but Multichannel intraluminal impedance and pH monitoring (MII-pH) represents the gold standard to discriminate GER from GERD. It also allows establishing relationships between symptoms and GER. Recently, further steps were taken to obtain reference values in infants, analyzing MII-pH traces obtained in infants with negative results.

Other diagnostic tools (such as upper gastrointestinal contrast study and sonography) could be useful to assess gastric morphology and emptying but should not be routinely used to diagnose GERD.

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Firstly, a conservative approach must be used, improving feeding tolerance and stopping xanthines as soon as possible. Hydrolyzed protein formulas could reduce esophageal acid exposure and improve gastric emptying, but they should be administered only for a brief period since they are hypocaloric.

Secondly, no studies demonstrated a symptom reduction in preterm and full term infants after treatment with proton pump inhibitors (PPIs). Considering the higher risk of necrotizing enterocolitis, nosocomial infections, and mortality described for infants exposed to ranitidine, due to acid suppression, PPIs should be reserved only for patients with documented reflux esophagitis or acid-GER-related symptoms.

Keywords

Premature infants · Apnea of prematurity · Feeding intolerance

Introduction

Gastroesophageal reflux (GER), the passage of gastric contents into the esophagus, is a physiological phenomenon in the neonate, especially if born preterm [1]. A physiological GER frequency of about 2–4 events per hour has been detected in neonates [2].

Among factors contributing to GER in preterm infants, there are the prolonged lying position and the relatively large fluid intake (180 mL/kg per day would correspond to a daily intake of about 14 L/day in adults). However, most events are due to the immaturity of the lower esophageal sphincter (LES) with transient LES relaxations (TLESRs) and the still impaired esophageal motility typical of this age group [3].

GER events can be classified, according to esophageal pH recorded during the event, as acid (pH < 4), weakly acidic (pH 4–7), or weakly alkaline (pH > 7) [4].

In preterm infants, GER events are mainly nonacid due to the buffering effect of frequent milk feeds [2, 5]. Only in a minority of preterm infants, GER is pathological and known as gastroesophageal reflux disease (GERD) [6, 7]. This occurs when the acidity of refluxes, their number, and duration increase excessively and interfere with growth and life habits. This may also depend on the presence of risk factors such as the presence of gastric tube, respiratory distress, and bronchopulmonary dysplasia. [8].

In symptomatic infants with less than 34 weeks of corrected age, the degree of immaturity is such that any manifestation of GERD should be considered above all an expression of "feeding intolerance" (FI). Therefore, pharmacological therapies aimed directly at the resolution of GERD should not be considered the first-line treatment, but it is advisable before implementing all the procedures aimed at improving feeding tolerance [9].

Although a possible association between GER and apneas of prematurity (AoP) has been frequently hypothesized and continues to be a topic of significant debate and investigation, there is still a lack of evidence supporting a temporal association

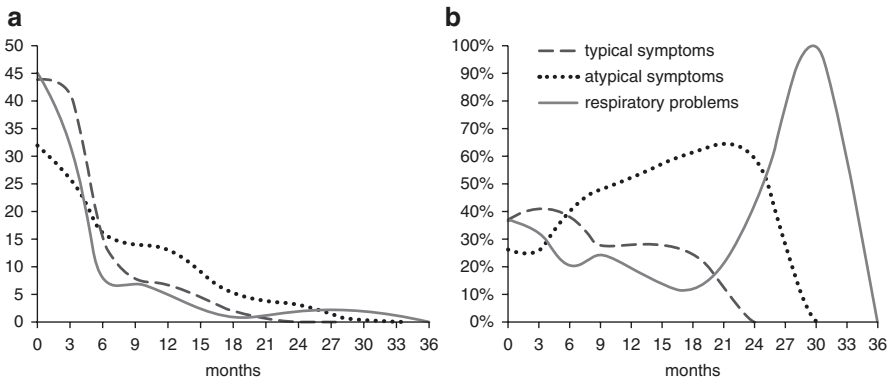

Fig. 6.1 Frequency of GERD symptoms by symptom category during follow-up. (**a**) Absolute frequencies. (**b**) Normalized frequencies [2]

or even a causal relationship. Indeed, in clinical practice, apneas are frequently detected during postprandial periods when the majority of GER events typically occur [10]. Cresi et al. reported that these episodes are associated with reflux only in 12% of cases. In these infants GERD is severe and reflux acts as a trigger to elicit apnea. Therefore, they should not be treated with drugs or dietary therapy for GERD, without specific diagnostic tests.

In symptomatic infants with more than 34 weeks of corrected age, GERD symptoms can be depending on food allergies (such as cow's milk allergy—CMA) as well as dysmotility patterns and feeding intolerance. Moreover, CMA and GERD may manifest similar symptoms in infants making the diagnosis challenging [11]. These associations, if confirmed by clinical and instrumental examinations, may be worthy of treatment.

Furthermore, clinicians should consider that GERD symptoms tend to change over time and usually resolve spontaneously with the growth and maturation of the newborn, as shown by Cresi et al. in Fig. 6.1 [2].

Diagnosis

Clinical Evaluation

Clinical evaluation is the main tool leading to the diagnostic suspicion of GERD and sometimes to a diagnosis. GERD symptoms in preterm can be classified as:

- Typical/Gastrointestinal (excessive regurgitation, vomiting);
- Atypical (irritability, bowing and feeding difficulties, sleep disturbances, failure to thrive);
- Respiratory (apnea and desaturation, cough, laryngeal stridor, worsening of lung disease) [2].

However, a clinical score could be useful to better and objectively evaluate symptoms and monitoring effects of introduced therapies. Although no questionnaires showed a high sensitivity and specificity for GERD in infants [12], the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) is a validated tool to monitor the evolution of symptoms during an intervention trial [13].

Multichannel Intraluminal Impedance and pH Monitoring (MII-pH)

Nowadays, Multichannel intraluminal impedance and pH monitoring (MII-pH) represents the gold standard to discriminate GER from GERD [6].

MII-pH can detect GER and discriminate episodes not only by pH values but also by duration and proximal extent. MII-pH also allows to establish relationships between symptoms and GER, if associated with a precise clinical diary or cardiorespiratory monitoring, such as symptom index (SI: number of GER related symptoms out of the total number of symptom episodes x 100; positive if ≥50%) and symptom association probability (SAP: the likelihood that the patient's symptoms are related to GER, computed analyzing consecutive 2-min segments through Fisher contingency table; positive if ≥95%) [4].

As MII-pH is an invasive test, for ethical reasons it cannot be performed on healthy infants, making it challenging to obtain traditional reference values for MII-pH parameters, i.e., from a normal, healthy population. However, further steps were recently taken to obtain reference values, analyzing MII-pH traces obtained in neonates and infants with negative results [14].

Furthermore, MII-pH can be used to determine the effectiveness of adopted treatments.

There are still three main limitations to using MII-pH in preterm infants: (1) there are no specific MII-pH probes for infants with a weight less than 1500 g; (2) its feasibility is limited during noninvasive ventilation; (3) there are no reference values for tube-fed infants (apart from data reported by López-Alonso et al. in a little sample of 21 preterm newborns fed by a modified nasogastric tube [15]).

Other Diagnostic Tools

Upper gastrointestinal contrast study could be useful to identify anatomical problems that cause GER but it should not be used to diagnose GERD, because of its low sensitivity [16]. Furthermore, it does not provide information on the quality and quantity of refluxes and involves the use of radiation. It can be reserved for those going for surgery and those with negative MII-pH results but strong clinical suspicion of GER [17].

Sonography should not replace 24 h MII-pH monitoring for detecting GER in preterm infants but is suitable to study the activity and characteristics of the pylorus and gastric emptying time in infants with vomit [18].

Use of Proton Pump Inhibitors as a Diagnostic Test

A trial with proton pump inhibitors (PPI) for a week ("PPI test") with careful monitoring of symptoms could be diagnostic in preterms with severe symptoms and unresponsive to first level treatments, in which MII-pH is still not feasible (low birth weight, noninvasive ventilation, tube feeding, etc.). However, no studies clearly demonstrated a symptom reduction in preterm and full term infants after treatment periods ranging from 2 to 4 weeks [19].

Use of Extensively Hydrolyzed Protein Formula as a Diagnostic Test

The use of an extensively hydrolyzed protein formula (eHPF) could be evaluated for reducing esophageal acid exposure in preterm infants with feeding intolerance and symptoms of GER after 34 weeks of corrected age, due to its buffering property and effects on gastrointestinal motility [20].

Corvaglia et al. reported a significant reduction in the number of GERs detected by pH monitoring in a sample of preterm infants with symptoms of feeding intolerance (large gastric residuals, abdominal distension, and constipation) and GER (frequent regurgitations and/or postprandial desaturations) nourished with an eHPF, when compared to their peers managed with standard preterm formula (SPF) [21].

Treatment

Conservative Approach

Improvement of Feeding Tolerance

The definition of FI varies and different strategies to improve feeding tolerance should be addressed. An excessive volume of meals may overwhelm the capacity of neonatal gut; thus, a reduction in the volume of meals fractioning them in smaller but more frequent meals could be useful to optimize enteral nutrition [22].

Slow advancement of enteral feed volumes is historically considered as a safe strategy to improve feeding tolerance, but current evidence actually indicates that advancing enteral feed volumes slowly (daily increments up to 24 mL/kg) compared with faster rates (30–40 mL/kg/day) probably does not reduce the risk of necrotizing enterocolitis, death, or feed intolerance in very preterm or very low birth weight (VLBW) infants. Even if advancing enteral feeding at a faster rate seems safe in terms of feeding tolerance [23], no specific data on how it can influence GER is reported. Therefore, feeding strategy should be the same as for healthy preterm infants while fractioning meals and monitoring GER as a sign of feeding intolerance.

How to administer feeding is another area of uncertainty: infants receiving continuous nasogastric milk feeding, using an infusion pump, every 2 or 3 h, may reach full enteral feeding slightly later than their peers receiving slow intermittent feeding

[24]. Intermittent bolus milk feeds may be administered by a syringe to gently push milk into the infant's stomach (push feed). Alternatively, milk can be poured more physiologically into a syringe attached to the tube and allowed to drip in by gravity (gavage feed). To date, there is still not enough literature to determine whether the use of push compared with gavage feeding results in a more rapid establishment of full gavage feeds without increasing side effects in this category of neonates [25].

Furthermore, routine monitoring of gastric residual (GR) in preterm infants gavage-fed is a common practice, in the absence of real advantages. This practice should be abandoned, considering that avoiding routine GR monitoring has been postulated that can reduce late-onset sepsis and promote an earlier achievement of full enteral feeding and an earlier discharge from the hospital [26].

In addition to feeding strategies also body positioning can play a role in improving feeding tolerance. Indeed, different postures can influence gastric emptying and GER. The prone or left lateral position in the postprandial period is a simple intervention to limit GER in preterm infants. Corvaglia et al. analyzed MII-pH traces in a cohort of premature infants, showing a lower esophageal acid exposure in these positions [27].

Probiotics may be an useful tool in improving early feeding tolerance in preterm infants, but it is difficult to assess the real impact due to heterogeneity of administered species and in available studies [28].

The administration of xanthines for AoP (caffeine) should be stopped as soon as possible in neonates with clinical suspicion of GER, given the detection of pepsin (a reliable marker of gastric aspiration) in tracheal aspirates from preterm ventilated neonates during xanthine therapy, due to its effect on LES relaxation [29].

Use of Hydrolized Protein Formula

Extensively hydrolyzed protein formulas (eHPFs) are often used in these infants due to their effects on gastrointestinal motility, gastric emptying time, and GER episodes [21].

Patients fed with standard formula reach faster a gastric pH below 4 during gastric emptying [30], explaining the decrease in acid refluxes observed after meals with eHPFs by Corvaglia et al. [21].

Hydrolysis of lactose can improve feeding tolerance in some cases, although evidence is still lacking (and further studies are needed to compare lactase-treated feeds and placebo) [31].

However, the nutritional characteristics of hydrolyzed formulas are not adequate for preterm infants [32], since they are hypocaloric. Therefore, they should be reserved for severe cases and only for a brief period (1–2 weeks).

Medications

First-Line Treatments

Commercial thickened formulas provide controlled concentrations of different thickening agents (locust bean gum/carob flour, tapioca, potato, rice, corn starch),

reducing the frequency and severity of regurgitations: they are indicated in formula-fed infants with persisting symptoms despite reassurance and verify of appropriate feeding volume intakes [33]. However, a possible association between thickened feedings and necrotizing enterocolitis has been identified in preterm infants [34]. Therefore, they are not suitable for premature infants. They should be taken into consideration only in case of dysphagia (on logopedic indication), or in cases of GERD with poor growth secondary to excessive regurgitation and vomiting.

Alginate-based formulations, acting as physical protection of the gastric mucosa, are commonly employed to treat GERD. In the presence of gastric acid, sodium alginate precipitates to form a low-density but viscous gel, while sodium bicarbonate, usually contained in these formulations, is converted to carbon dioxide, with a buffering and thickening effect [35]. Sodium alginate (Gaviscon Infant®) seems to significantly reduce acid GER episodes, with the advantage of a nonsystemic mechanism of action and a favorable safety profile [36]. No effects on GER-related apneas were detected by Corvaglia et al. using MII-pH [37].

Second-Line Treatments

Despite lack of evidence and increasing safety concerns, Slaughter et al. warned about the increase in prescription of Histamine-2 (H2) Receptor Antagonists (H2RA) and proton pump inhibitors (PPIs) to extremely preterm neonates and those with congenital anomalies, often continuing them also through discharge [38].

H2RA (i.e., ranitidine) compete with histamine for the H2 receptor in the parietal cells in the stomach, reducing hydrochloric acid secretion and buffering intragastric pH.

Terrin et al. reported that the risk of NEC, nosocomial infection, and mortality were significantly higher in the infants exposed to ranitidine [39].

Nevertheless, H2RA was frequently prescribed for infants in whom GER is clinically diagnosed. However, the finding that ranitidine spontaneously breaks down to a cancer-causing chemical caused its removal from the market in the US and other countries in 2020.

Proton pump inhibitors (PPIs, i.e., omeprazole, esomeprazole, etc.) dramatically reduce gastric acidity, inhibiting the last step of gastric acid secretion in the parietal cells regardless of the stimulus for acid secretion. Data on the safety and efficacy of PPIs in preterm neonates are few and controversial [35] and their use is still off-label for infants.

Omari et al. yielded a reduction in the frequency of acid GER events and esophageal acid exposure using omeprazole in preterm infants, although without significant changes in the number of symptomatic events [40]. Similarly, Orenstein et al. reported no significant changes in typical GER symptoms among term and preterm infants treated with lansoprazole or placebo. On the contrary, serious adverse events, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo [41].

To date, there are no studies that examined the association between PPIs and necrotizing enterocolitis in preterm infant, but all are based on H2RA [42]. However, acid suppression is higher in patients who receive PPIs [43], causing the disruption

of gut ecosystem and enhancing thus the growth of pathogens that could be pivotal in the pathogenesis of NEC [44].

Therefore, PPIs should be reserved only for patients with documented reflux esophagitis or acid-GER-related symptoms.

Regarding the use of prokinetics (i.e., erythromycin, domperidone, etc.), there is still no evidence of the positive effects on GERD in preterm infants. They can be used to improve gastric emptying, intestinal mobility, and feeding tolerance only in selected cases and in cases of documented LES incontinence (enhancing its tone) [45]. Indeed, prolongation of QTc interval is a well-known side effect of prokinetics; cardiac monitoring or at least serial ECGs should be performed before and during administration [46].

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GER and Respiratory Diseases

7

Valeria Dipasquale and Claudio Romano

Abstract

Gastroesophageal reflux disease (GERD)-related extraintestinal manifestations lack objective standards and often lead to overmedication. Among them, GERD-related respiratory diseases include asthma, chronic cough, laryngospasm, and laryngopharyngitis. Diagnostic as well as therapeutic management of respiratory symptoms of GERD is not evidence-based. Combined multichannel intraluminal impedance and pH (MII-pH) testing should be reserved for patients with suspected extraintestinal manifestations with poor response to conventional treatment. Antiacids should not be routinely used for the treatment of poorly controlled asthma, chronic cough, and laryngopharyngeal disease.

Keywords

Asthma · Cough · Extraintestinal symptoms · GERD · Laryngopharyngeal disease · Laryngospasm · Respiratory

Introduction

Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus with or without regurgitation and/or vomiting [1]. GER becomes pathologic and is referred to as GER disease (GERD) when the reflux causes troublesome symptoms and/or complications, which may be strictly intestinal (vomiting, dysphagia) or extraintestinal (respiratory, otolaryngological, neurological, hematological,

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etc.) [1]. However, GERD-related extraintestinal manifestations lack objective standards and often lead to not evidence-based clinical practice and overmedication. The cost of managing patients with suspected extraintestinal symptoms has been estimated at over five times that of patients with typical symptoms [2, 3]. GERD-related respiratory diseases mostly include asthma, chronic cough, laryngospasm, and laryngopharyngitis [3]. These airway entities are commonly encountered in pediatric practice but continue to be conditions with more questions than answers. There is very limited evidence on diagnosis and management in the neonatal and pediatric age groups compared to the adult population. The multichannel intraluminal impedance-pH (MII-pH) monitoring has recently been used for the identification of GER in infants and children. This method allows the detection of liquid, gas, or mixed reflux in addition to acid, weakly acidic, or weakly alkaline reflux, and can be considered more useful for assessing GERD-related extraintestinal manifestations [1–3].

Mechanisms of Association Between GER and Respiratory Disease

Several studies have attempted to explain the hypothesized link between GERD and respiratory symptoms with different pathogenetic mechanisms, including aspiration of gastric contents into the respiratory tree, vagal reflexes induced by the presence of gastric contents in the esophageal lumen, and/or sensitization of the central cough reflex [3, 4]. However, the results coming from these research studies are affected by some confounding factors, such as the use of different diagnostic methods, the lack of a standardized definition for respiratory diseases and/or symptoms, or the lack of a precise temporal relationship between the onset of respiratory and esophageal symptoms [4]. Moreover, it is difficult to evaluate whether children with GERD are at an increased risk of respiratory diseases if the prevalence of the same disorders is not assessed in a control group. Another confounding factor is that the assessment of GERD prevalence in children with respiratory disorders by using diagnostic methods cannot be extrapolated to the general population since pediatric gastroenterologists generally investigate children only after the failure of conventional therapy [4]. In the pediatric population, some groups are at higher risk for the development of these conditions, such as children with psychomotor delay or patients with a history of repaired congenital esophageal atresia, typically associated with tracheoesophageal fistula (EA/TEF).

In this chapter, they have been reviewed the mechanisms, clinical presentation, and current evidence on the diagnosis and treatment of the most common GERD-related respiratory diseases in children, including asthma, chronic cough, and laryngopharyngeal reflux disease.

GER and Asthma

Asthma may lead to reflux, and reflux could trigger asthma or cause asthma-like symptoms. The two conditions may coexist, with reflux being an irrelevant finding [3, 5, 6]. Many studies have reported an association between asthma and GERD, but the results

are often contradictory or inconclusive. Indeed, the reported prevalence of GERD in children with asthma ranges from about 20% to 80% [3]. In a large retrospective cross-sectional study of 1980 children with GERD and 7920 controls, a significantly higher occurrence of sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis in patients suffering from GERD was showned [7]. In another study, although there seemed to be a significantly higher prevalence of asthma in children with GERD presenting with respiratory symptoms compared to subjects presenting with intestinal symptoms only (35.3% vs. 5.3%, respectively), the overall prevalence of asthma in patients with and without GERD was similar [8]. In controlled studies, the pooled odds ratio for the association between GERD and asthma in children was 5.6 [9].

Pathogenetic Mechanisms

The potential mechanisms of the association between asthma and GER are various [10]. More than 70 years ago, Mendelson et al. proposed the so-called acute asthma-like reaction following the aspiration of gastric contents during the induction of anesthesia [11]. Macro-aspiration (more common in the absence of an altered level of consciousness) has been shown to cause reflex airway closure associated with chemical damage [12]. According to the "reflux theory," micro-aspiration leads to bronchospasm directly through the stimulation of the laryngeal-tracheal receptors. As the tracheal-bronchial tree and the esophagus have common embryonic foregut origins and share autonomic innervation through the vagus nerve, another potential mechanism is the stimulation of the esophageal mucosal receptors by acidification that activates the vago-vagal reflex and increases bronchial resistance ("reflex theory") [13]. Several studies documented the occurrence of bronchospasm after esophageal acidification in patients with asthma, and showed that atropine inhibited this effect, thus suggesting a vagal mediation [14]. Moreover, methacholin-induced bronchial hyperreactivity was increased in both adults and children with asthma after intraesophageal administration of acid [13, 14].

GER can induce, but also result from, an alteration in the mechanics of breathing. Bronchospasm may, in turn, trigger GER by increasing transdiaphragmatic pressure thus directly promoting reflux.

Indeed, during airflow obstruction, increased transdiaphragmatic pressure could pump gastric contents into the esophagus. Alternatively, if the diaphragm is directly involved in the maintenance of the anti-reflux barrier, then the geometrical flattening of the diaphragm during bronchospasm may adversely affect diaphragmatic action [3, 10, 13].

Moreover, predisposing factors for GERD may include some asthma medications, but the underlying mechanisms are still poorly understood [3, 10]. Beta-2 adrenergic agonists and theophylline were associated with the reduced tone of the lower esophageal sphincter (LES) thus promoting reflux [15]. In contrast, inhaled beta-2 adrenergic agonists, and inhaled and/or oral corticosteroids do not appear to alter LES tone [10]. Nevertheless, in adults with stable, moderately persistent asthma, oral steroids increase the esophageal acid contact times at both the distal and proximal pH probes, even in the absence of GER symptoms [10].

The Role of Anti-acid Drugs in Asthma

Untreated GERD has been postulated to contribute to inadequate asthma control despite intensive treatment [3]. Observational studies suggest that treatment with proton pump inhibitors (PPIs) can be effective, leading to inappropriate prescribing [16]. A systematic review of 12 randomized, placebo-controlled trials in adults and children reported that anti-acid treatment was ineffective in improving respiratory symptoms, lung function or the use of asthma medications in uncontrolled asthma [17]. In 38 children with uncontrolled asthma and symptomatic GER, omeprazole did not improve asthma course [18]. A large study on school-age children with poorly controlled asthma and asymptomatic GER showed that the addition of lansoprazole to asthma medications for 24 weeks did not improve outcomes but led to an increase in adverse events, irrespective of whether the pH study was positive [19].

The ineffectiveness of anti-acid treatment led to the hypothesis that GER can provoke its effects through mechanisms other than acidic refluxate [3]. Because acid suppression can convert acid reflux to nonacid reflux, persistent reflux may still cause extraintestinal symptoms. Experimental data suggest that gastric contents from patients prescribed anti-acid medications can still cause a significant inflammatory reaction in human bronchial epithelial cells [20]. Pepsin can induce the secretion of inflammatory mediators in hypopharyngeal tissues under nonacidic conditions, and inhibition may prevent at least some of these changes [21]. Although more reflux events are detected if combined MII-pH monitoring—a technique that can detect nonacid reflux—is used, there is no evidence that these cause asthma symptoms [22, 23].

The Problematic Severe Asthma in Childhood Initiative group recommended that GERD should be excluded when asthma is uncontrolled on optimized medical therapy, but the document is not evidence-based [24]. If there are no reflux symptoms, PPIs should not be prescribed [3]. If symptomatic GER is present, a 3-month therapeutic trial with PPIs could be reasonable, and medication should be weaned down if symptoms improve [3].

GER and Chronic Cough

The diagnosis of GER-related chronic cough may be challenging, first because acid reflux in children with chronic cough does not necessarily mean causatino, and also because children do not always exhibit typical GER symptoms [3]. In the largest study systematically investigating children with chronic cough in a hospital setting, GERD accounted for less than 10% of diagnoses [25]. A study presenting a multidisciplinary evaluation of children with chronic cough showed that GER and cough were present in nearly half the patients, and a quarter had multiple underlying conditions [26].

Pathogenetic Mechanisms

Chronic cough in patients with GER may be caused by direct irritation of the trachea-bronchial tree after aspiration of gastric contents or by stimulation of the esophageal-bronchial neural cough reflex [27]. Pressure gradient changes between the abdominal and thoracic cavities while coughing may also lead to a cycle of coughing and GER [27].

Although acid reflux appears to be the main determinant of GER-related cough, cough can be associated with all types of reflux. A study showed that nearly 90% of cough spells in children did not correspond with a reflux event documented by pH probe [28]. Borrelli et al. compared the type and physical characteristics of reflux episodes in 24 children with GERD-related cough with those found in children with erosive GERD [29]. No differences between the two groups were found in terms of total reflux episodes, number of acid, weakly acidic, and weakly alkaline reflux episodes, or extent of reflux episodes. However, it was shown that 66% of cough bursts were related to acid reflux episodes, while the remaining one-third of episodes were related to either weakly acid or alkaline reflux. In another study of 145 children, they have showed similar numbers of proximal reflux episodes in patients with GERD-related respiratory symptoms compared to children with GERD presenting with only intestinal symptoms [30]. On the contrary, significantly higher numbers of weakly alkaline reflux in children with GERD-related respiratory symptoms rather than acid reflux were noticed. This supported the hypothesis that reflux acidity is not the main cause of respiratory symptoms [30].

The Role of Anti-acid Drugs for Chronic Cough

A meta-analysis including 19 studies (13 in adults, 6 in children) concluded that PPIs are not effective for cough associated with GERD symptoms in young children and in adults and should therefore not be used [31]. The BTS guideline stated that in otherwise healthy children with nonspecific cough, empirical anti-acid treatment is unlikely to be effective and is generally not recommended [27]. Children with chronic cough and typical symptoms of GERD should undergo medical treatment, such as dietary, lifestyle modifications, and anti-acid therapy [27]. Some other authors suggested considering a three-stage therapeutic trial before diagnosing GER-related cough in children: (1) a clear-cut response to a 4–8-week treatment with PPIs; (2) a relapse on discontinuing medication; and (3) a new response to recommencing medication, with weaning down therapy according to clinical symptoms [3].

GER and Laryngopharyngeal Disease

The reflux of gastric contents into the larynx and/or oropharynx has been claimed to be responsible for nonspecific clinical manifestations overall known as “laryngopharyngeal reflux disease” [3, 32]. The laryngopharyngeal reflux disease is an

undefined clinical entity in childhood. Indeed, many of the symptoms attributed to it in adults are nonspecific or caused by other conditions in children [3].

No standard diagnostic criteria for laryngopharyngeal reflux disease exist. A recent study in children with chronic cough undergoing direct laryngoscopy, bronchoscopy, esophagogastroscopy, and MII-pH testing found that the Reflux Finding Score, a validated eight-items visual score for airway inflammation (subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma/granulation tissue, and thick laryngeal mucus) did not identify GERD [33]. Therefore, the role of laryngoscopy may be to exclude other pathologies. Combining the Reflux Symptom Index and the Reflux Finding Score—which incorporates both laryngeal symptoms and laryngoscopic findings—improved the diagnostic workout in a randomized, placebo-controlled trial of adults with symptoms and signs associated with laryngopharyngeal disease [34]. Unfortunately, no studies have been conducted in children.

The Role of Anti-acid Drugs for Laryngopharyngeal Disease

There are anecdotal reports of responses to anti-acid therapy, but there is a high (about 40%) placebo effect [3]. In adults with suspected laryngopharyngeal reflux disease, otolaryngologists recommended PPIs with both the diagnostic Reflux Symptom Index and the Reflux Finding Score [35]. In the absence of placebo-controlled, double-blind, randomized controlled trials, anti-acid treatment for supposed laryngopharyngeal reflux disease in children is not recommended [3].

Conclusion

There is a possible association between GERD and respiratory disease, but there is not enough evidence to support causality, especially in children. Diagnostic as well as therapeutic management of extraintestinal airway symptoms of GERD is not evidence-based. Combined MII-pH testing should be reserved for patients with suspected extraintestinal manifestations with poor response to conventional treatment. Anti-acids should not be routinely used for the treatment of poorly controlled asthma, chronic cough, and laryngopharyngeal disease. More attention to the relationship between GERD, chronic cough, and other respiratory manifestations should be focused on high-risk populations (neurological impairment and repaired congenital EA/TEF).

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GER and Apnea

8

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Abstract

The relation between gastroesophageal reflux (GER) and apnoea is still debated both in infants and children. From a mechanistic point of view, acid and non-acid GER may cause apnoea through aspiration of gastric content and vagal reflex that may be also triggered by esophageal distention and inflammation. Nonetheless, glottal closure, a brief apnoea, and cough are physiological protective mechanisms to prevent the entrance of refluxate in the respiratory tract. Moreover, respiratory abnormalities may induce GER by creating negative thoracic pressure or positive abdominal pressure. In the first weeks of life and particularly in premature neonates, cardiorespiratory events, including desaturation, apnoea, and bradycardia may often occur but temporal and causal relationship with regurgitation and reflux are rarely proven. Similarly, children with obstructive sleep apnoea (OSA) are not routinely investigated for GER making the association difficult to establish. Esophageal pH-impedance with simultaneous polysomnography is considered the most useful diagnostic technique to detect GER and its temporal association with respiratory events. Nevertheless, data on infants and children with apnoea are scarce because of technical difficulties, high cost, need for expertise, and limited reference values making the relation between GER or GER-disease and respiratory manifestations difficult to clarify. Acid suppressive agents are often started in patients with recurrent respiratory events

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without a proven diagnosis of GER-disease. However, pharmacological empirical treatment is not recommended due to lack of evidence of efficacy and possible adverse events.

Keywords

Reflux · GER · Regurgitation · Apnoea · ALTE · OSA · pH-MII · Children

Introduction

The relation between gastroesophageal reflux (GER) and apnoea has long been advocated and explored but still needs to be fully clarified [1–10]. Desaturation and apnoea in preterm neonates, brief resolved unexplained event (BRUE) and Apparent Life-Threatening Event (ALTE) are often attributed to GER, particularly when occur in postprandial time, despite the temporal and causal relation are not demonstrated in most cases [7, 10, 11]. Reflux episodes and regurgitation occur several times per day in healthy infants and naturally decrease during the first year of life. Nonetheless, brief apneas are present in many preterm infants and progressively disappear without intervention [4, 8]. In school age children few studies investigated the role of GER in sleep apnea [12–16]. The heterogeneity of the population recruited, of definition and of diagnostic criteria of both pathological apnea and GER-disease as well as the lack of intervention trials and follow-up data contribute to the uncertainty of the correlation between these two conditions [7–11].

Pathogenic Links

GER episodes occur several times per day in normal individuals, particularly in postprandial period and in the first months of life, without causing any symptom or complication in the vast majority of cases [7, 9]. GER can be facilitated by different conditions including negative intrathoracic pressure (i.e., in tracheomalacia) or increased abdominal pressure (due to recurrent cough or obesity), congenital malformation (i.e., esophageal atresia, tracheoesophageal fistula), comorbidity (i.e., neurological impairment, cystic fibrosis, achalasia, impaired esophageal motility, achalasia). Two major mechanisms are considered for respiratory symptoms and aponea related to GER: (micro)aspiration of gastric contents during a reflux episode and vagal reflex [10].

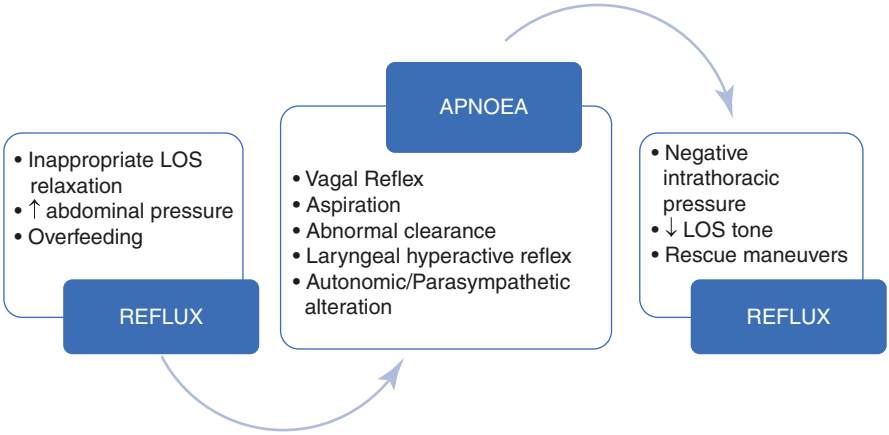
In healthy individuals, a series of anatomic barriers and protective responses prevent refluxed gastric contents from entering the airway. These include the upper esophageal sphincter, esophageal-glottal closure reflex (with consequent protective apnoea), efficient swallowing and pharyngeal clearance, cough and airway clearance of aspirated materials [17]. When GER is of small volume, the upper esophageal sphincter contraction may maintain the content in the esophagus to be cleared by subsequent swallowing and esophageal peristalsis. In case of large-volume reflux, esophageal distention leads to vagal reflexes that cause vocal cord closure

with brief apnea, while upper esophageal sphincter relaxation allows the entrance of refluxate into the pharynx with eventual regurgitation out of the mouth or swallowing to clear the pharynx and rapid resumption of respiration [17]. If reflux enters the larynx a cough burst expels the material from the airway and bronchoconstriction prevents aspirated material from reaching the lower airways [17]. If any of this complex sequence occurs out of order or abnormally, respiratory complications may happen [17].

The neural theory is based on the stimulation of esophageal afferent receptors by esophageal distention or inflammation or laryngeal irritation caused by GER with subsequent respiratory spasm via vagal airway efferent circuits. Noteworthy, preterm infants often present a hyperreactive laryngeal chemoreflex response that may cause apnoea when stimulated by reflux [8]. Apnoea and hypoxia may also decrease lower esophageal sphincter tone thus precipitating reflux [18]. Moreover, since many years a primary or secondary autonomic or parasympathetic alteration has been related to impaired regulation of the lower esophageal sphincter (LOS) and to GER [19]. The contributing factors to the GER-apnoea and apnoea-GER sequence are illustrated in Fig. 8.1.

Adult patients with GERD showed reduced vagal tone in a 24-h analysis of heart rate variability [20] and a lower rate of heart high frequency was reported in patients with laryngopharyngeal reflux compared to healthy subjects [21]. Data in children are limited. In neonates, a significant increase in the sympatho-vagal ratio (+32%, $P = 0.013$) was observed in the period immediately prior to reflux (due to a 15% reduction in parasympathetic activity ($P = 0.017$)) compared to the control period. This phenomenon was observed during both wakefulness and active sleep [22].

However, the potential role of inflammation and cause-effect relation is still unclear. Individual hypersensitivity to esophageal stimuli can also contribute to



Legend: LOS = lower oesophageal sphincter; ↑ = increased; ↓ = reduced

Fig. 8.1 The contributing factors and sequential correlation between gastroesophageal reflux and apnoea

autonomic variation even in healthy subjects [23, 24]. Esophageal or respiratory hyper-reactivity or hypersensitivity or impaired airway protection may contribute to the occurrence of prolonged apnea and aspiration but all these variables are difficult to investigate. Nonetheless, apnoea can also induce GER by creating a negative intrathoracic pressure [7, 25] and esophageal sphincter relaxation [26].

Noteworthy, both acid and non-acid GER can even play a protective role for ALTE and sudden infant death syndrome (SIDS) by facilitating arousals and awakening during sleep [4, 27–29].

Furthermore, the vigilance state may modulate the distribution of GER events, with 53% observed during wakefulness, 38% observed during active sleep, and only 9% observed during quiet sleep [22]. A number of studies have associated poor quality of sleep characterized by irregular breathing patterns with reflux [2, 4, 27, 30–33]. Pain or discomfort related to weakly acid and acid reflux episodes [34] may also contribute to arousals. Both acid and non-acid refluxes have been reported to be associated with apnoea. However, the temporal relation and specific association with different type of apnoea (obstructive, central, or mixed apneas) is still controversial.

In children and adults GER has been linked to obstructive sleep apnoea (OSA) syndrome (OSAS). OSA is characterized by repetitive narrowing or collapse of the upper airway during sleep, with the development of large negative intrathoracic pressures during inspiratory efforts against the occluded airway, until restoration of airway patency with arousal from sleep [35]. In adults, OSA has been associated with increased occurrence of nocturnal symptoms of GER [36] as well as increased number and length of overnight GER episodes (2000). In children the relation has been poorly investigated so far.

Continuous positive airway pressure (CPAP), the mainstay therapy for OSA (in adults), may reduce reflux events and improve symptoms of nocturnal GER [36] through a beneficial effect (increase pressure and/or reduced transient relaxations) on LOS [37].

Interestingly, obesity predisposes to OSA and GER(D) both in adults [35] and in children [7].

The clinical relevance of the proximal extension of a reflux in generating respiratory events or other symptoms is still unclear. A strong association between symptoms and proximal reflux was sustained by some authors [38, 39] but could not be confirmed by others [40–42]. The majority of reflux events in asymptomatic preterm reached the proximal esophagus or pharynx, and there were no differences between acid and non-acid reflux [43]. Thus, besides macro- or micro aspiration, hypersensitivity to reflux may precipitate respiratory symptoms [43].

One report investigating 20 preterm infants (10 with ALTE and 10 controls) with simultaneous pharyngoesophageal manometry, respiratory pletismography, and nasal thermistors suggested a role of esophageal motility in generating apnoea. The authors found more frequent and prolonged spontaneous respiratory events (defined as apnoea >2″ with ≥2 “missing” breathing), less contraction of upper esophageal sphincter, more frequent disturbed esophageal propagation, mixed apnoea, and gasping in patients with ALTE compared to controls [44].

Apnoea, ALTE, and GER(D)

The relation between apnoea or ALTE and GER was originally based on concurrent regurgitation and/or results of esophageal pH monitoring which was reported as pathological pH monitoring in a wide range of 20% [45]–77% [30] in infants with ALTE and of 32% [46]–100% [47] in infants with apnoeas. In the last decades a number of studies investigated infants with esophageal pH-impedance (pH-MII) and simultaneous cardiorespiratory or polysomnography monitoring but still showing conflicting results. In highly selected cases, reflux is temporally associated with central and obstructive apnoea [28] but no study has conclusively shown a cause and effect relation between reflux and pathologic apnoea [10].

APNOEA and GER(D): Studies in Infants

A number of old studies that used pH monitoring to detect GER reported an occasional correlation of GER with obstructive or short mixed central apneas (5–15 s) [2–4, 46, 48], but also many unrelated respiratory events [49]. Large case series did not find a significant relation between GER and pathologic apnoea or ALTEs [27, 31]. One retrospective study showed that GER-related apnoea improved rapidly starting gastrojejunal feeding, suggesting that in selected cases reflux may cause apnoea [50]. In 1999, Wenzl introduced pH-MII monitoring in infants and first demonstrated that 30% of episodes of apnoea longer than 5 s were associated with GER and that the majority (78%) of reflux episodes were not detectable by pH monitoring only, as they had non-acid content [51]. Since then, investigating infants with pH-MII and polysomnography or cardiorespiratory monitoring, different authors suggested a relation between (long, >30 s) apnea or desaturation or bradycardia (in preterm infants) and acid and non-acid reflux [52, 53] while others denied this association [43, 54–57]. No difference was found regarding proximal extension or duration of GER between reflux events associated or not associated with apnoea [58]. Similarly, the findings of laryngeal inflammation at laryngoscopy is not significantly related to pathological pH-MII [25, 59].

The influence of body position on GER and eventual apnoea has also been explored. In ten healthy preterm infants, a "cross-over position study" and postprandial evaluation showed more liquid GER in the right than in the left lateral position (median 9.5 [range 6.0–22.0] vs. 2.0 [range 0.0–5.0] episodes/hour; $P = 0.002$). Conversely, gastric emptying was faster in the right than in the left lateral position (37.0 + 21.1 vs. 61.2 + 24.8 min; $P = 0.006$) [60]. In another report enrolling 22 preterm babies with regurgitation and postprandial desaturations, the number of acid and non-acid reflux episodes was significantly reduced when the subjects were in the prone and left-side position than when they were in the supine and right-side positions [61].

The NICE [62] and ESPGHAN-NASPGHAN 2009 and 2018 guidelines [7, 9] showed that GER only rarely causes apnoea or ALTEs, and recommended synchronous pH-MII in combination with polysomnography in selected cases of

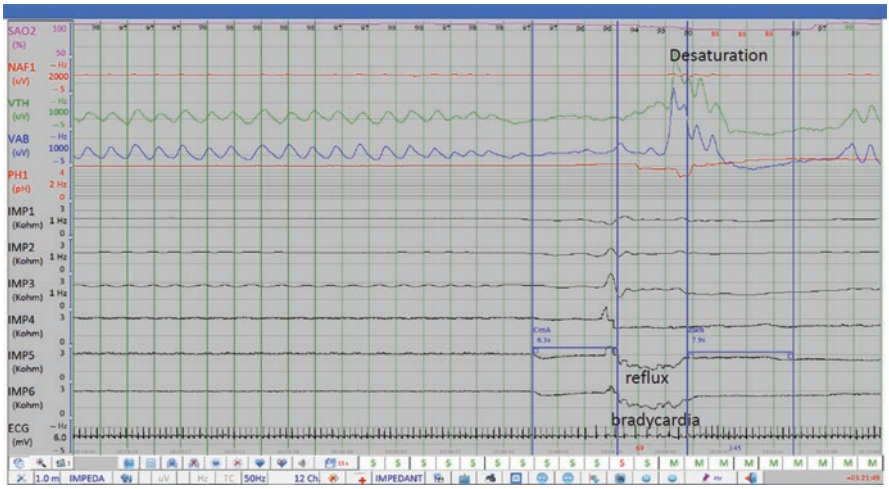


Fig. 8.2 A reflux episode detected by pH-MII and a temporally associated cardiorespiratory event

unexplained recurrent respiratory events. Figure 8.2 shows an example of a reflux episode detected by pH-MII temporally associated to a cardiorespiratory event showed by a polysomnography.

In a large cohort or preterm newborns (7.5% out of 1,384,013 singleton births) a multivariate analysis identified two apnoea predictors, GER (OR = 3.19, 95% CI = 2.80–3.63) and early gestational age (OR = 0.83 for 1-week GA increase, 95% CI = 0.82–0.84) [63].

In another group of 66 infants (aged 18–45 days) enrolled in Neonatal Intensive Care Unit because of cardiorespiratory (CR) events (apnoea/desaturation or bradycardia) and submitted to pH-MII and simultaneous cardiorespiratory monitoring, the symptom association probability index for GER was positive in seven (12%) infants. These infants had greater reflux frequency, duration, and proximal extent compared to the negative infants. GER episodes preceded CR events in 83% of these temporal (within 30 s) associations and had higher proximal extent but showed no differences in pH content [64]. A similar result was found in a prospective observational study of 47 preterm and term infants. Only a minority (12%) of events were temporally (within 2 min) associated with GER episodes; symptom association probability detected by pH-MII was positive in 11% of patients and in half of them GER preceded the CR event with no correlation with the chemical content of the refluxate [65].

Conversely, in another cohort of 40 infants apnoeas were not more frequent following GER (within 5 min period) than during GER-free periods. The frequency of apnoeas and reflux episodes were inversely related to post-conceptional age at testing, but were not significantly correlated with each other [66].

A retrospective study reviewed 101 full-term infants (age under 12 months) diagnosed with apnoea of infancy when apnoea-hypopnea index (AHI, defined as the number of apnoea and hypopnea events per hour of sleep) was greater than 1 based

on multichannel pneumogram or an overnight polysomnogram. The underlying three most common etiologies were GERD in 48% of cases, upper airway abnormalities/obstruction in 37% and neurological diseases 19%, determined according to the physician clinical assessment and eventual investigations in selected cases [67].

Two systematic reviews [10, 68] highlighted the limited data available on the association between GER and apnoea in infants. The conflicting results, the small population recruited, the heterogeneous inclusion and diagnostic criteria for both pathological apnoea and reflux, the lack of follow-up data and therapeutic outcomes do not allow to draw a general conclusion. Moreover, empirical pharmacological treatment for GER is not recommended because no symptom or characteristic of respiratory event accurately predicts the result of pH-MII, because there is no evidence of efficacy of reduced GER and apnoea with prokinetics or acid suppressive agents while possible adverse events have been documented (i.e., increased incidence of infections with acid inhibitors and cardiac problems with prokinetics) [8, 9, 34].

ALTE and GER(D)

GER(D) has long been considered the most common cause of ALTE and reported in a range of one third to two third half of cases [69–73]. Nevertheless, proper investigations for GER(D) were rarely performed and diagnosis of GERD was mostly based on reported regurgitations concomitant to the episode or in previous weeks though regurgitation is extremely common in the first months of life in healthy infants and is neither specific nor sufficient to the diagnosis of GERD.

In selected patients with ALTE, acid perfusion of the esophagus induced obstructive apnoea [74] or oxygen desaturation [75], suggesting that one mechanism for ALTE is acid stimulation of laryngeal, pharyngeal, or esophageal chemoreceptors with subsequent laryngospasm. Abnormal pH monitoring was found in 42% of 62 infants with episodes of paleness possibly suggestive of an ALTE, compared with 8.5% of the 378 control infants [4]. However, in the early 1990s, three small studies showed no significant difference in terms of acid reflux percentage or duration between infants who had experienced an ALTE and controls [5, 27, 76]. In 67 infants with ALTE investigated with Ph monitoring for ≥10 ore, Arad-Cohen reported pathological GER in 53% of infants but 81% of apneic events were not associated with GER and apnoeas preceded GER in nearly all (94%) of the minority of associated episodes [6]. Another study reported less frequent ALTE in 173 infants with GERD (defined as a reflux index greater than 5% on pH monitoring) than in 169 healthy controls (20% vs. 31%, $P < 0.12$) [45].

In retrospective reviewed records from a group of 313 infants hospitalized for ALTE, GERD was the most common (49%) discharge diagnosis but reflux investigation (pH monitoring) was performed only in one patient. Interestingly, within 6 months, 14 patients (9%) of this GERD group had recurrent ALTE [77]. A large revision of 12,067 American infants experienced ALTE, confirmed that GER was

the most common associated diagnosis, occurring in 37% of cases, but with a considerable heterogeneity in the diagnostic criteria among hospitals. An increased likelihood of readmission for patients discharged with a diagnosis of cardiovascular disorders (odds ratio [OR] = 1.68; 95% confidence interval [CI] = 1.30 to 2.16) and GER (OR = 1.32; 95% CI = 1.03 to 1.69) compared with other discharge diagnoses was also reported [78].

Another retrospective cohort study of 469 infants admitted for ALTE found that adverse outcomes associated with GERD (including aspiration pneumonia, failure-to-thrive, or anti-reflux surgery), second ALTE, or death were rare (3.8%) and significantly related to neurological impairment or long hospital staying, in a follow-up period of approximately 8 years [11].

In the last two decades, despite the advent of pH-MII, clinical diagnosis of GER in subjects admitted with ALTE is still frequent [79].

Mousa et al. [80] performed pH-MII in a group of 25 infants (11 preterms) who presented with an ALTE event or pathologic apnoea. Only 15.2% of apnoea were temporally linked to a reflux episode (despite the large temporal window of 5 min established by the authors to detect the association between the two phenomena). Of these episodes, half were related to an acid reflux episode and half to a non-acid reflux episode [80]. Another analysis of 39 infants with ALTE reported abnormal GER pH-MII parameters in 33 (85%) of cases of whom only 14 (36%) could be detected with only pH monitoring, confirming an increased frequency of non-acid reflux events [81].

As a new episode of ALTE during the investigation is extremely rare, pH-MII can only identify underlying GER-disease and/or temporal association with episodes of apneas/desaturation during the monitoring [73].

The effect of GER treatment in infants with ALTEs is not clinically predictable and has not been adequately studied. The incidence of ALTEs diminishes with age and without therapy in most cases, suggesting that anti-reflux therapy should be reserved in the rare case in whom ALTEs and apnoeas are demonstrated to be GER-related [7]. Moreover, despite supine position is associated with increased rate of reflux events, it should be promoted to decrease the risk of SIDS.

SIDS has been associated to a previous ALTE and GER [28, 32, 82]. However, in none of these patients a correlation between esophageal acidification and a cardiopulmonary event was ever recorded. At present there is no evidence that the characteristics of the ALTE or the polysomnographic record can predict which infants with ALTE are at risk for future life-threatening episodes or sudden death or GERD.

In 2013 a review on ALTE [72] concluded that routine investigation for GER is not necessary but patients with recurrent ALTEs or symptoms of GER not responsive to behavior and diet treatment can benefit from pH (or, better, pH-MII) monitoring combined with symptoms (and polysomnography) registration to establish a cause-effect relation or another etiology [72].

In case of brief resolved unexplained events (BRUE) GER can be associated with or without overt regurgitation and should be considered as a (co)factor for respiratory abnormalities and recurrent events [73, 83].

In conclusion, the available evidence suggests that in the vast majority of infants, GER is not related to pathologic apnoea or to ALTE [7, 10, 11, 26, 73] and thus there is no evidence to support an empirical treatment of GER in infants presenting with a respiratory event regardless the presence of regurgitation. However, in unexplained recurrent episodes pH-MII in combination with polysomnographic recording is recommended to identify underlying GER-disease [7, 9, 10, 73].

Studies in Children

The role of acid and non-acid GER in respiratory symptoms in children still need to be fully clarified [9, 84]. GER can be primary present or secondary to respiratory symptoms. Moreover, during the investigation respiratory events may not happen or when they occur the correct temporal sequence of "respiratory-reflux" or "reflux-respiratory" or "respiratory-reflux-respiratory" is often difficult to determine without combined sensitive tools. Polysomnography has demonstrated a better accuracy compared to cardio-monitoring or transcutaneous oximetry to detect and define apnoeas. However, polysomnography is not widely used because of the cost of the equipment and the complexity of the analysis [85]. Furthermore, most studies used synchronization of the internal clock of the two instruments (polysomnography and impedance) without showing the simultaneous tracings on the same screen of the computer limiting the accuracy of the temporal association and sequence between apnoea and GER.

OSAS and GER

It is estimated that 9–10% of children are habitual snorers or have sleep disordered breathing related illnesses [86]. Snoring and occasional apneic breath holding in sleep is common, but only when witnessed repetitive apnoeas and symptoms of sleep fragmentation, such as excessive daytime sleepiness, occur a diagnosis of obstructive sleep apnea (OSA) syndrome (OSAS) can be made [85]. Conventionally, an apnoea is considered as a cessation of airflow for 10 s and is often associated with oxygen desaturation, whereas a lesser reduction in airflow is termed a hypopnea [85]. Sleep studies measure the apnoea/hypopnea index (AHI), which is the number of respiratory events an hour. According to adult studies, daily sleepiness is prevalent when the AHI exceeds five events an hour, and this value is considered the cut-off for the diagnosis of OSAS [85].

The ideal method for diagnosis of sleep apneas is full polysomnography, which involves overnight admission for supervised multichannel recording, including electroencephalography [85]. Overnight oximetry is widely available and oxygen desaturation of 4% is used to indicate apnoea [85]. Obstructive sleep apnea occurs in approximately 3% of children, most frequently aged from 2 to 6 years [86]. OSAS diagnosis is clinically relevant because recurrent episodes of air flow cessation, oxygen desaturation, and sleep disruption are associated with behavior

disorders, neurocognitive deficits, disturbances of somatic development as well as cardiovascular and metabolic sequelae [84, 87].

The etiology of OSAS is multifactorial consisting of a complex interplay between airway anatomical characteristics and dynamic control of upper airway muscular tone [88]. Obstructive sleep apnea is hypothesized to be influenced by genes involved with obesity, craniofacial development, inflammation, and ventilator control [89]. Adenotonsillar hypertrophy is recognized as the most frequent cause of OSA in childhood [90]. The association between GER and OSAS in children has been less explored compared to apnoea in infants and, as well as in adults, remains controversial.

Adult studies reported an association between nocturnal GER episodes and apnoea or hypopnea in a range of 54–70% [35, 91–93], suggesting a (mild) causal relationship between obstructive respiratory events and nocturnal GER events, but also, reflecting the large number of apnoeas and hypopneas that occur during the night in patients with OSA, the high probability, by chance, of a nocturnal GER event occurring in proximity to any given respiratory event [35].

In several studies acidification of the distal esophagus was suggested in the mechanism of OSA in children and adults and in persisting OSAS after adenoidectomy [12, 94–97]. A report in 18 children with adenotonsillar hypertrophy and OSAS evaluated the OSA-18 questionnaire, nasofibrolaringoscopy and full overnight polysomnography performed simultaneously with esophageal pH monitoring. Seven children (41%) presented episodes of acid reflux during the registered sleep time. The authors concluded that GER is frequent and should be assessed in children from 6 to 12 years with OSAS [12]. However, reflux parameters did not correlate to OSAS severity and a temporal relationship between GER and apnea-hypopnea events was not observed [12].

In the last years a number of studies evaluated the presence of GER in children with obstruction OSA and sleep disorders breathing (SDB) but their relationship is still uncertain.

A multivariate linear regression analysis of data from 770 Canadian infants and young children whose parents completed the 22-item sleep-related breathing disorder (SRBD) scale found a significant association between GER-disease and early-onset (peak symptoms at 9 months) and late-onset (peak symptoms at 18 months) SDB [14].

Among 82 infants and children under 2 years of age referred for a brief unexplained respiratory event or for sleep apnoea, investigated with polysomnography, esophageal pH-MII and nasopharyngoscopy the authors found tonsillar and adenoidal hypertrophy more detected in the group aged 12–24 months, while laryngomalacia and GER were more frequent in the younger group and associated with grade of apnoea-hypopnea index severity [15].

A retrospective analysis of children presenting SDB reported a significantly higher prevalence of pharyngeal/swallowing disfunction and GERD in the 73 subjects with early-onset (before 4 years of age, range 1.75–3 years) disorder while 147 later onset patients (range 4–16 years) more commonly presented with associated asthma or obesity [13].

A retrospective case series of 413 children under 3 years of age who had polysomnogram because of OSA found that infants more commonly had GERD (38% vs. 23%, $P = 0.014$). In contrast, tonsillar hypertrophy was more common in children over 2 years of age (56% vs. 34%, $P = 0.001$) and represented a predictor of severe OSA (OR: 1.97, 95% CI = 1.28–3.02, $P = 0.002$) as well as the presence of Down syndrome (odds ratio (OR): 3.16, 95% confidence interval (CI) = 1.14–8.68, $P = 0.026$) [98].

Using a big data approach in a cohort of 9773 infants and young children with a diagnosis of sleep apnoea disorders, GER(D) was one of the most common comorbid diagnoses that also include micrognathia, congenital airway abnormalities, chronic tonsillitis/adenoiditis, and anomalies of the respiratory system [16].

The main treatment options of OSAS are essentially continuous positive airway pressure (CPAP), oral appliances, and upper airway surgery. Weight loss and bariatric surgery may also be appropriate interventions in obese individuals [85].

In adults, treatment of GER has been shown to improve OSAS [96, 99] and OSAS therapy with CPAP has reported to reduce GER [100] confirming a bidirectional association between these two conditions. The favorable effect of CPAP on nocturnal GER is possibly due to an increase in nadir LOS pressure and decrease in the duration of LOS relaxation [35].

In eight newborn lambs pH-MII and polysomnography were performed for 6 h during both spontaneous breathing and nCPAP application at 6 cmH_2O, in a randomized order. CPAP virtually abolished GER (mean ± SD reflux number for 6 h = 9.1 ± 8.6 without nCPAP vs. 0.6 ± 1 with nCPAP, $P = 0.05$) and decreased the depth and duration of LOS relaxation suggesting that nCPAP may enhance the barrier function of the LOS reducing (acid and nonacid) GER episodes [101, 102].

The low basal pressure of LOS detected in some OSA patients raises the possibility of weakening of the gastroesophageal junction from repetitive strain associated with obstructed breathing events.

Prospective studies assessing natural evolution of patients with concomitant GER and apneas and benefit of GER treatment in children are lacking.

Conclusion

The association between GER and apnoea in infants and children has long been considered. However, in most cases the temporal and causal association as well as the benefit of GER treatment have not been demonstrated. Moreover, the limited number of studies, the small and heterogeneous population recruited, the different diagnostic criteria for both respiratory events and GER-disease do not allow to clarify the relationship between the two conditions. The occurrence of regurgitation during or before the apnoea does not provide a diagnosis of reflux disease and empirical pharmacological treatment is not recommended due to the lack of evidence of efficacy and possible related adverse events. In selected cases of recurrent unexplained or life-threatening respiratory events, pH-MII with simultaneous polysomnography recording should be performed to detect underlying GERD and to identify the relationship with apnoeas.

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GER in Cystic Fibrosis

9

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Abstract

Increased levels of gastroesophageal reflux (GER) are common among people with cystic fibrosis (CF). Multiple intraluminal impedance-pH (MII-pH) studies involving small sample sizes (n = 11–44) of children and adults with CF (not taking anti-reflux medications and no history of fundoplication) have shown that most children and adults with CF experienced increased GER. Among children, 46.4–81% were diagnosed with GERD disease (GERD). Among adults,

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66.7–100% had GERD. Approximately two-thirds of the detected GER events were acidic (pH < 4) and a third of these events reached the proximal esophagus. The presence of proximally reaching GER episodes remains a constant concern for clinical management of GER in children and adults with CF. Data from the few available studies suggest that Nissen fundoplication decelerates lung function decline, improves weight gain, and reduces the frequency of pulmonary exacerbations. Future studies are needed to assess the impact of CFTR modulator therapy on GERD in people with CF.

Keywords

Cystic fibrosis (CF) · Gastroesophageal reflux (GER) · GER frequency in CF GER Disease (GERD) frequency in CF · GER treatments in CF

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder among Caucasians, caused by variants in the gene encoding the CF transmembrane conductance regulator (CFTR) protein [1]. Interestingly, because CFTR heterozygotes express 50% of the normal CFTR protein on the surface of epithelial tissues, it has been posited that CFTR variant heterozygosity provides protection against cholera toxin-induced secretory diarrhea and therefore a survival advantage in the pre-antibiotic period [2, 3].

CFTR is an anion channel that regulates chloride, bicarbonate, and associated fluid secretion on the apical epithelia of numerous tissues of the respiratory, gastrointestinal, and reproductive tracts along with sweat glands and immune cells [4]. Inheritance of two CFTR alleles that results in nonfunctional (or insufficient amounts) CFTR protein will cause accumulation of thick mucus in the lungs, impaired intestinal secretion and absorption, and a loss of exocrine pancreatic function [3, 5].

Gastroesophageal reflux (GER) is known to occur frequently in people with CF and studies have suggested that GER is associated with CF-related lung disease [6–8]. Advances in science, technology, and patient care have resulted in tremendous increases in the longevity and quality of life for people living with CF, but how these new advances impact GER and its impact on health in CF remains poorly understood.

This chapter provides a brief review of the current literature that describes GER, CF, and the relationship between GER and progressive lung disease in people with CF.

Gastroesophageal Reflux and Gastroesophageal Reflux Disease

GER is the retrograde movement of gastric contents into the esophagus. Clearance of GER from the esophagus occurs in two phases, the first being the volume clearance phase wherein the bulk of the refluxate is cleared by peristalsis. Volume

clearance is accomplished by mechano (stretch)-receptor triggered secondary peristalsis followed by swallow-induced peristalsis. The second phase of esophageal clearance is chemical clearance wherein the esophageal mucosa is returned to pre-reflux conditions by saliva that is carried through the esophagus by swallow-induced primary peristalsis. Acid GER is neutralized by bicarbonate present in saliva, and that which is secreted into the esophageal lumen from submucosal glands [9–14].

Refluxed material is mainly composed of pepsin, hydrochloric acid, and gastric lipase from the stomach and occasionally trypsin and bile acids from the duodenum [15]. Depending upon the contents of the most recent meal, the refluxate can be either acid (pH < 4) or nonacid (pH ≥ 4). In infants who receive frequent feeds of human breast milk and/or milk-based formula, the majority of GER events are non-acid [16].

While GER is a physiological phenomenon occurring most often immediately following a meal when increased intra-abdominal pressure causes the lower esophageal sphincter (LES, a major component of the anti-reflux barrier) to relax, GER disease (GERD) occurs when GER is associated with symptoms [17]. GERD symptoms include both esophageal symptoms and extraesophageal symptoms. Esophageal symptoms include heartburn, chest pain, globus, dysphagia, and vomiting. Extraesophageal symptoms may include respiratory symptoms like coughing, gagging, choking, wheezing, hoarseness, non-cardiac chest pain, chronic throat clearing, and chronic sore throat [18].

Cystic Fibrosis

CF is a common autosomal recessive lethal disease that affects upwards of 30,000 people in the USA and nearly 70,000 worldwide [19]. The severity of the disease is dependent upon the nature of the variant (type and location). The most recent classification scheme used to group CFTR variants are (Class I) variants that effect protein production, (Class II) variants that effect protein processing, (Class III) variants that effect gating, (Class IV) variants that effect conductance, (Class V) variants that result in insufficient amount of protein, and (Class VI) variants that lead to conformational destabilization or the addition of alternative trafficking signals [20–22]. CFTR is expressed throughout the body, leading to multi-system disease effects including severe respiratory and gastrointestinal manifestations [21, 23, 24].

Due to abnormal CFTR function and subsequent altered ion conductance, people with CF produce thick secretions that are difficult to expel from the lungs and GI tract. In the lungs, failed mucociliary transport in combination with dysregulated immune responses results in recurrent infection, inflammation, and progressive lung damage. Exacerbations of chronic pulmonary symptoms along with malnutrition are leading causes of morbidity and eventual mortality [25].

GI manifestations in CF are common, including exocrine pancreatic insufficiency, GERD, hepatobiliary disease, dysmotility, dysbiosis, distal intestinal obstruction syndrome, and malignancies. GERD is the second most common GI disorder in CF and is likely underdiagnosed due to lack of typical symptoms, but

effective treatment strategies remain controversial. Feigelson and Souvegrain were the first to report GER in people with CF and prevalence estimates of acid GER range between 35% and 81% [26].

What is the Mechanism of Increased GER in CF?

The mechanism of GER in people with CF is like people without CF in that it involves transient lower esophageal sphincter relaxations (TLESR) to release gastric contents into the esophageal lumen [27]. Interestingly, Pauwels and collaborators [28] found that while the number of TLESRs were no different between CF and non-CF controls, the number of TLESRs during which GER occurred was significantly more frequent in people with CF. Previous work suggests that the increased GER during TLESRs is due to the lower inspiratory intrathoracic pressure observed in CF by the high gastroesophageal pressure gradient between the thoracic and abdominal cavities [28, 29]. These investigators also found that GER ascended to the proximal esophagus more often in the CF cohort when compared to healthy controls.

Interestingly, despite the numerous factors (Table 9.1) [6, 28, 30–33] that predispose people with CF to GER, Blondeau et al. [34] showed that GER is a primary phenomenon in children with CF, and not secondary to CF-specific factors or advanced lung disease. In a study of 11 patients with CF who were tested simultaneously with multichannel intraluminal impedance and pH monitoring (MII-pH) and manometry, these researchers identified the reflux-to-cough series in eight children (72.7%) and the cough-to-reflux series in only 3 (27.3%). Additionally, a positive symptom association probability (SAP ≥ 95%) for reflux-to-cough was discovered. Pauwels et al. however found that GER can be a secondary phenomenon to advanced lung disease in adults, with GER occurring during inspiration [28]. Their data also showed that the esophagogastric junction barrier can be overcome in these patients

Table 9.1 Factors that predispose patients with cystic fibrosis to gastroesophageal reflux

Predisposition	GER mechanism
• Airway hyperinflation from obstructive lung disease	• Causes diaphragmatic dysfunction → effects a change in the pressure gradient between the thorax and abdomen
• Frequent cough	• Causes increases in abdominal pressure → LES relaxation
• Hyper-alimentation to mitigate malabsorption	• Maintains increased intra-abdominal pressure from a feed
• Delayed gastric emptying	• Maintains the pressure of a feed longer—increased intra-abdominal pressure
• High-fat diet	• Fat → refluxogenic (long-chain fatty acids receptors mediate LES relaxation)
• Positional changes related to chest physiotherapy	• Leads to sporadic increases in intra-abdominal pressure → LES relation
• Frequent use of bronchodilators	• Decreases LES tone

when the inspiratory gastroesophageal pressure gradient is increased thus allowing GER to occur [30].

Esophageal Motility in CF

Esophageal clearance is accomplished largely by peristalsis; mechanoreceptor-induced secondary peristalsis and swallow-induced primary peristalsis [11]. The vast majority of refluxed material is cleared by secondary peristalsis (volume clearance), leaving behind residuals of refluxed material that are cleared by swallowed saliva (chemical clearance) during primary peristalsis [9, 12, 13]. In an investigation of 14 children with CF (range 5 months to 16 years) and 10 age-matched symptomatic children without CF, Cucchiara et al. [27] recorded significantly lower amplitudes of primary peristalsis in the CF cohort. Also, the ability to clear the esophagus by primary peristalsis following an acid GER event was significantly lower in the CF group [27]. In a study of ten adults with CF assessed using standard manometry, Ledson et al. [35] found that 3 (30%) patients lacked coordinated peristalsis [35]. In a later study of 12 adults with CF, Pauwels et al. [28] found 2 (16.7%) patients with frequent failed peristalsis and 3 (25%) with absent peristalsis. While these data suggest suboptimal volume clearance in adults with CF, in a retrospective study of 16 children with CF (ages 3–17) and 16 age-matched symptomatic controls, we found that volume clearance was more efficient in the CF cohort. Furthermore, the percentage of total GER reaching the proximal esophagus was significantly lower in the children with CF [36] compared to non-CF controls. In a more recent study aimed at comparing the velocity of saliva transport in this same cohort (16 children with and 16 without CF), our group used combined MII-pH and found no difference in saliva transport velocity between groups (5.21 ± 0.28 cm/sec [non-CF] versus 5.15 ± 0.34 cm/sec [CF], $p = 0.904$) [37].

Incidence of GER and GERD in Children with CF

A review of the literature identified six studies in which MII-pH was used to assess GER in children with CF who were (1) not receiving anti-reflux medications and (2) did not have a history of fundoplication prior to the MII-pH assessment. These studies are reviewed below and summarized in Table 9.2.

In an assesment of 24 children with CF (0.3–13 years, 12 females) Blondeau et al. [34] detected 1051 total GER events (mean 40 per patient, range of 33–59). Approximately two-thirds (62.7%) of the reflux events were acidic and about a third (31%) reached the proximal esophagus (impedance channel Z1). Using an acid reflux index (ARI) of >12% for infants (≤12 months) and >6% for children (>1 year) [40], 16 (66.7%) participants had GERD. Interestingly, seven of the 16 children with GERD (43.7%) did not have any symptoms that were associated with reflux. CFTR genotype was not identified as a modifier in this study.

Table 9.2 Combined impedance and pH monitoring in children with cystic fibrosis who were off anti-reflux medications and no lung transplants

Authors	N	Age	Genotype (DF508(2)/ DF508(1)/other)	#GER per subject	%AGER (pH < 4)	%NAGER (pH ≥ 4)	%Prox-GER (criteria)	Criteria for GERD	GERD# (%)
Blondeau et al. 2010	24	Mean 4 yrs range (0.3–13)	5/8/11	Mean 40 (range 33–59)	62.7%	37.3%	31% (Z1)	≤1 year – ARI >12% >1 year – ARI > 6%	16 (66.7%)
Doumit et al. 2012	20	Median 12 mos range (8–34)	12/8/0	Median 45 IQR [30–55]	63%	37%	72% (Z1)	≤1 year - ARI >12% >1 year - ARI > 6%	10 (50%)
Carldaro et al. 2014	31	Mean 12.6 yrs range (4–17)	NR	Mean 66 range (32–126)	65.2%	34.8%	28% (Z1?)	positive pH-MII test	17 (54.8%)
Woodley et al. 2014	16	Median 8.2 yr range (3.1–17.7)	10/4/2	Mean 54.2[b] range (16–110)	88.7%[b]	11.3%[b]	55.7% (Z2 or Z1)	ARI > 5%	13 (81%)
Dziekiewicz et al. 2015	44	Mean 10.4 yr range (3.0–17.8)	NR	Median 35 IQR [20.0–46.3]	75.6%	24.4%	43.6% (Z1?)	ARI > 6%	24 (54.5%)
Hauser et al. 2016	28	Median 4.4 yrs range (1–17)	11/7/5[c]	Mean 35.5[a]	66.6[a]	33.3%[a]	NR	ARI > 5%	13 (46.4%)

Formatting was adapted after Bongiovanni et al. [38] and Ng et al. [39].

IRQ interquartile range, *ARI* reflux index, *#GER* mean or median number of gastroesophageal reflux events, *GERD* GER disease, *%AGER* percentage of acid gastroesophageal reflux events, *%NAGER* percentage of nonacid gastroesophageal reflux events, *yrs* years, *%Prox-GER* percentage of total GER events that reached the proximal esophagus, *NR* not reported

[a]Values are the product of extrapolation from data published in the original paper; percentages were calculated using the published median values for GER, AGER, and NAGER. These values therefore represent estimates

[b]Data not published in the original study

[c] There were five patients in the Hauser study who had unknown genotypes

Doumit et al. [41] studied a group of 20 infants and toddlers with CF (8–34 months, 12 females). Of the 1374 total reflux events detected (median 45, IQR 30–55), approximately two-thirds (63%) were acidic and almost three-quarters (72%) reached the proximal esophagus (Z1). Again, using an ARI of >12% for infants (≤12 months) and >6% for children (>1 year) [40], 10 (50%) of the 20 children had GERD.

In a study of 31 children with CF (4–17 years, 21 females), Caldaro et al. [42] detected an average of 66 events per patient with two-thirds (65.2%) of them being acidic and less than a third (28%) of them having reached the proximal esophagus (proximal channel not reported but assumed to be Z1). Studies were considered abnormal if the DeMeester score was ≥14.72 and the total number of GER episodes was ≥50. Based on these criteria, 17 (54.8%) children had GERD. None of the subjects had symptoms that were significantly associated with GER.

In an investigation of 16 children with CF (3.1–17.7 years, 10 females) [36], our group detected an average of 54.2 events per patient with over three-quarters (88.7%) of them being acidic and more than half (55.6%) of them reaching the proximal esophagus (either Z1 or Z2). MII-pH results were considered pathological if the ARI were >5% [43]. With this criterion, 13 of the 16 children (81%) had GERD. Data presented here originated from that study but were not published [36].

Dziekiewicz et al. [44] studied a group of 44 children with CF (ages 3.0–17.8 years, 22 females). A total of 1585 GER episodes were detected with three-quarters (75.6%) of them being acidic and less than half (43.6%) of them reaching the proximal esophagus (channel Z1 assumed). Studies were considered to be abnormal if the ARI was >6% [40]. Based on this criterion, 24 of the 44 subjects (54.5%) had GERD. Typical GER symptoms were absent in most patients.

In an assessment of 28 children with CF (ages 1–17 years, 14 females), Hauser and collaborators [45] detected a median of 35.5 GER episodes per patient with approximately two-thirds (66.6%) of them being acidic; the number of proximal GER were not reported. A MII-pH study was considered to be abnormal if the AGER index was >5% [40]. Using this criterion, 13 of the 28 children (46.4%) had GERD. AGER and NAGER percentages and median GER presented here are estimates calculated from data in the original paper (Table 9.2).

Taken together, these studies indicate that the frequency of GER in children with CF is approximately 42 per day, with two-thirds (60.6%) of them being acidic and more than a third (43.6%) of them reaching the proximal esophagus. They also show that among children with CF and GER, who are off anti-reflux medication and have no history of fundoplication, over half of them (median 54.6% [range 46.4–81%]) have GERD.

Incidence of GER in Adults with CF

A review of the literature revealed only three studies in which MII-pH studies were conducted with adults with CF who were off anti-secretory medications prior to testing and had no prior history of fundoplication (Table 9.3).

Table 9.3 Combined impedance and pH monitoring in adults with cystic fibrosis who were off anti-reflux medications and no lung transplants

Authors	N	Age	Genotype (DF508(2)/ DF508(1)/other)	#GER per subject	%AGER (pH < 4)	%NAGER (pH ≥ 4)	%Prox-GER (criteria)	Criteria for GERD	GERD# (%)
Blondeau et al. 2008	23	Mean 26 yrs, range (18–55)	16/5/2	Median 66, range (51–85)	60.6%[a]	34.8%[a]	33.3% (Z1)	Positive pH-MII tests	20 (86.9%)
Pauwels et al. 2011	42	Mean 29 yrs, range (18–58)	25/12/5	NR	58%	42%	NR	Positive pH-MII tests	28 (66.7%)
Woodley et al. 2019	12	Median 24.3 yrs, range (18–49)	6/5/0[c]	Mean 61.5[b], range (10–116)	91.2%[b]	8.8%[b]	37.4%[b] (Z2 or Z1)	ARI > 7%	12 (100%)[b]

Formatting was adapted after Bongiovanni et al. [38] and Ng et al. [39]

IRQ [interquartile range], *ARI* acid reflux index, *#GER* mean or median number of gastroesophageal reflux events, *GERD* GER disease, *%AGER* percentage of acid gastroesophageal reflux events, *%NAGER* percentage of nonacid gastroesophageal reflux events, *yrs* years, *%Prox-GER* percentage of total GER events that reached the proximal esophagus, *NR* not reported

[a]Values are the product of extrapolation from data published in the original paper; percentages were calculated using the published median values for GER, AGER, and NAGER. These values therefore represent estimates

[b]Data not published in the original study

[c] There was one patient in the Woodley study who had unknown genotype

Blondeau et al. [46] recruited 33 people with CF into a study in which they aimed to assess GER, aspiration, and respiratory symptoms. Ten patients were lung transplant recipients. The remaining 23 were ages 18–55, mean 26 years, and 11 female. MII-pH testing detected an average of 66 events per subject with approximately two-thirds (60.6%) of them being acidic and one-third (34.8%) of them having reached the proximal esophagus. (Note: These percentages AGER and NAGER were extrapolated from median data reported in the original paper.) Using threshold MII-pH parameters above the 95th percentile of normal data obtained from healthy volunteers [47], 20 patients (86.9%) had GERD.

Pauwels et al. [31] recruited 53 adults (28 females) with CF into a study in which they aimed to assess the dynamics of different types of reflux (acid, nonacid, and bile) and their impact on gastric emptying (GE). Among the 42 patients (ages 18–58, mean 29 years) who were assessed by MII-pH, the average or median number per patient of total events was not reported, 58% were acidic and approximately one-third (30.9%) reached the proximal esophagus. Using threshold MII-pH parameters above the 95th percentile of normal data obtained from healthy volunteers [47], 28 patients (66.7%) received a GERD diagnosis.

Our group [23] retrospectively reviewed MII-pH for 28 patients (16 children and 12 adults ≥18 years) with the aim to assess the impact of aging on GER in people with CF. Among the 12 adults with CF (ages 18–49, six females) in the study, the average total GER was 61.5 per subject with 91.2% being acidic and 37.4% of them reaching the proximal esophageal. Using 7% as the threshold for normal acid exposure [48], all 12 adults (100%) had GERD. Data presented here were part of the original data [23] set but not published in the original paper.

Taken together, these few studies indicate that the frequency of GER among adults with CF, who are off anti-reflux medications and with no fundoplication history, is slightly greater than 60 per day, with slightly less than two-thirds (60.6%) of them being acidic and approximately one-third (35.3%) of them reaching the proximal esophagus. They also show that the percentage of adults with CF (median 86.9% [range 66.7–100%]) with GERD is very high. These data suggest that as people with CF continue to age, clinicians should maintain vigilance to evaluate for GER-related pathology.

Diagnosing GERD in CF

Approaches to GERD diagnosis in people with CF are (in general) no different than for people without CF who are also referred to our facility with symptoms suggestive of GERD. Patients are generally prescribed a brief (4–8 week) empirical trial [49] with acid suppression therapy using either a proton pump inhibitor (PPI) or a histamine-2 receptor antagonist (H_2RA). If the response is positive, then slow reduction in therapeutic treatment is implemented. If the symptoms do not respond, then combined MII-pH testing is performed to evaluate the patient during a 24-h study. Laboratory tests, contrast imaging, manometry, and upper endoscopy and imaging may also be part of the diagnostic evaluation at this point, to assess for alternate

etiologies of GERD-like symptoms, including anatomic obstruction, esophageal dysmotility as well as infectious, autoimmune and allergic pathology [47]. While these diagnostic tests can effectively evaluate for alternate etiologies and assess for reflux-related mucosal injury, MII-pH has become the preferred method for assessing GER in infants, children, and adults [50–52]. The benefit of MII-pH over pH alone is that pH monitoring alone does neither permit assessment of nonacid GER events nor does it permit monitoring of the proximal extent of the refluxate. Additionally, the presence of several pairs of impedance electrodes (that form multiple impedance channels) along the length of the MII-pH catheter permits assessment of the intraluminal flow of both liquid and gas (air-swallows, supragastric and gastric belches). The ability to monitor proximal ascent of GER events is of particular importance for people with CF, for whom aspiration of gastric contents is a grave concern.

GER is common among people with CF but not every person with CF and GER has GERD. While attempts have been made to establish a consensus of definitions and terminology [17], criteria for GERD are variable; among institutions these criteria include (1) Patients who have an acid reflux index (RI) more than an established/recommended threshold value. For infants (≤12 months), the threshold ARI is >12% and for children (>12 months), the threshold ARI is either 5% [43] or 6% [40]. Another threshold used for infants ≤12 months is >10% [48]. (2) Patients who have positive symptom-GER associations, determined using one or more of the symptoms indices (symptom index [53], symptom sensitivity index [53], and symptom association probability [54]). (3) Patients with one or more positive pH probe and/or MII parameters [42]. (4) Patients who have MII-pH parameters greater than the 95th percentile of normal data values obtained from healthy subjects [31, 46, 55].

Other diagnostic modalities used for GERD include upper gastrointestinal series with contrast and esophagogastroduodenoscopy (EGD) with and without biopsy; however, these studies are neither sensitive nor specific for the diagnosis of GERD [47, 56]. We use a combined approach of MII-pH parameters, the RI, as well as a positive symptom-reflux association(s) established using MII-pH.

To date, there is neither a standard template for reporting MII-pH results nor are there universally accepted standards (reference values) for basic MII metrics, that include (1) the maximum number of acid GER and nonacid GER (some groups divide nonacid GER into weakly acidic event [pH ≥ 4 and <7] and weakly alkaline event [pH ≥ 7]), (2) mean GER duration for acid and nonacid events and for the combined total, (3) mean bolus exposure time for combined acid and nonacid, and (4) mean percentage of proximal events for both acid and nonacid GER and for the combined total. Reference values for combined pH-impedance monitoring have been reported for infants [55, 57], children [55, 58], and adults [47, 52, 59–62].

In addition to basic impedance metrics, two novel parameters have been described. The first is the median post-reflux swallow-induced peristaltic wave index (PSPW) Index, which is the percentage of total impedance-detected GER events that are followed within 30 s by a swallow. Because chemical clearance of the esophageal mucosa following a reflux event is very highly dependent upon "efficient" transport of bicarbonate-rich saliva through the esophageal lumen, it has been

suggested that the PSPW Index would be a parameter capable of evaluating chemical clearance in patients with GERD. Patients with poor chemical clearance would have fewer GER events followed by a clearance swallow in a timely manner. In a preliminary study of 16 people with CF and 16 age-matched people without CF, we [63] found that the PSPW Index for people with CF (median 41.8 [IQR 29.7–53.2]%) was significantly lower than for age-matched non-CF (median 55.1 [IQR 48.2–71.8]%) controls. We also found that PSPW was strongly correlated with mean durations of acid neutralization post-acid reflux, indicating the PSPW Index could be helpful for assessing chemical clearance in people with CF [63].

The second novel impedance parameter is mean baseline impedance (MBI). The MBI is a measure of the baseline conductance of the esophageal mucosa when the esophagus is at rest. When the esophageal mucosa is healthy, conductance will be low and the baseline will be high; when the esophageal mucosa has been damaged or otherwise compromised, intercellular spaces become dilated and filled with ion-rich fluid, and the conductance becomes high, and the impedance is low. While several proposals have been suggested for baseline measurements, this metric is most often calculated when the esophagus is empty and at rest (no swallows or belches and the esophagus is not acidified [pH < 4]). It has been suggested that the incorporation/implementation of both the PSPW Index and baseline impedance parameters could improve the diagnostic yield of MII-pH assessment when basic parameters fail to yield a diagnosis [64].

Research aimed at evaluating the efficacy of these novel applications of MII-pH for the assessment of GER in people with CF is ongoing. For example, in an examination of 28 people with CF (ages 3–49 years), we recently reported that baseline impedance in the distal esophagus is negatively correlated with age and that older people with CF were 11-times more likely to have abnormally low baseline impedance in the distal esophagus [23].

Relationship Between GER and Worsening Lung Function in People with CF

GER results in the proximal movement of gastric contents into the lumen of the esophagus; some events remain distally positioned closer to the LES, while others ascend into the oropharynx where contents can be aspirated into the lungs. Aspirated gastric contents (hydrochloric acid, pepsin, gastric lipase, bile salts, and trypsin) [15] can lead to respiratory problems, increases in the number of pulmonary exacerbations, and decreases in lung function. Aspiration in CF can worsen the effects on an already hostile pulmonary environment, riddled with infection and inflammation [6].

In addition to the direct effects of aspiration, it has been suggested that afferent chemosensory receptors within the esophageal mucosa respond to acid to trigger efferent motor neurons responses from the respiratory musculature that result in coughing and bronchospasm [6, 15, 65–68] and possibly an increase in neutrophilic airway inflammation [6].

Evidence of significant proximal ascension of GER in children with CF would suggest a possible role for GER in pulmonary exacerbations [6]. Our assessment of the data reviewed here suggest that about one-third of GER events reach the proximal esophagus in people with CF. Palm et al. [69] reported that children with CF experiencing increased GER had a higher incidence of *Pseudomonas aeruginosa* isolated on respiratory cultures compared to those with normal or low GER. They also showed an inverse relationship between GER and lung function.

Research by Reen et al. [70] suggests that GER-derived bile is a host determinant for *P. aeruginosa* and possibly other respiratory pathogens. These investigators found that exposure to sub-lethal levels of bile increased biofilm production, type six secretion, and quorum sensing in *P. aeruginosa*, which are all factors involved in the establishment of chronic infections. Type three secretion and swarming behavior in *P. aeruginosa* (behaviors known to occur during acute infection) were suppressed following exposure to bile. Their results suggest that aspirated bile may predispose *P. aeruginosa* (and perhaps other common CF pathogens) to a chronic and persistent lifestyle [70].

In addition to effects of GER on acute and chronic pulmonary symptoms in CF, GER can be associated with worse outcomes after lung transplant (LTx). Advanced lung disease due to CF is the third most common reason for adults to undergo LTx and the most common indication in children [1]. In general, lung transplantation is known to worsen GERD [71, 72].

In a retrospective study aimed to determine the prevalence of GERD in LTx recipients, Hadjiliardis et al. [71] studied 43 patients (8 CF, mean age 47.3 ± 12.4 years, 19 females) at 6 months post-LTx using 24-h pH monitoring. Of their entire cohort, 30 (69.8%) had abnormal total acid exposure (≥5%). Mean acid exposure times were 10% total, 11.8% upright, and 7.9% recumbent; reference values were <5%, <8%, and <3%, respectively. Total and upright acid exposure times were both negatively correlated with FEV_1.

In a separate study aimed at comparing pre- and post-LTx reflux studies, Young et al. [73] evaluated 23 patients (4 CF, mean age 51.5 ± 11.9 years, 14 females) at: (1) a median of 100 days post-LTx using 24-h pH monitoring. Before LTx, 35% of patients had abnormal acid exposure compared to 65% after LTx. Acid contact time increased by a mean of 3.7% for total exposure time and 6.4% for recumbent exposure at post-LTx. The investigators concluded that changes in acid exposure times were not explained by changes in esophageal or gastric motility and only 3 of 15 patients (20%) with abnormal acid exposure time were symptomatic [71].

To assess GE in people with CF scheduled for LTx, Bodet-Milin and collaborators [72] evaluated 30 patients (mean 22 ± 6.4 years, 10 females) before (mean 1.58 ± 1.11 years) and after (5.8 ± 2.6 weeks) LTx (n = 17) or heart-lung transplantation (n = 13) and compared their results to 53 healthy volunteers. Before transplantation, 20 patients (67%) had delayed GE for solids and 4 had delayed GE for liquids. After their transplant, 29 patients (97%) had very delayed GE (compared to controls) and 20 had delayed GE for liquids. In another study comparing 10 people with CF (median 29 [range 18–56], 18 females) post-LTx with 23 people with CF (median 26 [range 18–55], 11 females) without LTx, Blondeau et al. [46] found no

difference in reflux parameters between the two groups. They found that acid exposure (median 5.5 [range 2.9–13.2%] vs median 7.1 [IQR 1.2–13.2%]), bolus exposure (median 1.7 [IQR 1.2–2.4%] vs median 1.2 [IQR 0.9–1.5%]), total number of GER events (median 66 [IQR 51–85] vs median 61 [IQR 41–98]), and number of GER events that reached the proximal esophagus (median 22 [IQR 16–37] vs median 22 [IQR 6–43]) were not different between the LTx and no LTx groups.

There are a number of potential factors that contribute to GERD in LTx recipients [71]. The use of immunosuppressant therapies (tacrolimus, cyclosporine, and prednisone) and anti-hypertensive medications often used by LTx recipients can produce a hypotensive LES. From a surgical perspective, the vagal nerve is severed during the LTx. Finally, advanced disease prior to the actual transplant appears to be a risk factor for post-LTx GERD. It remains unclear whether delayed or prolonged GE that may occur post-LTx contributes significantly to GERD in people with CF.

Bronchiolitis obliterans syndrome (BOS) is a complication of LTx whereby the terminal bronchioles are destroyed and is the most common type of chronic lung dysfunction (CLAD) [1, 3]. BOS is the leading cause of death among LTx patients surviving >1 year [1]. Although GERD has been implicated in the development of BOS [74, 75], further exploration is needed and is beyond the scope of the current review.

Delayed Gastric Emptying and GERD

GI dysmotility is common in CF, and small bowel and total intestinal transit time have been found to be delayed. However, the impact of CF on gastric emptying is less clear, as well as the relationship between delayed gastric emptying and clinical symptoms of nausea, vomiting, bloating, postprandial fullness, early satiety, and abdominal pain (gastroparesis) [76–79]. In a systemic review of gastroparesis in CF by Corral et al, the frequency of this diagnosis was found to be 38% (95% CI 30–45%) in pooled analysis but was highly variable based on diagnostic modality, and overall frequency was not more prevalent than for healthy controls [80].

The relationship between delayed GE/gastric dysmotility and GERD is dependent upon numerous different factors and causes. In general, increases in abdominal pressure that occur during a feed cause a reduction in the tonicity of the LES to allow unimpeded transport of masticated foods across the esophagogastric junction into the stomach and to also vent gases. Transient relaxations of the LES are the chief mechanism of GER [81–83]. While it is generally accepted that delays in GE would prolong the intra-abdominal pressure imposed by the meal (and in fact prokinetics like baclofen, that increase the tonicity of the LES and speed up GE, are used to treat GERD), the impact of delayed GE on GER in people with CF remains unclear as studies are inconsistent. None of the studies have shown an association between delayed GE and GERD [84].

In an investigation aimed to assess the association between GE and GER, Hauser and colleagues [45] studied 56 children with CF (ages 1–17 years, 24 females) who

were divided into two groups; group 1 was tested by MII-pH and GE breath test and group 2 was tested with GE breath test alone. Analyses found delayed GE in 21.4% of group 1 with no association between delayed GE and GER, and no delayed GE in group 2.

In a retrospective analysis of 30 LTx recipients (ages 1–21 years), Jamie Dy et al. [85] found that abnormal GE was significantly associated with development of chronic lung allograft dysfunction (CLAD) that was not related to GER. The investigators suggest that patients with more severe illness may have poor GE and that CLAD could be related to possible changes in the gastric microbiome (due to delayed GE) with resultant changes in the lung microbiome [85, 86].

In an investigation of 33 adults (mean 28 [range 19-58] years, 15 females) with CF, Pauwels et al. found delayed GE in 33% but there was an association between delayed GE and GER [31].

While gastric emptying, as measured by either scintigraphy or breath test, is used clinically as a surrogate for gastric motility, it does not provide a true assessment of gastric myoelectric activity. In the research setting, gastric myoelectric activity has historically been measured by electrogastrography (EGG), which measures the frequency of gastric slow waves and power of gastric contractions [87–89]. In people with CF, multiple EGG studies have identified abnormal patterns of gastric motility; however, the data from these studies are heterogeneous with respect to both the patterns of dysmotility and their correlation with clinical symptoms [88, 90, 91]. No studies have compared EGG to GER as determined by MII-pH in individuals with CF.

Further studies are needed to assess the impact of delayed GE and gastric dysmotility on GER in CF.

Barrett's Esophagus and Esophageal and Gastroesophageal Junction Adenocarcinoma in CF

While oncologic complications of chronic GER typically manifest in adulthood, and are rarely seen in healthy youth, this risk is increased in youth with chronic medical conditions associated with severe GER in childhood [92–94]. CF is one such medical condition in which complications of chronic GER arise in youth. The incidence of Barrett's Esophagus is threefold higher in individuals with CF as compared to those without CF, and appears at younger ages than in the general population, The incidence of esophageal adenocarcinoma is also higher in CF [95]. Additionally, Falk et al. identified a relationship between obesity and incidence of esophageal and gastroesophageal junction adenocarcinomas [96]. Given the increasing prevalence of obesity in the era of CFTR modulator use, future studies are needed to determine if this, or other clinical factors, impact the development of esophageal malignancies in CF, which may inform screening guidelines in this population.

Evidence of Aspiration in Children with CF

It is difficult to show evidence of active aspiration. Recent studies have employed the use of gastric/duodenal biomarkers (pepsin or bile acids) to search for evidence of aspiration in biofluids that include bronchoalveolar lavage (BAL) fluid, exhaled breath condensate (EBC), sputum and saliva. BAL sampling is extremely invasive and requires the use of general anesthesia; therefore, it is not routinely used to test for aspiration. Collection of EBC is noninvasive and is an attractive alternative to BAL collection; however, the components of EBC are highly diluted and thus biomarker detection generally falls below the limits of detection. Sputum is an excellent source of aspiration biomarkers if the aspiration has been recent; however, collection of sputum may be challenging for young children or people on CFTR modulators. Saliva is relatively easy to collect but the presence of one or more of the biomarkers is not reliable if sampling occurs at a time long after the aspiration event. It is also important to note that the presence of the biomarker in saliva would not be 100% diagnostic of aspiration as not all GER events that reach the oropharynx are aspirated. Nonetheless, the presence of an aspiration biomarker in saliva would signal a potential high-risk patient.

In an assessment of children (ages 0.3–13 years, mean 4 years) with CF, Blondeau et al. detected bile acids in the saliva of 23 of 65 (35.4%) children with CF compared to zero bile acid-positive saliva samples among healthy controls [34]. Interestingly, in these 23 children with bile acid-positive saliva, an inverse relationship between bile acid concentration and lung function was discovered.

In an investigation aimed at assessing whether pulmonary aspiration occurred in a group of 77 clinically stable preschool children with CF (mean age 3.7 years) and 12 non-CF controls (mean age 3.6 years) undergoing routine surveillance bronchoscopy, Clarke et al. [97] found that BAL pepsin levels were not significantly different between groups (385 ± 68.7 pg/mL vs 198 ± 54.2 pg/mL, $p = 0.81$). High levels of pepsin (>2 SD above the control mean 573 pg/mL) were found in a subset of the patients with CF (18/77, 23%) compared to all others with CF but this was not found to be associated with pulmonary infection, inflammation or symptoms (respiratory or gastrointestinal) [97].

Gastric lipase, another gastric protein, has also been suggested as a possible alternative biomarker for aspiration. In a group of 29 patients with CF (median age 18, range 6–47 years), we assessed parallel BAL fluid and EBC samples for the presence of gastric lipase, collected from patients undergoing nasal polyp removal. For the gastric lipase assay, the non-fluorescent EnzChek® lipase substrate produces a green-fluorescent product in the presence of lipases. Gastric lipase was not detected in either the BAL fluid or the EBC samples. Importantly, gastric lipase was not detected in BAL fluid samples that tested positive for pepsin [98].

Combined, these studies suggest that continued evaluation and refined detection methods for gastric biomarkers are needed to identify people with CF who are actively aspirating to facilitate optimization of treatment outcomes.

How does GER Differ Between Children with CF and Symptomatic Children Without CF?

Although GER is increased in CF, a clinically relevant question is how children with CF are different from other children who present in clinic with GER symptoms. Information such as this would be helpful for developing clinical management strategies tailored specifically for the child with CF.

Toward this end, we conducted a study in which 16 children with CF who were off anti-reflux medications and did not have a fundoplication prior to MII-pH testing were enrolled retrospectively and compared to 16 randomly selected age-matched children without CF who were similarly off anti-reflux medications (proton pump inhibitors, histamine-2 receptor antagonists, and prokinetics for 7, 5, and 3 days, respectively) and did not have a fundoplication prior to MII-pH testing [36]. Comparison of impedance and pH probe variables revealed no difference among common impedance parameters, with the exception of median bolus contact time (significantly prolonged in children without CF), but numerous significant differences among pH probe variables that included mean acid duration, longest acid event, DeMeester score, and acid index, all being significantly higher in children with CF. Interestingly, we found that fewer GER events reached the proximal esophagus for the CF cohort (55.7%) when compared to the controls (78.8%), but only statistically significant ($p = 0.039$) when acid and nonacid events were combined [36].

These results prompted an interest in differences in volume clearance (VC) and chemical clearance (CC) between CF and no-CF with the hypotheses being that VC was significantly delayed in children without CF and CC was significantly delayed in children with CF. We had recently demonstrated our ability to assess the VC and CC efficiency within individual acid reflux events [14]. The results showed that VC was more efficient in the CF cohort, but this difference failed to achieve statistical significance ($p = 0.057$). CC, on the other hand, was significantly delayed in the children with CF ($p = 0.001$); CC lasted almost twice long in the CF cohort (122.8s vs 65.9s) [36]. Importantly, it was discovered that the median pH nadir of the acid events was significantly more acidic for the CF cohort (1.1 vs 1.8, $p = 0.003$) [36].

In a further examination of these two cohorts [99], the question of whether the CC durations were "abnormally low" was asked and answered using reference CC values that were derived in our facility [100]. Using the 114.4 s threshold, we found that 9 of 16 (56.3%) children with CF had a mean acid neutralization duration during CC that was outside the physiological range compared to only 3 of 16 (18.8%) children without CF [99]. We also found that children with CF were twice as likely ($p = 0.0412$) to have abnormally prolonged acid neutralization during CC compared to children without CF. Additionally, we found that children with abnormally prolonged acid neutralization during CC were 1.5-times more likely to have CF, with 75% sensitivity and 65% specificity [99].

This study showed that while in general children with CF will be more likely to have acid neutralization duration outside the physiological range during CC, not all children with CF will have abnormally prolonged acid exposure following an acid

reflux event. It was suggested that some CFTR genotypes may influence acid neutralization efficiency, possibly in combination with non-CFTR-related genetic modifiers and/or environmental factors [99, 101, 102]. Targets of this interaction to cause prolonged acid exposure could be ineffective esophageal motility or reduced esophageal motility [101, 102] that would affect transport of saliva through the esophageal column, reduce bicarbonate (and other buffers) composition in saliva or that which is secreted from submucosal glands directly into the esophageal lumen [9, 12, 13, 56, 103], and/or gastric hyperacidity [36, 104].

Aging in CF: Impact on GER

Advances in science, technology, and medicine have drastically increased the life expectancy of people with CF. Consequently, people with CF now must be concerned with age-related comorbidities that include GERD. Aging results in the breakdown or reduction of several mechanisms known to facilitate proper clearance of GER as well as anti-reflux barriers that prevent abnormal amounts of GER from occurring. Aging in healthy people without CF is often associated with swallowing disorders that increase choking and aspiration in response to GER and curtail transport of saliva that is important for clearing the esophagus post-reflux. Increased esophageal exposure to gastric contents occurs due to age-related changes that include (1) reduction in salivary flow, (2) bicarbonate secretion, (3) increased likelihood of a hiatal hernia which reduces pressure on the lower esophageal sphincter (LES), (4) shortening of the LES, and (5) reduced esophageal motility [23, 105]. Other age-related factors that contribute to promoting GERD include the deterioration of the anti-reflux barrier (comprised predominantly of the LES with support from the crural diaphragm) [106], incomplete or delayed esophageal clearance (both volume and chemical), reduced mucosal resistance, and delayed GE [23, 107].

As people with CF are known to be at greater risk for GERD [34, 46] and reflux is known to worsen with age [108, 109], we recently conducted a study (n = 28) using combined MII-pH monitoring and correlation analysis to assess the potential effect of age on GER in people with CF [23]. There was a significant positive correlation of age with events >5 min and DeMeester Score (r = 0.38, p = 0.047 and r = 0.47, p = 0.011, respectively). The significant correlation of age with DeMeester score is particularly remarkable because the DeMeester score is a composite score of esophageal acid exposure, influenced by pH variables that include the acid reflux index, total acid GER events, number of acid events >5 min, and the longest acid reflux event [23, 110]. Despite the absence of more abundant correlation, which likely was influenced by the small sample size, we speculated that the significant association of age with DeMeester score and events >5 min suggested that age is associated with increased esophageal acid exposure in people with CF [23].

Because increased acid exposure is known to be related to impaired mucosal integrity and reduced baseline impedance [23, 111–120], we tested the association of distal baseline impedance with pH parameters and found median to strong negative associations with reflux index, total number of acid events, number of events

>5 min, and the DeMeester score [23]. Importantly, age was moderately to strongly negatively correlated with distal baseline impedance ($r = -0.424$, $p = 0.023$). When compared to children, adults with CF were determined to be 11 times more likely to have distal baseline impedance below the normal range [64], suggesting that aging adults with CF are potentially at risk of mucosal injury due to increased acid exposure and thus should be kept under surveillance and appropriately treated as necessary [23].

Treatments for GERD in CF

PPI/H_2RA/Prokinetics

People with CF have increased GER, increased amounts of gastric acid, and prolonged acid exposure following an acid reflux event [28, 36]. Because there are no medications available that are capable of eliminating GER, clinical management of GER for most people with CF includes a PPI or a H_2RA (to a lesser extent), both of which are used to reduce gastric acidity. Additionally, both PPIs and H_2RAs are used as adjunctive therapy with pancreatic enzyme replacement to improve fat absorption. However, existing studies have not consistently demonstrated this relationship, and further studies to determine the impact of acid blockade on pancreatic enzyme replacement efficacy are ongoing [121, 122].

Clinical management strategies should take into consideration potential negative effects of ongoing use of a PPI [123–125]. Additional therapeutics include prokinetics, which are used to increase LES tonicity and promote more rapid GE. By increasing the rate of GE there is a reduced time during which the feed contributes to increased intra-abdominal pressure and subsequent relaxations of the LES. Non-antibiotic prokinetics, like baclofen (a gamma-aminobutyric acid GABA-B receptor antagonist) are typically used only in the most serious cases of GERD due to their clinically relevant side effects [126].

Notwithstanding concerns regarding possible increases in hospitalization [125] or earlier and more frequent pulmonary exacerbations [123], anti-reflux medications (PPIs especially) are commonly prescribed to people with CF [6], and aggressively when esophagitis is detected [127]. According to the 2020 Annual Data Report [128] from the Cystic Fibrosis Foundation, PPIs were prescribed to 43.3% of patients and H_2RAs were prescribed to 15.3%; H_2RAs tend to be given more often to younger patients while more older patients receive PPIs [128].

Concern for the prolonged use of PPI for both children and adults has been mounting. There is a growing concern for the prolonged exposure of esophageal mucosa to nonacidic gastric contents that will still contain noxious compounds like pepsin, trypsin, and bile acids. Nonacid GER has been implicated for its potential involvement in PPI-nonresponsive symptoms [129], Barrett's esophagus [130], and adenocarcinoma [131]. Our review of the literature revealed a dearth of studies in which GER in people with CF was assessed by MII-pH while on acid suppression medications. In a MII-pH study of 35 children with CF (mean age 13.5 ± 5.8 years),

in which the majority (34/35, 97%) were on a PPI, Palm et al. [132] detected 2040 GER events, with a mean per person of 60 ± 37, 50% were acidic and approximately one-third of the total events reached the proximal esophagus. Thirty-five percent patients had abnormal MII-pH and 37% patients had abnormal pH monitoring results.

Additional studies involving MII-pH are needed to assess the value of continued PPI use in people with CF and it should be noted that assessment by MII-pH is advised in patients who fail to respond to an empiric trial with an acid suppressant [38].

Lifestyle Changes

Typically, in non-CF populations, lifestyle modifications would be the initial consideration but given the challenges requiring a high-calorie diet for people with CF, medical therapy should be employed for up to 8 weeks. As some foods are known to be "refluxogenic" because they produce hypotension of the LES, patients should be made aware of what foods to potentially avoid; these may include peppermint and spearmint, onions and garlic, chocolate, high acid foods such as tomatoes or tomato sauces, and citrus fruits and juices. Alcohol effects both the LES and esophageal peristalsis resulting in reduced pressure in the LES, disordered esophageal motility, and reduced peristaltic propulsion [133]. Cigarette smoke causes LES hypotension due to the effects of nicotine or the release of β-adrenergic agents [133, 134] therefore patients should be advised to avoid even passive cigarette smoke exposure. Since eating large meals leads to LES hypotension caused by increased intra-abdominal pressure, many patients will benefit from eating frequent but smaller meals ("grazing") throughout the day [135]. However, this strategy is difficult in CF due to the need for pancreatic enzyme replacement with fatty meals for most individuals. Short "meal-to-sleep" or "meal-to-bedtime" has been shown to be a high-risk factor for nocturnal GER and some investigators have suggested that the last meal should be 4 h before bedtime [136, 137]. Body position has been shown to effect GER. In the upright position, GER occurs more frequently due to more frequent relaxations of the LES [138, 139] but clearance of GER is added by gravitational effect [140]. This can play a role during positional drainage of airway sections in infants. There are data to suggest that lying in the left lateral decubitus position can reduce the frequency of GER [139].

When contemplating lifestyle changes as part of clinical management of GER in people with CF, consideration must be given to balancing quality of life with CF-specific nutritional needs.

Nissen Fundoplication

In people with CF and severe GERD with possible risk of aspiration (determined by MII-pH), surgical options should be considered based on collaborations with

surgical colleagues. A fundoplication is an open or laparoscopic procedure in which the proximal portion of the stomach (the fundus) is wrapped around the base of the esophagus to increase the tonicity of the LES. Among the types of fundoplication, i.e., Nissen 360° wrap, Toupet 270° wrap, and Watson anterior 180° wrap, the Nissen has become the most popular in recent years [141]. People with CF who are PPI-refractory (as objectively documented using MII-pH) are often surgically treated [142]. Potential complications related to laparoscopic fundoplication should be discussed during surgical evaluations.

In a retrospective study of 48 people with CF (median age 14 years [range 1–36], 24 females) to evaluate the safety and efficacy of Nissen fundoplication, Sheikh et al. found that Nissen slowed the decline in lung function, improved weight gain, and reduced the frequency of pulmonary exacerbations.

What is on the Horizon?

Since 2012, novel medications known as CFTR modulators have revolutionized care, bringing hope and promise to people with CF, and particularly those with advanced pulmonary disease. There are currently four CFTR modulators (Ivacaftor, lumcaftor/ivacaftor, tezacaftor/Ivacaftor, and elexacaftor/tezacaftor/Ivacaftor) that are approved for use in Europe and the USA [1]. Higgins et al. [143] recently published an observational study using data from the US Cystic Fibrosis Foundation Patient Registry and the UK Cystic Fibrosis Registry to evaluate the effect(s) of ivacaftor. People with CF on ivacaftor in the registry were matched to patients never having taken ivacaftor. The endpoints of interest were death, organ transplant, pulmonary exacerbation, and hospitalization. The data suggest significant improvement in predicted FEV [1] and pulmonary exacerbation in the ivacaftor group [1]. Limited data exists on CFTR modulator treatment outcomes on GER in CF. In an assessment of 12 adults (ages 17–38) with CF who were asked to complete symptom reflux and Hull airway questionnaires, Zeybel et al. [144] reported a significant reduction in extraesophageal symptoms associated with treatment with ivacaftor. There are no available studies on GER outcomes with the newest CFTR modulator combination elexacaftor/tezacaftor/ivacaftor combination, which has become the most widely used modulator in CF. Of note, both ivacaftor and elexacaftor/tezacaftor/ivacaftor are associated with significant weight gain in individuals with appropriate CFTR mutations, and overweight and obesity are now emerging problems in the CF population [145, 146].

Conclusion

More than half of children and over three-quarters of the adults with CF have GERD. Of the total GER per day, which averages out to about 42 for children and 60 for adults, two-thirds are acidic and about one-third reach the proximal esophagus. Despite possible side effects, both children and adults continue to be treated

with PPIs, often for extended periods of time. Aging in people with CF is associated with an increase in acid exposure and subsequent decreases in distal esophageal baseline impedance. The frequency of GER increases for those people with CF who require LTx. Despite its potential complications, fundoplication remains the best choice for managing refractory GER that poses a threat to aspiration and consequent deterioration of lung function. The effects of high-efficiency modulator therapy on GER should be tested so that acid suppression therapy can be minimized or even eliminated from clinical management.

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GER and Esophageal Atresia

10

Frederic Gottrand, Audrey Nicolas, Rony Sfeir, and Madeleine Aumar

Abstract

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is one of the most common digestive malformations whose prevalence varies between 1.8 and 2.4/100,000 births. Although mortality decreased dramatically to about 5%, digestive problems remain frequent in children with EA both in early infancy and at long-term follow-up. These patients are at major risk of presenting gastro-esophageal reflux disease (GERD) and its complications: anastomotic strictures, esophagitis, failure to thrive, and Barrett's esophagus. Concerns in adults include esophageal adenocarcinoma and epidermoid carcinoma which have been occasionally reported. Recent recommendations help for the management of gastrointestinal complications, although they are mostly nonevidence-based. It is recommended that GERD be treated with proton pump inhibitors (PPI) in all EA patients from the neonatal period to the first year of life, or longer, depending on persistence of GERD. Endoscopy with biopsies is mandatory for routine monitoring of GERD in patients with EA. Every EA patient, including asymptomatic, should undergo monitoring of GERD (impedance/pH-metry, and/or endoscopy) at the time of discontinuation of anti-acid treatment and lifelong. Systematic endoscopy is recommended throughout childhood: one after stopping PPI therapy, one before the age of 10 years, and one at transition to adulthood. Thereafter, a regular clinical follow-up in every adult patient with EA is recommended with routine endoscopy every 5–10 years.

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Esophageal atresia · Gastroesophageal reflux disease · Barrett's esophagus · Anastomotic stricture

Introduction

Esophageal atresia (EA) is one of the most common digestive malformations whose birth prevalence is 1.8–2.4 per 10,000 births worldwide [1–3]. The prognosis of EA has benefited from advances in medical care, including neonatal and surgical procedures, and has therefore improved significantly over the past three decades. Its survival rate now exceeds 95% and an increasing number of patients reach adulthood [4–6]. EA is no more just a neonatal surgical problem but a lifelong problem. In addition to respiratory problems, nutritional and gastrointestinal (GI) issues are prevalent, not only in the first years of life but also in adolescence and adulthood. Gastroesophageal reflux disease (GERD), peptic esophagitis, gastric metaplasia, Barrett's esophagus, anastomotic strictures, feeding disorders, dysphagia, esophageal dysmotility, and, more recently reported, eosinophilic esophagitis are the most frequent GI short- and long-term complications encountered in children and adolescents. Concerns in adults include esophageal adenocarcinoma and epidermoid carcinoma which have previously been reported [7].

In 2016, clinical practice guidelines for the management of GI complications have been published by ESPGHAN/NASPGHAN and the International Network on Esophageal Atresia to help in the care of these patients [8]. Statements (all expert opinions) concerning GERD are reported in Table 10.1. Recent position papers addressed more specifically the perioperative care for EA, long-gap EA, and respiratory complications in EA patients [9–12].

GERD is Frequent in Patients with EA

Patients with EA are at major risk of presenting GERD [13]. Several factors contribute to the pathophysiology of GERD in EA (Table 10.2).

In EA patients, GERD is the most frequent digestive complication with a reported prevalence ranging from 22 to 63% in EA/TEF, while in infants and children with isolated EA GERD is reported in almost all patients [24]. A recent systematic review identified complications in patients following EA repair, including GERD and esophagitis. A total of 65 publications met the selection criteria, representing 4882 EA patients. Prevalence of GERD was 43% and 47% of esophagitis. No correlation appeared to exist between the severity of symptoms and the occurrence of a complication [25]. GERD is much more frequent in early infancy compared to older children and adults with EA [26] but most of the cross-sectional studies have demonstrated significant rates of GERD at any age [27], much higher than expected in the general pediatric population [28].

Table 10.1 Recommendations related to GERD in EA patients (from [8])

Statements
It is recommended that GERD be treated with acid suppression in all EA patients in the neonatal period
PPIs should be the first-line therapy for GERD
It is recommended that GERD be systematically treated for prevention of peptic complications and anastomotic stricture up to the first year of life or longer depending on the persistence of GERD
pH monitoring is useful in evaluating the severity and symptom association of acid reflux in patients with EA
pH-impedance monitoring is useful to evaluate and correlate nonacid reflux with symptoms in selected patients (symptomatic on PPI, on continuous feeding, with extra-digestive symptoms, ALTE, GERD symptoms with normal pH probe and endoscopy)
Endoscopy with biopsies is mandatory for routine monitoring of GERD in patients with EA
All EA patients (including asymptomatic) should undergo monitoring of GERD (impedance/pH-metry, and/or endoscopy) at the time of discontinuation of anti-acid treatment and during long-term follow-up
Routine endoscopy in asymptomatic EA patients is recommended. The expert panel recommends three endoscopies throughout childhood (one after stopping PPI therapy, one before the age of 10, and one at transition to adulthood)
Severe esophageal dysmotility predisposes EA patients to post-fundoplication complications. However, EA patients may benefit from fundoplication for: 1. Recurrent anastomotic strictures, especially in long-gap EA 2. Poorly controlled GERD despite maximal PPI therapy 3. Long-term dependency on transpyloric feeding 4. Dying spells
Barium contrast study, endoscopy with biopsies, and pH-metry, at minimum, should be performed prior to fundoplication
If pH-metry or pH-MII is performed, symptom correlation during reflux testing, rather than total reflux burden, is the most important indicator of reflux-associated symptoms
Acid suppression should be used with caution in patients with extra-esophageal manifestations of reflux
The incidence of esophagitis and esophageal gastric and intestinal metaplasia (Barrett's) is increased in adults with EA as compared to the general population
While current studies show no increased incidence of esophageal cancer (adenocarcinoma, squamous cell carcinoma) in adults with EA, esophageal cancer remains a concern
We recommend regular clinical follow-up in every adult patient with EA, with special reference to the presence of dysphagia, GERD, respiratory symptoms, and anemia with: 1. Routine endoscopy (with biopsies in four quadrants at gastroesophageal junction and anastomotic site) at time of transition into adulthood and every 5–10 years 2. Additional endoscopy if new or worsening symptoms develop 3. In presence of Barrett's as per consensus recommendations

GERD is Associated with Complications in Neonates and Infants Operated for EA

Several complications in the short, medium, and long term have been reported in EA patients (Table 10.3). Noncontrolled studies suggest that GERD is a major risk factor for recurrent anastomotic strictures [29–33], or showed an association

Table 10.2 Potential mechanisms of GERD in EA

Causes	Mechanisms	References
Excessive tension at the esophageal anastomosis	• Decrease in lower sphincter tone • Shortening of the intra-abdominal esophageal segment • Deformity of the cardio-esophageal junction	[14, 15]
Abnormal esophageal motility	• Reduction of esophageal clearance • Longer acid and bolus clearing times • Transient lower esophageal sphincter relaxation	[16–18]
Slow gastric emptying (occasional)	• Congenital (microgastria) • Surgically induced vagal nerve injury	[13, 19–21]
	• Disturbed neuromuscular function • Antral hypomotility	[19, 22, 23]
Long gap	• Exacerbation of predisposing factors mentioned above (shortening intra-abdominal segment, esophageal dysmotility, microgastria…)	

Table 10.3 Complications of GERD in EA patients

Time of occurrence	Complication	Frequency
Short term	Laryngomalacia aggravation	
	Anastomotic stenosis	18–60%
	Peptic esophagitis	9–53%
	Feeding difficulties	6–11%
Middle term	Recurrent anastomotic stenosis	6%
	Bronchial hyperreactivity	
Long term	Barrett's esophagus	5–36%
	Esophageal adenocarcinoma	4 cases reported

between fundoplication and anastomotic strictures [34]. With a routine screening of GERD in infancy and an aggressive treatment of GERD (including antireflux surgery), Deurloo et al. observed a dramatic fall in the number of patients requiring multiple dilatations of an anastomotic stricture (10–2%) [29]. However, establishing a direct cause-to-effect relationship in non-interventional noncontrolled studies is difficult. One could not rule out bias due to the fact that (recurrent) anastomotic strictures prompt to look for GERD or to perform fundoplication. Feeding difficulties are observed in up to 40% of EA children aged 2–3 years and have been reported to be due to esophageal dysmotility and GERD [35].

Pulmonary complications associated with GERD are persistent atelectasis, aspiration pneumonia, asthma/increased airway reactivity, chronic lung disease with bronchiectasis, and worsening of tracheomalacia [12, 29, 30, 36]. Airway obstruction and/or acute life-threatening episodes (ALTE) can result from either proximal GERD reaching the larynx or GERD in the lower esophagus that could be reflexively responsible for respiratory symptoms [37].

In addition to GERD, the gastrointestinal causes of pulmonary symptoms are variable and include aspiration during swallowing, due to mucus or due to food retention in the proximal pouch or distal esophagus, anastomotic stricture, impaired

esophageal motility, congenital esophageal stenosis [38], recurrent or missed fistulae, eosinophilic esophagitis, and esophageal pooling over a fundoplication.

To date, no studies systematically evaluate respiratory symptoms in children to determine the frequency of GERD in pulmonary symptoms. No studies either try to determine the impact of esophageal dysmotility, independently of reflux, on respiratory symptoms [12].

GERD Impacts Quality of Life of EA Patients

Among the digestive symptoms, GERD has been reported to significantly impact the quality of life (Qol) of EA patients at any age: in adolescents, "physical health Qol score" decreased in case of GERD and "emotional Qol score" decreased when they presented dysphagia [39]. Symptoms of post-traumatic stress, mental strain, and GERD were predictors of reduced quality of life in adolescents in another study [40]. Similarly, adult patients born with EA complaining of dysphagia had lower scores on "general health perceptions Qol score" [41]. A recent study showed that although children's Qol was comparable to the baseline values provided and rated as good, adult patients reported a reduced health-related Qol [42].

What is the Natural History of GERD in EA Patients?

There are few longitudinal studies about natural history of GERD in EA population, and, to date, the risk of recurrence has not been assessed. GERD seems to be particularly frequent during the first months of age, especially within the first 5 years in EA with tracheoesophageal fistula (TEF) patients [26]. Koivusalo has longitudinally assessed GERD with pH-metry and histology in 61 children and showed that the prevalence of GERD increased gradually from 16% at the age of 6 months to 51% at the age of 5 years, while 44% of children still have GERD at the age of 10 years [27]. After 3 years of age, new cases of GERD are rare and most of the patients presenting GERD are symptomatic [27].

How Should GERD be Diagnosed in EA Patients?

Twenty-four-hour pH monitoring quantifies the esophageal acid burden, to diagnose pathologic reflux, which is highly correlated with peptic esophagitis. The main use of pH-impedance monitoring (pH-MII) is rather to try to correlate extra-esophageal symptoms with reflux events. Specific norms are not available in EA patients. A pH-metry study including 13 infants with EA aged 12 weeks, with an uneventful follow-up and no clinical sign of GERD, showed a mean reflux index of 4.08% (range, 1–9.8%; median, 3.3%), a mean total number of reflux periods with a pH less than 4 of 21 (range, 3–60; median, 17), and a mean number of periods of pH less than 4 lasting longer than 5 min of 2.5 (range, 0–9; median, 2) [43]. These

figures are very similar to those found in normal infants of the same age by Vandenplas and Sacre-Smits [44]. One of the limitations of pH-MII testing in patients with esophagitis or motility disorders (both of which are commonly found in patients with EA), is that baseline impedances are 75% lower than control patients [45] with a high risk of underreporting of reflux. Experience with pH-MII is increasing in patients with EA and shows that reflux events are likely to be due both to nonacid and acid reflux [17, 18, 45–48]. As there are currently no effective medications to treat nonacid reflux, there is few therapeutical interests to demonstrate nonacid reflux in EA patients, except for consideration for fundoplication.

Esophagitis is very frequent in EA patients (Table 10.3). Multilevel repeated esophageal biopsies are recommended to screen for peptic and eosinophilic esophagitis (see below).

How Should GERD be Treated in EA Patients?

A systematic review addressed the management of GERD in EA [49]. Only 25 articles were selected for analysis, most of them were single center and retrospective, and there were no randomized control trials. Fifteen studies named the class of antireflux agents used, but only three gave the duration of the therapy and none either the dosage prescribed or the number of doses.

There are no efficient prokinetic drugs currently available; moreover, there is no study on prokinetics performed in EA population, except those by Bergmeijer et al. who studied in a small number of patients ($n = 12$) the use of cisapride and alginate, and suggest a nonsignificant reduction of mean index reflux from 3.8 to 1.47% after 6 weeks of treatment [50]. Intrinsic abnormal motility of the esophagus is a constant feature in EA where prokinetics should not be as efficient as in a normal child. Therefore, due to their potential side effects and lack of efficiency, the use of prokinetics is not recommended in EA patients.

Feed thickeners have no action on GERD, they only reduce the regurgitations (although not studied specifically in EA patients), and therefore are not recommended in EA patients for the treatment of GERD.

Positioning has not been studied in EA patients and, as for other pediatric patients is not recommended, even if supine 30° elevation could be of help for infant with severe tracheomalacia and respiratory obstruction.

There are no controlled trials on the medical management of GERD in patients with EA. Although the quality of literature regarding the use of antireflux medication in children with EA is extremely poor [49], medical management of GERD with proton pump inhibitors (PPIs) and H2 receptor antagonists has been reported to be successful by reducing GI and/or respiratory symptoms, or by allowing significant weight gain [49]. A recent study showed that patients with EA were significantly more likely to experience PPI-refractory, non-eosinophilic esophagitis than controls regardless of CYP2C19 metabolizer phenotype. This suggests that factors other than CYP2C19 genetics, including dysmotility, are the primary drivers of esophagitis in EA [51]. The same team previously reported a “paradoxical”

association between the use of PPI and peptic esophagitis in patients with EA. Histological esophagitis was highly prevalent even with high rates of acid-suppressive drug use, suggesting esophagitis is likely multifactorial in patients with EA [52].

The benefit/risk ratio of long-term PPI treatment should be balanced in this population, and the need for prolonged use of PPIs should be reassessed on a regular basis (Table 10.1). Long-term safety of PPI in this population has not been extensively studied, and concerns on consequences of acid suppression on microbiota and possible higher risk for gastro-intestinal and respiratory infections have recently been highlighted, as well as increasing the risk of eosinophilic esophagitis [53].

Should GERD Systematically be Treated with PPI in all EA Patients?

Given the high prevalence and complication risks of acid GERD in the first months of life in infants with EA, the ESPGHAN/NASPGHAN consensus statement recommends systematic treatment with proton pump inhibitors (PPIs) until the age of 1 year and checking for acid GERD thereafter [8] (Table 10.1). The clinical benefit of PPI prophylaxis remains however to be demonstrated [54]. Several papers—all retrospectives and noncontrolled—showed that prophylactic use of PPI does not reduce the rate of anastomotic strictures [55–57].

How Long Should GERD be Treated and Monitored?

There are no prospective controlled studies on the optimal duration of acid suppression in infants, children, adolescents, or adults with EA. GERD is very common during infancy and can persist long-term. A recent longitudinal study showed that the prevalence rates of acid GERD were 64.3% at 18 months and 22.8% at a median age of 65 months [26]. Complications due to GERD occur mostly during the first year of life (anastomotic stricture, esophagitis, dying/cyanotic spells, pulmonary problems, failure to thrive), but can also be observed later. A study showed that GERD tended to be more prevalent after 1 year of age (43%) than before (34%), and that significant complications could develop after 1 year of age even in children who were previously asymptomatic [6]. GERD is one of the factors contributing to failure to thrive in infancy [39]. The prevalence of peptic esophagitis is high throughout childhood and adulthood (Table 10.2). Barrett's esophagus is a long-term complication of EA [7, 58–60]. GERD also contributes to dysphagia in EA patients [30] and can negatively influence the quality of life (see above). GERD remains frequent in EA children after the age of 2 years, even in asymptomatic patients, and can persist lifelong. Complications due to GERD can be observed during childhood, adolescence, and adulthood and may include late or recurrent anastomotic stenosis, esophagitis, dysphagia, Barrett's esophagus, and pulmonary complications. There is no correlation between symptoms and GERD complications (see below).

Taking all this into account, treatment of GERD is often prolonged in EA patients, long after early infancy, and regular endoscopy with biopsies is mandatory for routine monitoring of GERD in these patients (see below). Every patient with EA, including asymptomatic, should undergo monitoring of GERD (impedance/pH-metry, and/or endoscopy) at the time of discontinuation of anti-acid treatment and during long-term follow-up.

Is Routine Endoscopy Useful in the Follow-up of EA Patients?

There are no studies showing the benefit of routine upper gastrointestinal endoscopy in the follow-up of patients with EA. However, GERD can be asymptomatic and esophageal mucosal abnormalities can be observed in up to 35% of EA patients at endoscopy, despite the absence of symptoms [61]. In addition, symptoms in EA patients do not correlate with GERD findings on eso-gastro-duodenoscopy [27, 62–65] making inappropriate the recommendation of endoscopic assessment solely based on symptomatology. A retrospective study analyzed the results of esophageal biopsies performed during routine esophagoscopy in 72 EA/TEF children followed up from 6 months to 19 years (mean 10 years) [61]. Eighty percent of the patients presented at least one esophagoscopy demonstrating moderate to severe esophagitis or gastric metaplasia at any time of the follow-up. The risk of occurrence of histological esophagitis or gastric metaplasia was maximal during the first 3–5 years of life. The risk of having "unfavorable" histology after 6 years of repeatedly "normal" biopsies was very low [61]. The goal of surveillance biopsies is to detect early esophagitis (with the opportunity for subsequent intervention) before the development of late complications of strictures, Barrett's esophagus, and cancer. When performed, endoscopy should carefully examine the upper part of the esophagus (inlet patch is more frequent in this population), eso-gastric junction, and anastomosis area. In addition, it should look for stenosis, diverticulum or fistula, hiatal hernia, and peptic or eosinophilic esophagitis. In any case, when endoscopy is performed and even macroscopically normal, at least four biopsies, in quadrant, 1 cm above the Z line in the lower part of the esophagus, four biopsies in the middle, and four in the upper part of the esophagus, are recommended for Barrett's and eosinophilic esophagitis screening. The number of biopsies should be increased in the presence of macroscopic abnormalities or for Barrett's esophagus screening (at least four biopsies in each quadrant 1 cm above the Z line). Endoscopy is also useful in children post-fundoplication as the recurrence of GERD and peptic esophagitis is possible [24, 66–68].

When do We Perform Fundoplication in EA Patients with GERD?

There is no controlled trial on the surgical management of GERD in patients with EA. Cumulative risk of fundoplication in children with EA ranges from 0 to 45%. In long-gap EA, GERD is particularly frequent and severe and leads to a high risk

of anastomotic stricture. This suggests that fundoplication should be considered in a large proportion of these children [10, 69, 70]. In patients with EA who have dysmotility and abnormal esophageal clearance, fundoplication may worsen esophageal stasis by preventing gravity-driven esophageal clearance. This, in turn, may worsen respiratory symptoms. Decision to perform a fundoplication for isolated respiratory symptoms should be made with caution. In a systematic review on the management of GERD in patients with EA, reasons stated for the need for antireflux surgery included failure of maximum conservative therapy for GERD, failure to thrive, acute life-threatening event, esophagitis, and a recurrent anastomotic stenosis [71]. Similarly, the ESPGHAN/NASPGHAN consensus stated that a fundoplication should be indicated in case of recurrent anastomotic strictures, especially in long-gap EA, poorly controlled GERD despite maximal PPI therapy, long-term dependency on transpyloric feeding, and dying spells (Table 10.1). Timing of fundoplication varies from one center to another but is often performed during infancy. In one series, 92% of the Nissen fundoplication was performed between 1 and 24 months after the atresia repair (median, 4 months) [72]. However, performing fundoplication early in life exposes to a higher risk of failure. In a series of 360 children who underwent Nissen fundoplication (including 50 EA patients), age at surgery was negatively associated with Nissen failure [73]. The failure rate of fundoplication is high in this population varying from 6 to 47% [72, 74–76]. In a large series of 360 children who underwent Nissen fundoplication for various indications, previous repair of EA (31.6% failure) and congenital diaphragmatic hernia (46.7% failure) were the only comorbidities predictive of Nissen fundoplication failure (odds ratio 2.50 and 6.6, respectively) [73]. A fundoplication redo was required in 29% of patients within 16 months after the first one in a population of long-gap EA [77]. In a series of 148 children who underwent fundoplication (87 in patients with EA), the recurrence rate was 16.1% in the children with EA and 6.5% in the other cases [67].

What Evaluations Should be Performed Prior to Fundoplication?

The preoperative evaluation should include reflux testing (24-h pH-metry or pH-MII testing), upper gastrointestinal barium contrast study, and endoscopy [8] (Table 10.1). pH-metry/pH-MII testing is required to confirm acid and weak acid reflux. Barium contrast study allows the diagnosis of hiatal hernia, associated congenital stenosis, assesses the anatomy of the cardiac region, the stomach size, the gastric emptying, and excludes other intestinal malformations. Endoscopy allows macroscopic evaluation and biopsies of the esophageal mucosa, for screening for peptic esophagitis, eosinophilic esophagitis, or Barrett's esophagus. To date, esophageal manometry, pH-metry, and pH-MII have not been shown to help to predict the risk of postoperative dysphagia [78, 79], but a recently published study on 16 pediatric EA patients and 13 controls showed abnormal bolus transport in EA patients [80]. There is currently no data on the predictive value of high-resolution

esophageal manometry for the occurrence of post-fundoplication complications in patients with EA. Role of High Resolution Impedance Manometry in the prediction of post-fundoplication dysphagia needs to be evaluated [80, 81].

What are the Long-Term Morbidities of GERD in Adults with EA?

In adult patients with EA, GI symptoms are common, whereas respiratory problems are less frequent. Despite the frequency of these GI symptoms, it is striking that most adults born with EA have grown accustomed to live with variable dysphagia and reflux symptoms and often do not consider them problematic enough to seek medical attention. This can result in suboptimal management of GERD. The prevalence of symptomatic GERD is significantly higher among the patients than among controls (34% vs. 8%), as reported by Sistonen [60]. Taylor et al. found that GERD symptoms were reported by 63% of subjects, and 25% of these had severe reflux symptoms, defined as occurring at least 3 days per week [82].

Sistonen et al. studied 101 patients with their native esophagus who systematically underwent upper GI endoscopy. GERD symptoms and dysphagia were equally common in individuals with normal histology, histological esophagitis, or with epithelial metaplasia [60]. Overall, endoscopic esophagitis was reported in 8–58%, histological esophagitis in 24–90%, and macroscopic Barrett's esophagus (BE) in 6–31%. Columnar epithelial metaplasia without goblet cells occurred in 0–19% of patients and with goblet cells in 4–12%. Based on these findings, the prevalence of Barrett's esophagus is at least fourfold higher among the adult population with repaired EA compared with the general population.

In a multivariate logistic regression analysis, Sistonen et al. showed that surgically treated anastomotic stricture during infancy, long gap requiring myotomy to enable primary anastomosis, recurrent tracheoesophageal fistula, as in adulthood, and patient age were the most significant predictive factors for the occurrence of epithelial metaplasia with or without goblet cells. Surgical complications, patient age, and impaired esophageal motility were significant predictors of the development of epithelial metaplasia. A multicenter prospective study included 120 EA patients aged 15–19 years who underwent upper endoscopy with multistaged esophageal biopsies. BE was suspected after endoscopy in 37% and confirmed by histology in 43% of patients (50 gastric and one intestinal metaplasia). BE was not significantly related to clinical symptoms. In multivariate analysis, BE was associated with EA without fistula ($P = 0.03$), previous multiple antireflux surgery ($P = 0.04$), esophageal dilatation ($P = 0.04$), and histological esophagitis ($P = 0.02$) [59]. In a prospective study of 151 adult patients born with EA (mean age 25 years, range 17–69 years), histologically confirmed gastric metaplasia was present in 17% of patients, while BE was reported in 7% of patients, which is four times higher than the prevalence in the general population [58]. BE is frequently occult and poorly correlated with the presence of reflux symptoms so that symptoms alone cannot be used to identify it [59]. In a recent systematic review including 6282 patients under

long-term follow-up, 317 patients with BE (including both gastric and instestinal) were reported. Of these, intestinal metaplasia was identified in 54 patients, gastric metaplasia in 227, low-grade dysplasia in one, heterotopic gastric mucosa in three patients, and type of metaplasia unspecified in 38 [7]. Overall prevalence of BE was 5.0%, with a mean age at detection of 13.8 years (range 8 months to 56 years). Prevalence of BE in series reporting endoscopic screening or surveillance is 12.8% [7]. Four cases of esophageal squamous cell carcinoma were picked up by endoscopic surveillance [58, 82].

As patients born with EA have an increased prevalence of esophagitis, gastric metaplasia, and BE there is a theoretical increased risk of esophageal adenocarcinoma. Adenocarcinoma in EA patients has been reported in a few young adult patients. Additionally, esophageal squamous cell carcinoma has been reported in EA patients likely to be caused by delayed esophageal clearance as a result of abnormal motility and scares (surgical anastomosis, repeated dilatations) [58]. In total, only 13 cases of esophageal cancers (4 adenocarcinoma and 9 epidermoid carcinoma) have so far been reported [7]. There is no study reporting the benefit of systematic surveillance in adults with EA. However, as early treatment can prevent the development of esophageal malignancy, endoscopic surveillance should be performed (Table 10.1): [1] systematically every 5–10 years, [2] if a new esophageal symptom occurs, and [3] if regular symptoms (such as dysphagia) worsen.

Conclusion

GERD is a long life problem in EA patients. Detailed studies are necessary to define the long-term benefit/risk of proton pump inhibitors prophylaxis and fundoplication. The real risk of esophageal carcinoma remains to be studied by appropriate long-term follow-up cohort studies.

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GERD and Cow's Milk Allergy

11

Rosan Meyer

Abstract

Gastroesophageal reflux disease (GERD) is currently listed by the European Academy for Allergy and Clinical Immunology, the European Society for Pediatric Gastroenterology Hepatology and Nutrition and other food allergy associations as a possible non-Immunoglobulin E (IgE) mediated food allergic disorder. Published studies have indicated that in up to around 40% of children, this may be associated with cow's milk allergy (CMA). However, the challenge is not only distinguishing between food protein and non-food protein driven GERD, as both exhibit the same symptoms, but also to be able to distinguish between acute vomiting as a result of an IgE-mediated reaction or Food Protein-Induced Enterocolitis Syndrome (FPIES). The elimination of cow's milk and its derivatives should only be considered once standard treatment, which includes avoiding overfeeding and thickening of feed, has been trialled, and/or when atopic co-morbidities and/or other symptoms associated with non-IgE-mediated allergies are present. A 2–4 week elimination of cow's milk, which may entail a maternal elimination in breastfed infants or suitable formula with proven hypoallergenicity with complementary food free-from cow's milk protein (CMP). The reintroduction of cow's milk, with re-appearance of symptoms, is a critical step for the confirmation of the diagnosis and to avoid the unwarranted elimination. Mother and child should be supported with optimal dietetic support, including vitamin (i.e., vitamin D) and mineral supplements (i.e., calcium) to avoid excessive weight loss for the mother and ongoing growth and development for the child. The prognosis of cow's milk allergy-associated GERD is good with most children becoming tolerant between 1 and 3 years of age.

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Keywords

Gastroesophageal reflux disease · Cow's milk allergy · Non-IgE-mediated allergy · Delayed food allergy

Introduction

Food allergy is defined as a reproducible immune-mediated reaction towards a food allergen and can be either Immunoglobulin E (IgE) or non-IgE mediated [1]. IgE-mediated allergies, typically occur immediately and up to 2 h after the ingestion of the trigger foods and common symptoms include urticaria, angioedema, hives, eczema, respiratory symptoms (i.e., wheezing), acute vomiting and in severe cases anaphylaxis [2]. Non-IgE-mediated allergies are delayed in the presentation of symptoms, usually occurring >1 h to 48 h after ingestion of the trigger food [3]. Symptoms typically affect the skin (i.e., eczema) and/or gastrointestinal tract, including acute (within 1–4 h after exposure), severe vomiting (i.e., food protein-induced enterocolitis syndrome (FPIES)) [4], persistent vomiting, diarrhea with/without blood in the stools, abdominal pain, vomiting (acute and chronic) and these symptoms may be associated with faltering growth [3].

There is a wide range in challenge proven prevalence of food allergies in children <5 years of age, ranging from <1% in Turkey to 10% in Australia [5, 6]. The most common trigger foods in pediatric IgE and non-IgE-mediated food allergy includes cow's milk, hen's egg, soya, wheat, peanuts, tree nuts, fish, and shellfish [7]. Cow's milk allergy (CMA) [8], one of the most common food allergies <1 year of age, has a challenge proven incidence of <1% in Europe, according to the EuroPrevall study, but great variation was seen between countries [9]. This study is to date, the only population-based study that has assessed through a double-blind food challenge both IgE and non-IgE-mediated CMA and found that the latter had a prevalence ranging from 0.13% to 0.72%, with the UK having more children with non-IgE- than IgE-mediated CMA [9]. Methodological concerns have been highlighted in particular related to the recognition of symptoms of non-IgE-mediated allergies, so it is likely that the incidence of this delayed allergy is much higher.

Gastroesophageal reflux disease (GERD) is currently listed by the European Academy for Allergy and Clinical Immunology (EAACI) [10], the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [11] and other food allergy associations as a possible non-IgE-mediated food allergic disorder [2, 12]. However, the role of food allergens as a cause of GERD remains controversial [13].

The Role of Cow's Milk Protein (CMP) in GERD

The joint ESPGHAN-North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) guidelines on GERD from 2009 already recognized the possible role of CMA [8, 14] and has further increased in

prominence in the treatment pathway in the updated guidelines from 2018, with the consideration of a cow's milk elimination diet prior to the use of medication in infants <1 year of age [15]. Cavataio et al. published a study in the year 2000 on 204 prospectively recruited infants <1 year of age with the diagnosis of GERD and found that 41.8% of these patients had challenge proven CMA [16]. In addition to this study, Borrelli et al. [17] found through 48-h multichannel intraluminal impedance-pH monitoring that children with proven CMA had more total reflux and weakly acidic reflux episodes during CMP challenge. A recent study by Omari et al. [18], found that the elimination of CMP significantly improved GERD symptoms in infants with non-IgE-mediated CMA when compared with controls. That study also showed improved esophageal peristaltic function and mucosal integrity, increased acid clearance and esophageal mucosal impedance [18]. Several further studies have also found a high prevalence of CMA in children with GERD, in particular those resistant to standard treatment [17, 19–21]. The challenge, however, highlighted by all publications is the difficulty in not only distinguishing between food protein and non-food protein driven GERD as both exhibit the same symptoms, but also to be able to distinguish between acute vomiting as a result of an IgE-mediated reaction or Food Protein-Induced Enterocolitis Syndrome [3]. From the published studies, CMA may be more relevant in infants with severe and persistent GERD with associated food aversion, faltering growth and other gastrointestinal symptoms commonly associated with non-IgE-mediated allergies, but also atopic manifestations including atopic dermatitis and/or urticaria and rhinitis [17, 22].

Diagnosis

As CMP-associated GERD is recognized as a possible non-IgE-mediated food allergy [23, 24]. A small number of studies have assessed the role of skin prick testing, patch testing, serum IgE measurement, IgG and IgG4 for the diagnosis of non-IgE-mediated food allergy per se, but none have yielded results supporting their routine use for the diagnosis of CMP-associated GERD or any other non-IgE-mediated condition [25, 26]. However, if the infant exhibits symptoms of an IgE-mediated food allergy and/or has eczema, the use of specific IgE testing and/or skin prick test as part of a food allergy focused history may be indicated to support a diagnosis [2, 27]. The role of endoscopy, pH-manometry, and other tests are discussed in Chap. 3 and should be considered where applicable as part of the diagnostic work-up, in particular with the overlapping symptoms of GERD (food protein and non-protein induced) and eosinophilic esophagitis (EoE). See Table 11.1.

The primary diagnostic tool therefore for CMP-associated (and other food protein) GERD is a trial elimination diet, with symptom improvement, followed by the reintroduction of CMP with symptom deterioration [11, 24, 28, 29]. This elimination diet should only be considered for children with GERD, who have failed standard treatment, which includes avoiding overfeeding and thickening of feed, as per ESPGHAN/NASPGHAN guidelines and/or have atopic co-morbidities and/or other

Table 11.1 Diagnostic work-up for cow's milk-induced GERD

General symptoms	Atopic co-morbidities	Food allergy focused history	Allergy test
Vomiting with discomfort Faltering growth Epigastric pain Excessive crying Feeding difficulties Back arching during feed Poor sleep	Atopic dermatitis Existing IgE-mediated allergies Other non-IgE-mediated allergies (i.e., rectal bleeding, diarrhea) Recurrent wheezing	When did symptoms appear in relation to breast/bottle feeding and complementary foods? Specific foods involved?	Skin prick/specific IgE test only required if symptoms of IgE-mediated allergy present and/or eczema

symptoms associated with non-IgE-mediated allergies [15, 27, 30, 31]. Studies on the length of diagnostic elimination diets vary between 24 hours to 4 months [32]. Three review publications [20, 32, 33] recommended a 2–6 weeks avoidance period of cow's milk, and two guideline papers [34, 35] recommend a 2–4 week period of CMP avoidance in GERD. Although the publication by Lozinsky et al. [36] was not specifically aimed at infants with GERD, it collected data on a cohort with non-IgE-mediated allergies, including food protein-induced GERD and found that 98% had symptom improvement after a 4 week elimination diet, although complete resolution of symptoms may require a longer and full resolution of symptoms may not occur in all infants. This implies that a minimum of 2 weeks is required to start seeing symptom improvement, but symptom resolution may only occur in some after 6 weeks, in particular, if symptoms are severe. It is, however, important to individualize the length of elimination and use clinical judgement when suggesting a diagnostic elimination diet as this may be influenced by the following factors:

1. Severity of symptoms
2. Breastfed/bottle fed
3. Whether complementary food has been introduced
4. Nutritional status (growth and vitamin and mineral status) of the mother/infant
5. Psychological well-being of the family

While the elimination and reintroduction diagnostic approach is highlighted in all current guideline papers, specific guidance on how to reintroduce CMP is scarce. A double-blind supervised challenge remains the gold standard also for the diagnosis of CMP-associated GERD, however, this is not practical for many healthcare systems, as reactions may take days to occur, which has a significant fiscal burden to either parents or healthcare system. Studies have shown that reintroduction of CMP (and other offending food allergens) can be performed safely at home, if IgE-mediated symptoms or FPIES are absent, but this requires sufficient time for monitoring symptoms, guidance on how to reintroduce and most importantly how parents should assess reactions [34, 37].

Publications have varied greatly in the method for CMP reintroduction for diagnostic purposes, and to date, no standard approach exists, as with IgE-mediated

allergies. The iMAP allergy guidelines specific for mild to moderate non-IgE-mediated CMA have suggested that breastfeeding mothers should reintroduce cow's milk and its derivates over 1 week back in their diet and monitor symptoms. For formula-fed infants, a 1 week reintroduction regime has also been suggested, ending with at least 210 mL of CMP-based formula per day [24]. While these suggestions are not evidence based, there seems to be consensuses amongst healthcare professionals that one should at least aim for a "normal portion" of CMP according to the child's age to confirm or refute the diagnosis. For cow's milk, a normal portion is considered 120–240 mL of infant formula or cow's milk for toddlers [38].

Dietary Management in Proven CMP-Induced GERD

Cow's milk and its derivatives is a primary source of nutrition for the breastfeeding mother as well as for the non-breastfed infant and during complementary feeding [11, 39, 40]. The elimination of CMP increases the risk of growth faltering/excessive weight loss post-pregnancy and vitamin and mineral deficiencies for both the infant and breastfeeding mother are well-reported [39, 41]. It may also be that the infant/breastfeeding mother is not only eliminating cow's milk but soya and other food allergens. Soya is commonly reported as concomitated allergen in particular in non-IgE-mediated cow's milk allergy [36, 42, 43]. However, data differs between countries. It is therefore crucial that parents receive dietary advice, ideally from a registered dietitian/nutritionist, not only on what to avoid, but how to replace the macro and micronutrients from cow's milk and other allergens (Table 11.2), as this has shown to improve growth and micronutrient status [44].

Breastmilk in the Management of GERD

Limited data exists on the presence of CMA in breastfed infants. However, in a prospectively recruited cohort of breastfed children by Høst et al. [45] 0.5% of the 2.2% children diagnosed with an IgE-mediated CMA presented while being exclusively breastfed. There is paucity of data on the incidence and severity of GERD in breastfed infants, but it is estimated that about 25% of infants (both breastfed and bottlefed) suffer from troublesome regurgitation [46].

Cow's/goats and/or sheep milk protein can transfer through human milk in the form of β-lactoglobulin (levels range from 0.9 to 150 μg/L), which is unique to most mammalian milks and can elicit symptoms of CMA and may therefore also be involved in CMP-associated GERD [24, 47–49]. Breastfeeding is strongly supported by EAACI, ESPGHAN/NASPGHAN and other food allergy guidelines as the best source of nutrition to support growth, development, and the immune system [11, 24, 28, 49, 50]. In 2019, the EAACI position statement outlining the management and diagnosis of non-IgE-mediated allergies in breastfed infants was published highlighting the importance of supporting breastfeeding, ideally in line with the World Health Organization (WHO) of exclusive breastfeeding until 6 months of

Table 11.2 Cow's milk sources its nutritional contribution and possible alternatives

Potential sources[a]	Macro- and micronutrients	Food alternatives
Cow's milk (fresh, UHT, evaporated, condensed, dried) butter, butter oil, buttermilk Cream Cheese Yogurt, fromage-frais Casein, caseinates, hydrolyzed casein, sodium caseinate Curd Ghee Lactoglobulin Lactose—(food grade) Milk solids, non-fat milk solids Whey, hydrolyzed whey, whey powder, whey syrup sweetener	Protein, energy, vitamins A, D, and B12, riboflavin, pantothenic acid, calcium, phosphorus	Dairy free spreads, olive/sunflower/coconut/canola oil Fortified coconut/pea/nut/soya[b] based yoghurts/cheese Plant-based fortified drinks (see guidance below on milk alternatives) Baked goods without butter/milk/cheese/cream

[a] This list is not exhaustive and may differ between countries
[b] Soya may also be eliminated in some infants

age [51, 52]. Breastfeeding mothers should receive support to maintain breastfeeding and their dietary adequacy needs to be considered at all time, which may include the supplementation of calcium, vitamin D, iodine, and other micronutrient as appropriate to their elimination diet and their nutritional status [48, 53]. An unwarranted elimination diet should always be avoided as this poses a nutritional risk to the mother and may impact on the quantity and quality of the breastmilk [54].

Formulas for CMA in the Management of GERD

Many guidelines on the diagnosis and management of CMA, include suggested formulas suitable for the management of CMA, when breastmilk is insufficient or not available [2, 28, 49, 50]. All formulas that are being used for the management of CMA should be tested and conform to current guidelines on hypoallergenicity, which requires a product to be tolerated by 90% of children with a challenge proven CMA at 95 confidence interval and support normal growth [55, 56]. All guidelines suggest an extensively hydrolyzed formula [EHF] based on either casein, whey or rice, as first-line treatment for CMP-associated GERD (Table 11.3) [57]. However, the impact of growth faltering on formula choice should also be taken into account and is discussed in some of the guidelines. Several studies have shown improved catch-up growth, in particular, longitudinal growth with amino acid formulas (AAF) possibly related to the resolution of mild ongoing gastrointestinal inflammation [58, 59]. In addition, the involvement of multiple organ systems and multiple food allergies may also require the consideration of an AAF as first-line formula [60, 61].

In recent years, studies have been published using formulas that have specifically been designed for CMP-associated GERD. There are now thickened EHF casein,

Table 11.3 Summary of guidelines for first-line formulas for GERD

DRACMA (2010)	ESPGHAN (2012)	Australian Guidelines (2009)	BSACI (2014)	iMAP (2017
EHF[a]	No specific mention for GERD but EHF is recommended as first-line formula for most presentation of CMA	EHF if <6 months Soy if >6 months EHF if >6 months if also presenting with faltering growth	EHF (unless faltering growth then AAF)	EHF

[a] When hydrolyzed rice formulas are available, these can also be considered as first-line formulas for GERD

rice and AAF formulas with proven hypoallergenicity suitable for this population [62–65]. The studies by Dupont et al. [64, 66] and Vandenplas et al. [63] also assessed regurgitation episodes, crying and sleeping time. In children that had challenge proven CMA, both thickened and un-thickened extensive hydrolysates were equally effective in the resolution of symptoms and supported growth. In the study by Dupont et al. [64] significantly more children had better quality of sleep and less irritability with a thickened AAF and several studies have shown improved stool frequency and consistency [64] [63]. These formulas are not yet included in any of the CMA guidelines.

As mentioned above, soy is a commonly reported concomitant allergen in children with non-IgE-mediated CMA. While some data indicates that up to 50% have a concomitant allergy to soy in non-IgE-mediated CMA [42, 43], this is not the same in other studies and very limited data exists on soy being a culprit food in GERD [67, 68]. While all European, Australasian, and American guidelines do not recommend the use of soy-based formulas below 6 months of age for any CMA (Table 11.3) [11, 24, 49, 57], careful consideration in regards to local resources and the cost to families and healthcare system needs to be taken into account when considering soy-based formula as an option for a non-breastfed infant with CMP-associated GERD [12, 69].

Complementary Feeding in Infants with GERD

Complementary food should ideally be introduced, as per WHO guidelines, around 6 months of age. It is acknowledged in all of the allergy prevention guidelines, that outside of the culprit food, the introduction of other food allergens, including egg, wheat, soy (if not eliminated), peanut, tree nuts and fish, should not be delayed beyond 6 months of age [70–72]. In fact, when eczema and/or IgE-mediated egg allergy is present, the early introduction of peanuts, in countries where peanut allergy is prevalent is recommended [71, 73].

Furthermore, studies have also indicated that increasing the diversity of foods, may also have a positive impact on the further prevention of food allergies, possibly through improving the gut microbiome [74–76]. The expansion of complementary foods does not only play a role in the contribution of nutrients and the

microbiome, but also in the development of oral motors kills and the prevention of feeding difficulties [77]. Feeding difficulties are commonly reported in infants with GERD, ranging from breast to bottle aversion to texture hypersensitivity [78]. In a study published by Rommel et al. [79], who assessed the underlying diagnosis of 700 children with feeding difficulties, 60% presented with GERD as an underlying diagnosis. While this is well-recognized in GERD, limited data is available on feeding difficulties in children with CMP- associated GERD. To date, only one retrospective study has been published on feeding difficulties in the whole spectrum of non-IgE-mediated FA diagnoses, including GERD [80]. In that study, 30% of children had feeding difficulties, as noted by clinicians in the medical notes, with the most commonly reported being a texture hypersensitivity (Table 11.4). More data exists in EoE, where similar symptoms are present, in particular in the infants with early onset of EoE compared to CMP-associated GERD [81]. In the publication on EoE up to 90% of children have maladaptive feeding behavior [82, 83].

Many parents will report worsening of their infant's GERD to other foods, including fruit and vegetables that have traditionally been classified as "hypoallergenic." There is paucity on data on other trigger foods outside of CMP and other common allergens. However, many alternative practitioners and websites may advocate for the elimination of various foods (i.e., acidic fruit and vegetables), which may limit the infants' complementary diet significantly, increasing the risk for nutritional deficiencies. While, hypersensitivity reactions may occur to other foods, healthcare professionals should guard against unwarranted dietary elimination and understand the impact of food characteristics (i.e., protein content, osmolality, fat content and particle size) on gastric emptying to recognize patterns and therefore possible trigger foods. Any elimination of complementary foods outside of CMP should always be followed up by a timely reintroduction.

Natural History of CMP-Induced GERD

The prognosis of CMP-induced GERD is poorly described and difficult to establish; however, it is assumed that tolerance occurs at least within the age range previously described for other non-IgE-mediated allergies, which can be as early as 1 year of age, according to the EuroPrevall study on both IgE- and non-IgE-mediated allergy but may be as late as 3 years of age for some [9, 84].

Table 11.4 Feeding difficulties commonly seen in infants with GERD [80]

Feeding difficulties reported in infancy
Breastfeed or bottle refusal/aversion
Gagging on textured foods
Sealing of mouth and pushing spoon away
Crying when seeing the spoon
Extended mealtimes

The DRACMA Guidelines [28], ESPGHAN [11], and iMAP guidelines [34] suggest that after a period of avoidance, usually between 6 and 12 months, periodic reintroductions of cow's milk should occur to determine if tolerance has developed and this should also occur for CMP-associated GERD. There is currently no consensus on how reintroductions should occur in children with confirmed CMP-associated GERD. Several countries have adopted a milk ladder approach, which introduces milk proteins in a very gradual manner, starting from lower doses of less allergenic forms of milk, such as baked goods and advances slowly, as tolerated. While the efficacy of milk ladders has yet to be established, it has the potential of improvement in quality of life using this method of reintroduction has been recognized [69, 85]. Meyer et al. [37] has recently published their experience with using the ladder approach for the common allergens in a cohort of children with non-IgE-mediated allergy, including CMP-associated GERD. That study indicated that many children needed 2–5 attempts at the milk ladder due to ambiguous results, because of concomitated illness and/or teething impacting on the outcome. Whatever method is used for reintroduction, it is important that this is not delayed and that parents are adequately supported with reintroductions to not delay the process and also provide an accurate answer on tolerance.

Conclusion

CMP-associated GERD is a recognized non-IgE-mediated condition that is difficult to distinguish from GERD not associated with a food allergy. It is therefore important when an elimination diet is commenced to already discuss the reintroduction of CMP with the parents as an essential diagnostic step. GERD has a significant impact on the quality of life of parents and the further elimination of CMP may compound this impact [86]. At all times, the nutritional status of the breastfeeding mother and infant should be at the center of the management of CMP-associated GERD.

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GER and Overweight/Obesity

12

Karolien Van De Maele

Abstract

Children and adolescents with overweight and/or obesity have an increased risk for the development of gastroesophageal reflux (disease) (GER(D)). The prevalence of GER(D) in pediatric populations with obesity is about 20%. There are several hypotheses regarding the linking mechanisms between both conditions, such as mechanical susceptibilities or chronic low-grade inflammation, but evidence is still lacking. Additionally, an association with asthma and disordered sleeping has been found in children with obesity and GER(D) as well. The main treatment focus is to address the weight problem; however, this might be very challenging. For adolescents with obesity, bariatric surgery might offer an opportunity to obtain weight loss, but there seems to be an increase in GER complaints after surgery.

Keywords

Gastroesophageal reflux (GER) · Gastroesophageal reflux disease (GERD) · Overweight · Obesity · Children · Bariatric surgery

Introduction and Epidemiology

Children and adolescents with overweight and obesity have become a growing population in recent years and the study and management of associated comorbidities have gained interest as well. Overweight in children is defined as having a body mass index (BMI) above the 85th age/sex-specific percentile, whereas obesity is

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defined as a BMI above the 95th age/sex-specific percentile [1]. In general, the prevalence of overweight and obesity in children is around 20%, with some regional differences [2].

The association between gastroesophageal reflux (disease) (GER(D)) and (abdominal) obesity has been studied extensively in adults, but data in pediatric and adolescent populations are scarce [3–7]. Current reported prevalence of obesity in pediatric populations with symptoms of GER(D) varies from 20% to 24% [3, 5, 6]. Reversely, we see that about 40 to 61% of children with overweight or obesity complain of GER symptoms [4, 5, 7]. Compared to their peers with a normal weight, children with overweight and obesity have more frequent and more severe complaints of GER. However, this reflux is often non-acid and histology is often reported to be normal [3–7]. Additionally, BMI might not be the only important indicator since a correlation between an excessive waist circumference (above 90th age/sex-specific percentile) and prevalence and severity of GER symptoms has been described as well [5, 7].

Pathophysiology

The specific pathophysiological mechanisms linking obesity to the increased risk of GER symptoms remain unclear; however, some hypotheses have been formulated. Firstly, changes in the function of the lower esophageal sphincter (LES) have been identified. Obesity seems to be related with lower pressure in the LES and therefore contributes to a decreased function of the main mechanical barrier against gastric reflux into the esophagus [8, 9]. Also, transient LES relaxations without swallowing episodes have been identified in populations with obesity, provoked by gastric distention (mainly of the proximal stomach) [8, 9]. Secondly, increased intra-abdominal pressure and increased prevalence of hiatus hernia appear to play an important role [10]. This finding is mostly deduced from adult studies, however, was also confirmed in a pediatric study where both total and abdominal obesity were independent risk factors for reflux symptoms in children [5]. The abdominal adipose tissue surrounding the stomach might cause gastric compression leading to a rise in intragastric pressure, a subsequent relaxation of the LES and consequent esophageal exposure to gastric acid in children with obesity [3]. The increased abdominal adiposity also slows the stomach emptying [7]. Except for these mechanical mechanisms, the increased state of chronic, low-grade inflammation might be a common denominator of both pathologies [9]. Additionally, dietary factors and inactivity have been suggested to contribute [4].

Other Associations

Obesity and asthma associate independently with GER symptoms in children, but the linking mechanisms remain controversial [3, 4, 10, 11]. The use of short-acting ß-agonist inhalers might cause a relaxation of the LES as a side effect, but there

might also be a misattribution of symptoms since children with obesity report more severe asthma symptoms with less airway inflammation [11]. However, nearly all asthmatic children with obesity report some type of GER-related symptoms [10, 11]. Evidence exists that GER can cause microaspiration and stimulation of esophageal, pharyngeal, or afferent vagal nerves and consequently trigger asthma [11]. The question remains whether the relationships between GER, obesity, and asthma are strictly pathophysiological or rather related to patient's perceptions and experiences [11].

In addition to this, a correlation between GER, sleep disorders, and obesity has been established as well [12]. Despite a decrease in LES relaxation during sleep, reflux episodes might be longer due to reduced saliva production, less frequent swallows, and increased esophageal sensitivity to acid (or hyperalgesia) [12]. Complaints of heartburn during sleep have an impact on sleep quality (even in the absence of obstructive sleep apnea) and functioning during daytime [12].

Specific Treatment Options

The general recommendations for the management of overweight and obesity consist of lifestyle modifications through diet and exercise in combination with psychotherapy and/or pharmacological interventions if necessary [1, 13]. However, to improve health outcomes, a substantial weight loss should be obtained, which can be very difficult. Therefore, bariatric surgery has gained interest in the adolescent population with severe obesity in recent years. Both laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy have been performed in adolescents with a BMI above 35 kg/m^2 with a severe comorbidity or a BMI above 40 kg/m^2 with any obesity-related comorbidity [13]. Both procedures appear to be safe and effective in adolescents [13, 14].

Nevertheless, in the presence of reflux complaints, the effects on the symptoms and the procedure of choice remain largely unstudied. Dewberry et al. describe a population of 228 adolescents at 5 years follow-up after their procedure and conclude that GER symptoms increase during the years following surgery [15]. These symptoms are even fourfolds higher in the sleeve gastrectomy-group compared to the adolescents who underwent a Roux-en-Y gastric bypass [15]. These gastrointestinal symptoms negatively influence the improvement in quality of life of adolescents after their surgery [16].

For younger children with obesity, bariatric surgery is not an option. In theory, that can be treated with a proton pump inhibitor (PPI). However, a PPI will only change acid reflux to non-acid reflux. Given the finding that histology is often normal in these children, a PPI will have limited efficacy. Given the chronic nature of both the conditions and a possible long-treatment with a PPI, discussion arose regarding the long-term safety of this treatment in children with obesity [17]. Therefore, a dosage regimen based on the lean body weight has been proposed superior to a dosing based on the total body weight to avoid excessive PPI exposure in these children [17]. Nissen surgery might be the only option if reflux symptoms are severe and reduction of overweight fails.

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GER and Eosinophilic Esophagitis

13

Jorge Amil Dias

Abstract

GERD and EoE cause chronic esophageal inflammation sharing some common characteristics. Distinction between them requires a detailed evaluation of clinical, endoscopic, and histologic features. The interplay between these pathologies is complex and still under active investigation. GERD and EoE may also coexist. Combined clinical, endoscopic, and histologic data may provide the best diagnostic criteria to identify the exact diagnosis and take appropriate therapeutic options. Proton-pump inhibitors are not only frequently used to treat GERD but are also effective in a large number of EoE patients, especially if some degree of reflux is also present.

Keywords

GERD · Eosinophilic esophagitis · Eosinophils · Mast-cells · pH-monitoring · Endoscopy · Histology · Impedance · PPI (proton-pump inhibitor) · Allergy · Food

Gastro-esophageal reflux (GER) and eosinophilic esophagitis are the most common forms of chronic inflammation of the esophagus in children.

However, the relation between these two conditions is far from clear and concepts have evolved rapidly.

For many years the presence of eosinophils in the esophageal mucosa was considered a reliable sign of acid exposure reflecting reflux [1]. In 1995, Kelly et al. described ten pediatric patients with a previous diagnosis of gastro-esophageal

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reflux disease (GERD) that failed to improve on treatment (including fundoplication in six) but had considerable improvement on diet with amino-acid formula. All these patients showed a considerable decrease in the number of eosinophils in the esophageal mucosa. Subsequent reports confirmed that this new entity was different from typical cases with acid reflux [2–4].

The new disease was termed Eosinophilic Esophagitis (EoE) and had some distinct features although a clear differential diagnosis was not always easy. The detailed pathophysiology and therapeutic alternatives for EoE are beyond the scope of this text that addresses the relation between GERD and EoE.

Comparing epidemiologic features of the two conditions, EoE prevalence is considerably lower despite a marked increase in recent years, has a male predominance, frequent relation with atopy or food sensitization, and high family association [5, 6]. Genome-wide microarray expression analysis revealed a consistent pattern of upregulated genes related to the production of Eotaxin-3 and Th2 related cytokines [7, 8].

EoE typically presents as food impaction, dysphagia, or heartburn but these symptoms are more common in adolescents or adults [9]. Infants and younger children may have signs of abdominal pain, food aversion, or failure to thrive. In many patients, in all age groups symptoms may also be identical to GERD [10–12].

Functional and morphologic tests may help clarify which is the diagnosis although the two conditions may overlap in some cases [13]. Esophageal pH and impedance monitoring have been used to identify GERD. However, studies have found that pH study is frequently abnormal in patients EoE that respond to PPI treatment. Esophageal impedance evaluated in 11 adults with EoE was also abnormal as compared to controls, showing lower impedance levels both in distal, mid- and proximal esophagus, without correlation with acid exposure [14]. This may reflect impaired mucosa integrity derived from allergic inflammation with eosinophils and mast cell degranulation.

Endoscopy and histology are the usual procedures that provide information to confirm EoE. The typical endoscopic pattern of EoE is edema of the wall that causes the longitudinal furrows in the lumen (Fig. 13.1). Other aspects common in EoE are exsudates and concentric rings that give a trachea-like, also called feline appearance of the esophagus (Fig. 13.2). Mucosa is frequently friable and tears can easily occur by minor trauma from the endoscope. In severe cases, mostly in adults, the mucosa may have multiple cracks giving an appearance of crêpe-paper and stenosis may occur. However, the morphologic endoscopic features of EoE may be subtle or even absent, especially in younger patients [15]. One study revealed that approximately 30% of pediatric cases of EoE had normal-appearing mucosa [16]. The typical aspect of the esophageal lumen may occur along the whole esophagus while in GERD lesions tend to affect the distal part and esophago-gastric junction with erosions, ulceration or metaplasia of the mucosa. Endoscopic features may be reasonably specific for one or the other disease depending on multiple factors, including local epidemiology [17, 18]. Practice of performing systematic biopsies among pediatric and adult gastroenterologists may be different and account for the sensitivity of accurate diagnosis of EoE [19].

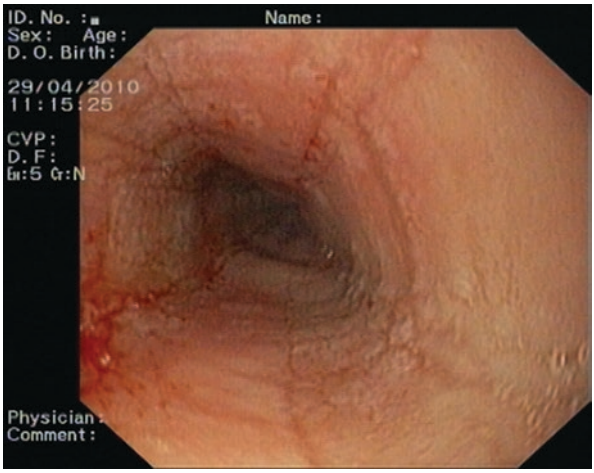

Fig. 13.1 Endoscopic image showing linear furrows from edema of the esophageal wall and friability of the mucosa with easy bleeding

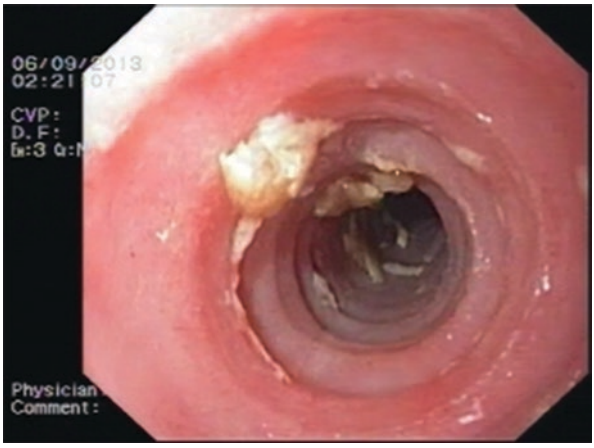

Fig. 13.2 Trachealization of the esophageal wall with remains from food impaction

Histology provides important features that usually distinguish EoE from GERD. Mild infiltration with eosinophils, especially in distal samples, is more typical of acid-related injury while higher density, usually more than 15 eosinophils per hpf (400× magnification), in multiple biopsies of distal and proximal esophagus are typical of EoE (Figs. 13.3 and 13.4). However, if the density of eosinophils is considerably higher (>30/hpf) in a single biopsy it may also be accepted as strongly in favor of EoE [12]. The mere presence of an increased number of eosinophils may not be enough and other features related to eosinophil-related inflammation are usually seen: degranulation, micro-abcesses of eosinophils, or dilated intercellular spaces (Table 13.1) [20, 21]. Features of inflammation and quantification of eosinophils in the mucosa are therefore important for accurate diagnosis. Peak eosinophil count should be registered. Other histological features of EoE are subepithelial fibrosis, increased angiogenesis, and mast cell infiltration [22–25]. Basal cell

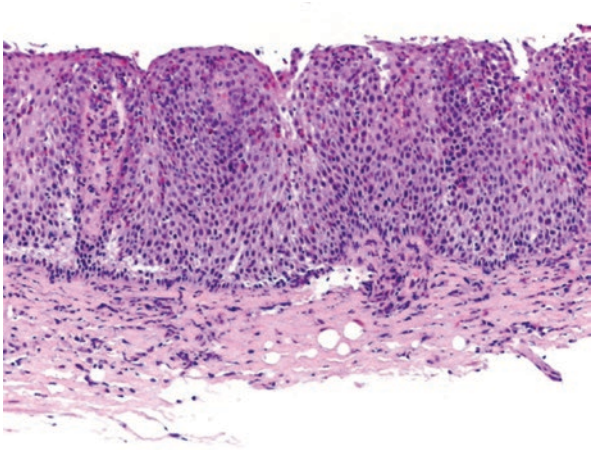

Fig. 13.3 Histology of the esophagus revealing elongation of the papillae and dense esonophilic infiltrate (courtesy of F Carneiro)

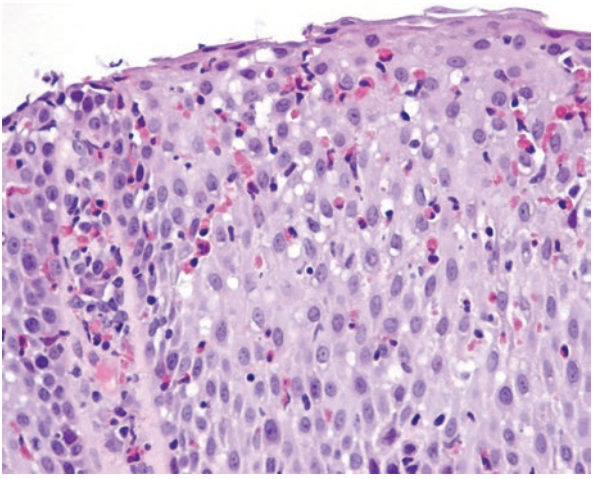

Fig. 13.4 Histology with higher magnification showing diffuse inflitrate of eosinophils and abundant granules (courtesy of F Carneiro)

Table 13.1 Histological features of EoE. Adapted from Collins [20], with permission

Greater than or equal to 15 intraepithelial eosinophils per HPF in at least one esophageal site Additional sections should be obtained from nondiagnostic but highly suggestive biopsies, and fewer eosinophils than the recommended threshold value may not eliminate the diagnosis in patients who otherwise would qualify for the diagnosis
Altered eosinophil character manifest as surface layering and abscesses
Epithelial changes such as basal layer hyperplasia, dilated intercellular spaces
Thickened lamina propria fibers

hyperplasia is seen more frequently in EoE than in GERD [26]. High-resolution endoscopic ultrasound also reveals thickening of the esophageal wall in EoE [27]. The allergic nature of EoE as compared to GERD has been investigated, namely the possible relation of IgG4 rise in patients undergoing oral immunotherapy for food

allergy and a reported increase of EoE in these patients [28, 29]. Some studies have indeed proposed that the identification of deposits of IgG4 in biopsy samples could help differentiate between GERD and EoE [30, 31].

The distribution of eosinophils in the esophageal mucosa may be irregular and patchy, sometimes sitting in deeper layers not always accessible to the usual endoscopic biopsy forceps [32]. For this reason, histological diagnosis of EoE requires multiple samples obtained at three different levels of the esophagus [9].

Clinical features, endoscopy and histology are the usual tools used in daily practice to establish the diagnosis of EoE [33].

The possible relation between GERD and EoE is difficult to establish, and the coexistence of both situations may differ in adults and children. Studies evaluating pH-monitoring in patients with EoE point to a higher frequency of pathological acid-reflux in adults than children [34–36]. On the other hand, the consistency and accuracy of pH-probe studies in inflammed esophagus infiltrated by eosinophils is also matter for some debate [37]. Various chemical products from eosinophil metabolism but also acid may cause some damage into the esophageal epithelium and tight junctions, affecting permeability and rendering it more susceptible to penetration of acid or antigens. The stimulus of acid on the epithelium may also lead to the release of cytokines that attract eosinophils. Therefore, the causality relation is difficult to establish and possibly not uniform in all patients [37]. It is also possible that the metabolites of activated eosinophils in the mucosa may affect esophageal motility and favor reflux or delay esophageal clearance when acid reflux occurs [37].

It is now clear that a distal, mild infiltration of eosinophils (<15/hpf) and abnormal pH-monitoring is more consistent with acid exposure and reflux while edema, friability, thickening of the esophageal wall and heavy eosinophilic infiltrate are typical for EoE [36, 38]. However, differential diagnosis is not always easy and these two conditions are not mutually exclusive [39]. Occasional patients may have both and cases have been reported where initial GERD treated with gastric-acid suppression evolved to a clear pattern of EoE [40]. This may be a rare circumstance but illustrates that the relation and distinction between the two diagnoses may be difficult [11]. It is also known that children operated for Esophageal atresia, undergo long PPI therapy to prevent acid reflux but have an increased incidence of EoE [41–44]. In fact, there may be an increase of EoE in infants exposed to treatment with PPI and the causality is still puzzling as these drugs have proved to be effective in many patients with EoE [45].

A review of adult patients originally diagnosed as having GERD and submitted to fundoplication identified some cases that did not improve following surgery. Some of these cases were retrospectively diagnosed with EoE. The authors concluded that younger age, symptoms of dysphagia, food allergy, presence of esophageal rings/furrows/plaques, absence of hiatal hernia, higher eosinophil counts, and eosinophil degranulation are related to EoE [46].

Due to the much higher prevalence of GERD than EoE it is not surprising that there may a considerable overlap of cases. Until 2017 it was accepted that there might be a specific entity, named PPI-responsive esophageal eosinophilia (PPI-REE), different from pure EoE and a therapeutic trial with PPI was recommended

before the diagnosis of EoE was established in those patients that did not improve. However, accumulated evidence showed that PPI-REE was merely a possible expression of EoE. Currently, the presence of the typical features as mentioned above should be regarded as EoE, and the previous recommendation of diagnostic PPI trial is not recommended any more [47].

Research showed that PPI have therapeutic effect in EoE-related inflammation by various pathways including decreasing eotaxin-3 levels [48–51]. Molina-Infante et al. reported clinical and endoscopic response in up to 50% of the cases and abnormal pH-monitoring was only partially predictive of a good outcome [52]. Response to PPI in EoE is usually higher in patients with abnormal pH monitoring. A meta-analysis involving 33 studies confirmed these results with little variation between adult and pediatric patients [53]. Furthermore, it revealed that the response was apparently better when PPI were given twice daily, therefore not dose-dependent but rather related to sustained therapeutic drug levels. One study in adult volunteers showed that patients with EoE exposed to instillation of HCl into the esophagus had earlier burning sensation than those with reflux or healthy controls, which might also explain the symptom remission of PPI treatment despite ongoing inflammation [54]. Other treatments for EoE, like elimination diets or topical steroids are unlikely to produce benefits in isolated GERD, although it must be taken into account that gastro-esophageal reflux may be an expression of food allergy, especially in infants.

Epithelial barrier function is normal in inactive EoE but decreases upon stimulation from Th2 cytokines and reduced Desmoglein-1 expression replicating the abnormal barrier defect in active EoE [55]. This supports the concept that inflammation leads to impaired epithelial integrity although acid exposure may also evoke cytokine stimulation [56].

A recent study in adults showed that higher efficacy of reflux-induced salivary reflex and more severe mucosal damage in the distal esophagus are associated with EoE response to PPI treatment [57].

Conclusion

Several clinical, endoscopic and histological features may help distinguish typical cases of pure GERD and EoE and the presence of elevated eosinophil count in multiple esophageal biopsies should evoke the possibility of EoE which may coexist with abnormal pH-monitoring or impedance tests. On the endoscopic evaluation of reflux-like symptoms, multiple biopsies should be obtained from proximal, mid and distal esophagus, regardless of the endoscopic appearance of the esophageal mucosa. Diagnosis of GERD and EoE are not mutually exclusive and PPI response (symptomatic and histological) occurs in approximately half of EoE patients, therefore it does not exclude EoE as a possible diagnosis. In the presence of inflammed mucosa and elevated eosinophil count (>15 eos/hpf in multiple biopsies or > 30 in single biopsy) diagnosis of EoE should be strongly considered regardless of concomitant GERD or improvement on PPI therapy. The interplay or causality

relationship between GERD and EoE are still under investigation and knowledge is rapidly evolving. The role of PPI in increasing the risk for EoE is still puzzling in view of its therapeutic beneficial effect.

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GER and *Helicobacter pylori*

14

Oya Yücel

Abstract

Helicobacter pylori (*H. pylori*) infection has been shown to affect the severity and course of gastroesophageal reflux disease (GERD). In this chapter, we have updated these complex relationships based on recent developments in children's studies, taking into account findings from studies in adults.

The effect of *H. pylori* on GERD differs according to the anatomical location of *H. pylori* infection (antrum, corpus, or pangastritis). The type of gastritis is also very important in the course of reflux esophagitis (acute, chronic, atrophic). *H. pylori*-associated gastritis in the corpus causes hypoacidity while antral gastritis causes hyperacidity. During childhood, *H. pylori* is associated with antral predominant gastritis and duodenal ulcers.

Gastrin is affected by the gastric localization of *H. pylori* infection, atrophic changes, and acute/chronic nature. In antral gastritis, hypergastrinemia occurs during the destruction of somatostatin-secreting cells during infection and it triggers acid production, and hyperacidity leads to the development or progression of GER and erosive esophagitis. In cases of antral gastritis that causes hyperacidity, reflux esophagitis may improve after *H. pylori* is eradicated. Chronic gastritis can lead to atrophic gastritis. Atrophic gastritis causes hypoacidity due to cell damage. In this case, GERD manifestations are provoked by the eradication of *H. pylori*. Histological studies have shown that atrophic gastritis is rare in children.

The determining factors that trigger *H. pylori*-related GERD are the location of gastritis in both children and adults, CagA/VacA positivity, and substances released from the stomach which lead to transient lower esophageal sphincter relaxations. Pangastritis causing gastric atrophy is associated with CagA strains

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and its protective effect against GERD has been demonstrated in corpus gastritis. *H. pylori* infection with CagA strains is associated with less severe reflux esophagitis in children. But, antral nodularity was found more frequently in CagA-positive patients. VacA, s1b positivity was associated with a lower frequency of esophagitis rate in children. Further studies are required to explain this complex relationship in childhood.

Keywords

CagA · Children · Cytokines · Gastritis · Gastroesophageal reflux · *Helicobacter pylori* · Microbiota

Abbreviations

BapA	Blood group antigen-binding adhesin A
BE	Barrett's esophagus
BMI	Body mass index
CagA	Cytotoxin-associated gene A
DupA	Duodenal ulcer promoting gene A protein
EAC	Esophageal adenocarcinoma
GERD	Gastroesophageal Reflux Disease
H. pylori	*Helicobacter pylori*
HpSA	*H. pylori* stool antigen
IL	Interleukin
NO	Nitric oxide
OipA	Outer inflammatory protein
OMPs	Outer membrane proteins
PGs	Pepsinogens
PPIs	Proton pump inhibitors
RE	Reflux Esophagitis
SabA	Sialic acid-binding adhesin
TLESR	Transient lower esophageal sphincter relaxations
VacA	Vacuolating cytotoxin A

Introduction

Helicobacter pylori (*H. pylori*) infection and Gastroesophageal Reflux Disease (GERD) are common diseases worldwide. Because of better living conditions, better hygiene, and frequent use of antibiotics in childhood, the prevalence of *H. pylori* infection is decreasing, while GERD is increasing. Gastroesophageal reflux (GER) is the most common esophageal disorder and affects 30% of the pediatric population. The prevalence of GERD varies by age and country. GERD has complex and

multifactorial pathogenesis associated with gastric acidity and esophageal motility, the protective barrier of the esophagus, and the rate of emptying of the stomach [1]. Characteristic specific symptoms include heartburn and acid regurgitation, but in pediatric patients, the symptoms vary with age.

H. pylori is a Gram-negative microaerophilic bacterium that usually colonizes the stomach and chronically infects half of the world's population. *H. pylori* is transmitted from person to person among family members by the fecal-oral or oral-oral route. Mother-to-child transmission is the main route of intra-familial transmission of *H. pylori* and infection is most likely acquired in childhood. The prevalence of infection in the pediatric age is high and varies from country to country and within the same geographic area. Infection is often acquired in the first 10 years [2–6]. *H. pylori* infection is a risk factor for the development of a peptic ulcer, atrophic gastritis, and gastric cancer and causes a variety of effects on the stomach and esophageal function. However, *H. pylori* infection is asymptomatic in most children and complications are less common [3, 6, 7].

H. pylori infection may contribute to GERD through different mechanisms. GERD appears to result from abnormal and transient lower esophageal sphincter relaxations (TLESR) and an imbalance between acid exposure of the esophageal mucosa and clearance mechanisms. In this context, nitric oxide (NO) dysregulation induced by the induction of inflammatory NO synthase associated with chronic *H. pylori* infection contributes to inappropriate TLESR [8, 9]. Research to elucidate the role of *H. pylori* infection in the pathogenesis of GERD has focused mostly on its potential to increase gastric acid secretion. Depending on the site of involvement, depending on the increase in acid secretion, *H. pylori* may play a protective and aggressive role in the incidence and severity of GERD [10–12].

H. pylori and GERD affect each other. Although a great deal of research has been done on this topic in adults, the number of studies on children is limited. However, the site of *H. pylori* colonization in the stomach and the severity of inflammation in children are extremely different from adults. In this chapter, we aimed to update the information based on recent studies investigating the relationships between *H. pylori* infection and GERD in children, while taking into account opinions in adult studies.

Diagnosis of GERD

Although GERD can be diagnosed by typical history and physical examination findings, it is difficult to define due to its extensive heterogeneity. The definition of symptoms is unreliable in children under the age of 8 years of age. The sensitivity of the pH-meter alone is especially low in infants, and it increases with age. The sensitivity in children above 8 years is higher. Furthermore, the pH-meter alone enables the differentiation between acid and non-acid reflux. Multichannel intraluminal impedance and pH (MII-pH) monitoring can determine non-acid reflux, and the content of reflux material. pH-MII monitoring shows a tendency to become the gold standard test for the diagnosis of GERD in the pediatric population [13]. However, there is still a lack of standard values for the pediatric population.

Moreover, studies assessing clinical and pH-MII predictors of reflux esophagitis (RE) are scarce [14]. Histology incorporates a limited way of diagnosing or excluding GERD. GERD evaluation includes the empiric proton pump-inhibitors (PPIs) trial, the esophageal pH/impedance monitoring, and endoscopic evaluation [15].

Diagnosis of *H. pylori*

In children, *H. pylori* can be detected with non-invasive methods (13C-urea breathing test and stool antigen detection; HpSA) and with invasive methods (histology, culture, rapid urease test). Although endoscopy is recommended for the initial diagnosis of *H. pylori* infection, noninvasive tests are used to evaluate eradication and reply to treatment [3, 16]. However, in children younger than 6 years, monoclonal *H. pylori* stool antigen (HpSA) testing is more suitable as a diagnostic test with high sensitivity (88%), specificity values (93%) [16–18]. HpSA test can also be used in epidemiologic studies. According to the 2017 guideline recommendations of ESPGHAN / NASPGHAN, using antibody-based tests (IgG, IgA) for *H. pylori* are not convenient to decide in childhood [2]. Invasive methods should be limited to patients in whom benefits are expected such as gastroduodenal ulcer, erosive gastritis, and with the purpose to rule out other causes [2, 3].

H. pylori Pathogenesis in Children

Studies have shown differences between the histopathological findings of children and adults with *H. pylori* infection. As the main histopathological finding, chronic inflammation (infiltration of lymphocytes and plasma cells) is often more prominent in children than in adults with acute active inflammation (neutrophil infiltration) [3, 19]. In a study involving 750 children from Turkey, the rate of chronic gastritis among children infected with *H. pylori* was found to be 74% [19]. In a study conducted in China, the prevalence of active inflammation was found to be 26.9%, chronic superficial gastritis at 41.9%, and atrophic gastritis at 21.7% [20]. In Koca et al. [21] study, peptic ulcers and erosions (5.1% ulcers and 2.1% erosions) were found in 7.2%, including 1026 children who underwent upper gastrointestinal endoscopy. *H. pylori* positivity was detected in 45.8% of these patients.

H. pylori and GERD

Many studies emphasize the coexistence of GER and *H. pylori* and infection may contribute to GERD through different mechanisms. The role of *H. pylori* infection in GERD is explained by gastric acid output. On the other hand, evidence from pathophysiological studies indicates that TLESRs are the predominant reflux mechanism in both children and adults with GERD without *H. pylori* infection.

H. pylori may have both a protective and aggressive role in the incidence and severity of GERD. These are explained by the anatomical location of *H. pylori* infection and the resulting hypoacidiy or hyperacidity. The serum level and effect of gastrin may vary depending on the anatomical region and the outcome of the infection. According to the currently accepted mechanism, the protective effect is mediated by corpus-limited gastritis from *H. pylori*, resulting in hypoacidity as a result of parietal cell destruction. This resulting hypoacidity leads to increased gastrin secretion, which results in rebound hyperacidity and GERD development after eradication [4, 22].

In contrast, in *H. pylori* infection confined to the antrum, hypergastrinemia occurs during infection due to the destruction of somatostatin-secreting cells. As a result, acid secretion from corpal parietal cells increases and hyperacidity triggers GERD. However, in the case of atrophic gastritis, the opposite happens. Gastrin level decreases due to antral G cell atrophy, and the resulting hypoacidity has a protective effect from GERD [4, 23, 24].

The obvious protective effect of *H. pylori* in GERD varies according to the location of the stomach injury and its histological features. Those with antrum-predominant gastritis had gastric acid hypersecretion, while those with pangastritis or corpus-predominant gastritis had reduced acid secretion. Decreased gastric acidity and consequent increase in gastrin and increased lower esophageal sphincter pressure may explain the inverse relationship between *H. pylori* infection and GERD. Within the scope of these hypotheses, gastrin, which is the main regulating hormone in acid secretion, gains importance. In addition, genetic factors alter the immune and inflammatory response to *H. pylori* infection [4].

The Effects on Children

Children and adolescents with *H. pylori* infection had antral gastritis predominantly. Prevalence ranging from 1.9 to 71.0 has been reported [25–27]. In a study comparing low (USA) and high risk (Colombia) groups, it was found that inflammatory lesions were mostly in the antrum in both groups [28]. In Carvalho's study [27], pangastritis was detected in 61.9% of children, followed by antral gastritis in (32.1%), and corpus gastritis in (5.9%) of children (mean 9.5 years). Besides, the *H. pylori* density in the antrum (32.1%) was higher than in the corpus (5.9%). In Austrian children, pangastritis was present in 46% of children who had *H. pylori* infection, with 50% antrum predominant (mean 10.5 years) [4, 25]. Langner [26] from Brazil found that, among children and adolescents, while the rate of *H. pylori*-associated gastritis located in the antrum was 27.3%, this rate was 4.5% in the corpus (mean 10.5 years). In another study from Chilean, the ratio was 83% for antrum-predominant gastritis [29].

In children, initially, *H. pylori* colonizes the antrum and can produce antral gastritis and if the infection persists nodular, pangastritis. The most frequent endoscopic diagnosis in children is nodular gastritis [3, 5]. Gastric atrophy and intestinal

metaplasia are less frequent as compared with adults and are more related to time exposure [2].

The prevalence of *H. pylori*-positive ulcers in children differed between countries. The prevalence of *H. pylori* with duodenal ulcers was higher than those with gastric ulcer in previous studies [30, 31]. Finally, during childhood, *H. pylori* is associated with antral predominant gastritis and duodenal ulcers [32–34]. However, corpus-predominant gastritis is more common in adults [35–37].

H. pylori and Reflux Esophagitis (RE)

GERD is categorized according to the endoscopic findings as reflux esophagitis and non-erosive reflux disease. RE, represented with endoscopically visible breaks in the distal esophageal mucosa. It has been well recognized that endoscopy has high specificity (90–95%) for GERD. However, poor sensitivity of around 50% has been reported [13, 14, 38, 39].

The effects of *H. pylori* in RE are explained by three mechanisms; hyperacidity, decreased TLESR, and indirect effects of gastric substances [14, 40, 41]. RE is the most common consequence of esophageal injury caused by acid reflux. Esophageal adenocarcinoma (EAC) can arise in patients with GERD and RE, as a result of glandular metaplasia of the normally squamous esophageal epithelium (Barrett's esophagus) [20].

The prevalence of RE in children varies. The prevalence of RE increased from 2007 (11.8%) to 2014 (37.7%). In Ristic et al. [13] study in 2017 (N.3413), the prevalence rate of endoscopically proven RE was 28.7% . In the study investigating the frequency of RE in children aged 1–10 and over 10 years of age with *H. pylori* infection, the highest frequency was found in children aged 1–10 (OR: 7.00 vs 5.99) [42].

The effect of *H. pylori* on the esophagus varies with the anatomic location of *H. pylori* infection. Depending on the type of gastritis, acid secretion may either increase or decrease. Gastritis in the corpus leads to hypoacidity, while antral gastritis causes hyperacidity. The distribution of gastritis is also important in the development of RE [4]. However, the studies that investigated the correlation between endoscopic findings and clinical symptoms in a cohort of children were not demonstrated any association [43–45]. Little is known about the exact histological features of reflux and its contributions to esophageal and gastric mucosal lesions in children with *H. pylori*-related gastritis. The studies which examined and scored the histological characteristics of the mucosa showed that in the presence *H. pylori*, esophagitis was less severe according to the Los Angeles classification system (grade A) [12, 37]. Higher histological scores were determined in antrum-predominant gastritis in children, as expected [4, 25–27, 29].

Unlike adults, the risk factors of RE in children are unclear. Of those that are known, risk factors in severe GERD during childhood include neurological disorders, congenital malformations including esophageal atresia and tracheoesophageal fistula, chronic lung disease, and extraesophageal disease [4]. According to

univariate analysis in a previous study, location of residency, age, and body mass index (BMI) was also significantly associated with the occurrence of RE [13].

Atrophic Gastritis

Long-term *H. pylori* infection causes inflammatory sequelae in the stomach such as atrophic gastritis and intestinal metaplasia. The result of chronic *H. pylori* infection is atrophic gastritis, in which acid production is reduced, even in antral gastritis. Atrophic gastritis predisposes individuals to gastric cancer.

Studies in children have shown that atrophy and metaplasia in childhood are quite rare (0–4%) [46]. The prevalence of gastric atrophy and intestinal metaplasia differs due to geographic/genetic origins and environmental factors [47]. Unfortunately, no pediatric studies are covering these issues.

The effects of *H. pylori* infection on GERD severity were detected in 27% of children in a study of 19 centers from 14 European countries. The frequency of ulcers and/or erosions in children develops in the second decade of life [48]. High-level histological scores that can lead to malignancy are seen in patients older than 20 years. Fortunately, atrophic gastritis in children is not common. Therefore, children are less prone to develop *H. pylori*-associated malignancy due to the length of time it takes for malignancy to develop [49].

The Effect of *H. pylori* Eradication on GERD

There continues to be controversy about the appropriate management of *H. pylori* infection in patients with GERD. Antrum-predominant gastritis is characterized by hypergastrinemia and more acidity. The risk of either peptic ulceration or GERD increases in patients with antral gastritis [50]. After eradication of *H. pylori*, acid secretion will return at least to normal in antrum-predominant gastritis. The expectation is that, in these patients, *H. pylori* eradication should improve or not affect RE [50–52]. The positive effects of *H. pylori* eradication on GERD symptoms are most likely due to antral predominant gastritis which is the most common type in childhood.

Most of the studies in children support the view that HP eradication does not affect the frequency and severity of GERD [37, 51]. In the study of Xinias [36], which draws attention with its interesting results, *H. pylori*-positive adolescents with antral gastritis had no clinical improvement after eradication despite increasing the mean lower esophageal sphincter pressure and decreasing the "Reflux Index." In another interesting study in neurologically impaired children, Pollet et al. [53] reported that HP eradication did not affect increasing or decreasing the manifestations of GERD. According to these results, while *H. pylori* aggravate GERD symptoms in children, eradication of HP does not play a role in GERD symptoms. This complex outcome can be explained by the rarity of chronic atrophic gastritis in children.

The region that secretes gastric acid is the body of the stomach filled with parietal cells. There is an association with decreased gastric acid production in cases of atrophic gastritis or severe corpus gastritis as a result of chronic inflammation of the corpus. This process is considered to be the main mechanism by which *H. pylori* infection prevents the onset of GERD [54]. In these cases, eradication of *H. pylori* may cause an increase in acid secretion and exacerbate symptoms of RE or GERD [50–52, 55, 56]. In the adult patient with pangastritis, there is an irreversible decrease in gastric acid secretion in contrast to patients with duodenal ulcer. In the case of pangastritis, gastric acid production decreases [55] and *H. pylori* infection prevents RE by reducing gastric acid secretion. In patients with *H. pylori*-positive gastritis and gastric ulcer, proton pump inhibitors (PPIs) are effective for the treatment of RE after eradication.

On the other hand, after the eradication of *H. pylori* in duodenal ulcers with hyperacidity, there was an improvement in pre-existing RE [51, 57].

In addition, the importance of the anti-reflux barrier should be kept in mind. In terms of RE development, patients with barrier disorders such as hiatal hernia will be more affected by the eradication of *H. pylori* [52, 58].

Medical treatment for RE focuses on reducing stomach acid production with PPIs. However, PPIs have some shortcomings in the treatment of GERD. PPIs are very effective at improving RE, but not so good at relieving GERD symptoms [59]. The Maastricht IV/Florence consensus report explains that prolonged treatment with PPIs in *H. pylori*-positive patients is associated with the development of corpus dominant gastritis. This accelerates the process of loss of special glands, which leads to atrophic gastritis. In patients receiving long-term PPIs, eradication of *H. pylori* improves gastritis and prevents progression to atrophic gastritis. Therefore, eradication therapy is recommended before long-term use of PPIs in patients with *H. pylori*-infected RE [60].

Barrett's Esophagus

RE and Barrett's esophagus (BE) are included in the complication of GERD. In the case of *H. pylori*, infection protects against GERD in corpus-predominant gastritis, the development of BE and esophageal adenocarcinoma (EAC) will decrease. In contrast, eradication of *H. pylori* infection will increase the risk of BE and EAC. However, BE in children is highly rare [61].

Gastric atrophy is the most widely accepted mechanism by which the distal esophagus is protected from abnormal acid exposure in patients with *H. pylori* infection. Epidemiologic studies indicate that cagA-positive strains are also protective of the distal esophagus against RE and EAC in adults [62]. Rubenstein et al. [63] observed trends toward an inverse association with esophagitis, but not with GERD symptoms.

Pediatric cohort studies pointed out that acute inflammation may be less intense in children, but that chronic inflammation may increase in intensity. In the study by Carvalho [27], the histological scores for esophagitis in Brazilian children and

adolescents were higher in the non-infected group than in the *H. pylori*-infected group and, among *H. pylori*-positive children, neither intestinal metaplasia nor gastric atrophy was determined. In a study from a high-risk population (58 Korean and 115 Colombian; mean 15 years), the atrophic mucosa was present in 16% of children (31% intestinal metaplasia; 63% pseudopyloric metaplasia; 6% both) [64]. In the case of atrophic gastritis or gastric cancer, *H. pylori* infection prevents RE by decreasing gastric acid secretion. Atrophic gastritis is a risk factor for the progression of malignancy even in children.

Persistent reflux promotes cancer in Barrett's metaplasia. It is not clear if PPIs prevent cancer in Barrett's metaplasia because the evidence is all indirect and not proven in controlled trials. Because of the shortcomings of PPI therapy, novel therapeutic targets, other than gastric acid production, are needed for treating RE and its complications such as BE. The study of Souza et al. [59], as a new perspective, showed that not only acid but also bile salts play a role in DNA damage in Barrett's cells. Bile salts also cause NF-κB activation in Barrett's cells, enabling them to resist apoptosis in the setting of DNA damage and likely contributing to carcinogenesis. Alternatively, oral treatment with ursodeoxycholic acid can prevent esophageal DNA damage and NF-κB activation induced by toxic bile acids.

Effects of *H. pylori* Infection on Gastrin, Ghrelin, and GERD

H. pylori infection alters prokinetic hormone levels; therefore, esophageal acid clearance and gastric emptying will be impaired in patients infected with *H. pylori*, contributing to the development of GERD. Acid exposure represents the critical event in GERD. Gastrin and pepsinogens (PGs) affect gastric acid secretion.

GERD, *H. pylori* and Gastrin

Gastrin is secreted almost entirely by antral G cells. Gastrins stimulate acid secretion by releasing histamine from enterochromaffin-like cells. If chronic *H. pylori* infection is not detected or treated, the bacteria or *H. pylori* causes proliferation and chronic inflammation of the gastric mucosa, resulting in atrophic gastritis. Atrophic changes increase the risk of gastric ulcer and non-cardia gastric adenocarcinoma, while hypoacidity leads to duodenal ulcers. As a result, it protects against GER complications caused by acidity [8, 9, 65].

George et al. [66] reviewed studies up to 2020 evaluating gastric injury and cancer-related biomarkers, including gastrin and PGs, in *H. pylori*-Infected children. In children infected with *H. pylori*, overexpression of serum gastrin has been reported in five previous studies. On the other hand, the five studies showed no differences in gastrin (serum or stomach). Most studies have been done on symptomatic children. One study [67] showed lower gastrin levels among infected symptomatic children compared to controls. However, gastric locations of *H. pylori* infection affecting gastrin levels were not mentioned in these studies. While

biomarkers were determined in symptomatic and asymptomatic infected children, PGs and gastrin were evaluated from blood or serum samples in asymptomatically infected children. In addition, PGs in gastric tissue of symptomatic children were also evaluated to demonstrate comparative results. These findings suggest that gastric injury can occur not only when symptoms occur in infected children, but also in apparently healthy children. For gastrin, the reported results seem controversial, as an expression in gastric tissue is increased in symptomatic children [67], whereas serum levels are decreased in asymptomatic children [68].

In the study of Eren et al. [22], no relationship was found between gastrin and ghrelin in children with symptomatic GERD. The reason for this difference may be predominantly corpo-antral infection in their patients. On the other hand, there were no children with atrophic gastritis in this study. Atrophic gastritis is rare in children [19].

In an adult study by Monkemüller et al. [69], serum gastrin and PGs levels did not differ with different grades of GERD. In another adult study, a significant negative correlation was found between the degree of corpus atrophy and both serum gastrin and PG-I levels in patients with both atrophic gastritis and GER. This inverse correlation was not confirmed between antral atrophy and gastrin [70].

Finally, chronic, atrophic, corpus-dominated gastritis in *H. pylori*-infected cases increases ghrelin levels and causes a decrease in gastrin levels. Antral gastritis is more common in children. Increased gastrin levels trigger acid production, ultimately leading to GER and RE.

On the role of overexpression among infected compared with uninfected children, prospective and long-term studies are needed to determine whether persistent infection produces sustained hypergastrinemia and possible carcinogenesis as children progress to older age [66].

GERD, *H. pylori*, and Pepsinogens (PGs)

PG-I and II are precursors of pepsin. PG-I is secreted by cells of the gastric corpus and is correlated with acid output and therefore used as a marker reflecting gastric acid secretion, PG-II is secreted not only by corpus cells but also by antral and duodenal glands [66]. PGs reflect overexpression at the protein level in serum of *H. pylori* infected children. In *H. pylori*-induced gastritis, both PGI and II are upregulated, with a greater increase in PGII and a consequent decrease in the PGI/II ratio [71]. PGI, PGII, and the PGI/II ratio decrease in atrophic gastritis [66].

In children, increased levels of PGI and II in gastric tissue have been reported in *H. pylori*-infected cases. Serum PGI and PGII levels of both symptomatic [72] and asymptomatic [73] infected children were also increased, and this increase was found to be higher in children older than 10 years of age. An age-related induction in PGI has been reported in cohort studies [74]. Also, although high serum PG levels predict *H. pylori* infection, they are not always correlated with histological gastritis. That is, PGs should not yet be used as biomarkers of gastric injury in asymptomatically infected children.

Gastrin and PGs have also been evaluated in the gastric tissue of symptomatic *H. pylori*-infected children in almost all studies in children. These findings are important in showing that gastric mucosal damage develops in asymptomatic children as well. George et al. [66], in their study comparing the PGI, PGII, and gastrin levels of symptomatic and asymptomatically infected children, reported that Gastrin increased in the gastric tissue of symptomatic children while serum levels of asymptomatic children decreased. The controversial results seem to require large-scale studies.

GERD, *H. pylori*, and Ghrelin

Levels of prokinetic hormones such as ghrelin and motilin are affected by *H. pylori* infection and may explain the occurrence of GERD in children [22]. Ghrelin is produced primarily in the stomach and regulates appetite, food intake, and body composition. It also affects gastric acid secretion as a stomach protector and increases gastrointestinal motility. Motilin is released from the duodenal mucosa into the bloodstream and allows the stomach to empty.

Two theories have been proposed regarding the mechanism by which *H. pylori* infection leads to a decrease in plasma ghrelin levels. One is the direct effect of *H. pylori* infection on ghrelin-secreting cells. Another proposed mechanism is the view that hypergastrinemia caused by *H. pylori* infection leads to a decrease in ghrelin secretion and that a decrease in gastrin levels after eradication may cause an increase in ghrelin levels and a decrease in GERD [22, 75, 76].

The stomach is the main source of circulating ghrelin. Plasma ghrelin levels reflect inflammation in atrophic events of the gastric mucosa. Ghrelin production is affected by atrophy that develops as a result of chronic permanent damage to the gastric mucosa caused by *H. pylori* infection [77–82]. As stated in previous studies, *H. pylori* eradication does not affect plasma ghrelin concentration in patients without atrophic gastritis [83, 84].

In the relationship between *H. pylori*, GERD, gastrin, and ghrelin, it has been predicted that the hypergastrinemia observed in *H. pylori* infection leads to a decrease in ghrelin secretion. A decrease in gastrin levels after eradication will lead to improvement in GERD but will trigger an increase in ghrelin [22, 75]. There is an inverse relationship between gastrin and ghrelin levels. As the second increases, the first decreases.

In an adult study, Isomoto et al. [85] determined that Ghrelin concentrations in *H. pylori*-infected RE adults were lower than in uninfected ones. Hypergastrinemia may negatively affect ghrelin levels [85]. As shown in previous studies, chronic inflammation is a common histological finding in children with *H. pylori* infection, mostly located in the antral region of the stomach. Therefore, the ghrelin level in *H. pylori*-infected children would be expected to be normal or lower than normal as a result of the increase in gastrin levels.

In a unique study, *H. pylori*-infected children (n.42) were evaluated for symptoms, total GER attacks, percentage of acid exposure, gastrin, ghrelin, and motilin levels before and after *H. pylori* eradication. No relationship was found between GER episodes and gastrin, ghrelin, and motilin levels. However, they confirmed that there was a decrease in gastrin level after eradication of *H. pylori*, conversely, an increase in both ghrelin and motilin levels. However, none of these changes were statistically significant. Corpo-antral gastritis was detected in children in this study, and no case with atrophic gastritis was found [22].

In prepubertal children (n.30), serum ghrelin concentrations are inversely proportional to the severity of *H. pylori*-associated gastritis. In these cases, long-term eradication of *H. pylori* infection was associated with a significant reduction in circulating ghrelin levels [86]. Recent studies have shown that *H. pylori* infection causes the release of many proinflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8. These cytokines act as a decrease in ghrelin production in patients infected with *H. pylori* [19]. In a previous study, plasma and tissue ghrelin levels increased after the eradication of *H. pylori* in children with functional dyspepsia associated with *H. pylori* [81].

Virulence Factors of *H. pylori*, and GERD

Influential factors related to the pathogenicity of *H. pylori* are bacterial virulence factors, gastric environmental factors, host genetics, host immune response, and exposure time [87].

When *H. pylori* reaches the protective mucus layer on the surface of the gastric mucosa, it first colonizes the antrum where there are no acid-producing cells to survive. It then adheres to epithelial cells using BabA, the blood group antigen-binding adhesin, and carbohydrates from gastric epithelial cells. It metabolizes urea in the stomach to ammonia, and carbon dioxide, producing urease to create a neutralized space where bacteria can live [87].

Virulence factors (CagA, VacA) and bacterial colonization factors (BabA, SabA, OipA, and HopQ) are required for gastric pathogenicity [87]. The virulence of *H. pylori* is closely correlated with the presence of a cag pathogenicity island (cag-PAI), which encodes a bacterial oncoprotein, CagA, and is associated with lymphocyte infiltration of the gastric mucosa, and another factor encoded by a different locus, the vacuolator cytotoxin A (VacA). VacA determines anion and urea output by causing intense vacuolation in epithelial cell lines that form pores in their membranes [6, 88].

Host genetic factors and CagA strains interact to determine the relationship between *H. pylori* and GERD. All virulence factors trigger intense inflammation [88]. Therefore, the degree and prevalence of gastritis are affected by these factors. In addition, the mucosa of GERD patients produces significantly greater amounts of various cytokines [52, 89] that activate immune cell recruitment and migration and are involved in the pathophysiology of the disease [1].

Virulence Factors of *H. pylori*

Cytotoxin-Associated Gene A (CagA)

CagA just present in some *H. pylori* strains. The genetic variability of *H. pylori* strains is dependent on the geographical and ethnic status of human hosts [90]. Pangastritis causing gastric atrophy is associated with CagA strains [90–94]. Clinically, infection with the cagA-positive *H. pylori* strain has been associated with severe atrophic gastritis, pangastritis, peptic ulcer disease, and gastric cancer, as well as higher degrees of gastric mucosal inflammation. *H. pylori* infection with CagA strains is associated with less severe RE due to pangastritis causing hypoacidity. In adult studies, the protective effect of cagA-positive strains of *H. pylori* against GERD has also been shown [4, 95].

CagA induces specific modifications in the morphology of epithelial cells. Within the host cell, CagA may consist of different segments of EPIYA [91]. *H. pylori* strains containing EPIYA-D or at least two EPIYA-C segments in its CagA gene are associated with a higher risk of developing cancer [96].

The rate of cagA-positive strains in children and adolescents with *H. pylori* infection shows regional differences (41.5% in Italy, 58% in Latvia, and 46% in Estonia) [97, 98]. In the study conducted by Gold [32], it was determined that gastric inflammation was more severe in children infected with CagA-positive strains. Eradication of *H. pylori* has resulted in improvement of both esophageal and stomach diseases at 6 months follow-up. Although *H. pylori* CagA-positive strains are less common in children, it has been shown that gastric inflammation is more severe [99].

VacA, particularly the virulent form s1m1, inhibits gastric acid secretion by disrupting gastric parietal cells. This may reduce acid exposure in the esophagus and result in fewer GER symptoms [56, 93, 100]. CagA+ and VacA s1m1 strains are considered the most pathogenic factors and carry a higher risk of precancerous lesions. Studies have reported CagA+ and VacA s1m1 more frequently in children and adolescents [101]. It is stated that if infection with these strains occurs in childhood, the risk of malignancy will be higher in the following years [3, 4].

Sökücü et al. [102] determined that esophageal lesions were less common in Turkish children infected with CagA-positive strains. But, antral nodularity was found more frequently in CagA-positive patients. In another study from the same region, Selimoglu et al. [103] found no difference between CagA-positive and -negative groups in terms of both peptic ulcer prevalence and histopathological features (N.98).

Vacuolation Cytotoxin A (VacA)

The gene is found in almost all bacterial strains. As a result, CagA and VacA affect the severity of the gastrointestinal disease. Recent studies have shown that CagA can block the apoptotic activity of VacA [95]. VacA mRNA is significantly associated with gastric inflammation levels in *H. pylori*-positive patients and contributes to the persistence of *H. pylori* by VacA i1-type strains [88, 95]. VacA also induces

an inflammatory response mediated by activation of NF-kB, increasing IL-8 [95]. Some changes by this virulence factor contribute to advanced gastritis [98]. VacA, s1b positivity was associated with a lower frequency of esophagitis rate in children [103].

Duodenal Ulcer Promoting Gene A Protein (DupA)

DupA promotes an increase in the production of IL-8 in the antral gastric mucosa. Enhanced IL-8 levels lead to mucosal inflammation and polymorphonuclear leukocyte infiltration, which contributes to antral gastritis and duodenal ulcers [98, 104].

Outer Inflammatory Protein (OipA)

OipA contributes to both adhesion and increased inflammation by inducing enhanced IL-8 production. The relationship between OipA and the increased development of peptic ulcers and gastric cancer was shown [98].

Adherence and Outer Membrane Proteins (OMPs)

OMPs which are present in all *H. pylori* strains can be altered through growth or under different conditions to ensure *H. pylori* survival. Adhesion to the gastric mucosa is the first and critical step in the infectious process. Among outer membrane proteins, BabA is an important protein involved in many inflammatory processes in addition to playing a role in the aforementioned attachment process [105].

Blood group antigen-binding adhesin A (BapA), sialic acid-binding adhesin (SabA), and outer inflammatory protein (OipA) are the most important adhesins of *H. pylori* [106]. BabA is an important protein in many inflammatory processes [105]. It binds to ABO/Leb blood group antigens and carbohydrates in gastric epithelial cells. This binding plays a role in host defense by inhibiting the proliferation of *H. pylori*. Interestingly, BabA affects acid sensitivity and plays an important role in acid adaptation of bacterium in response to changes in the acid secretion during disease progression [88].

Inflammatory Cytokines of *H. pylori*, and GERD

The genetic susceptibility of the host is dependent on polymorphisms of genes involved in *H. pylori*-related inflammation and the cytokine response of gastric epithelial and immune cells. *H. pylori* strains differ in their ability to induce a noxious inflammatory response. Cytokines are driven by *H. pylori* accelerates the inflammatory response and promotes malignancy. Chronic *H. pylori* infection causes genetic instability in gastric epithelial cells and affects DNA damage repair systems [106].

H. pylori establishes gastric homeostasis by using proinflammatory cytokines, inducing inflammation, thereby affecting the activity of gastrin-producing G cells and acid-producing parietal cells. CagA protein can induce the production of IL-8 and IL-1β. Thus, more pronounced inflammation develops in patients infected with CagA-positive strains [6].

H. pylori-associated corpus dominant gastritis may have decreased stomach acid, possibly mediated by cytokines such as IL-1. In children infected with *H. pylori*, gastric concentrations of IL-1β and/or TNF-α, both potent inhibitors of gastric acid secretion, are increased [93]. Kutukculer [107] found that TNF-α levels in gastric juice and gastric biopsy were significantly higher in children with *H. pylori*-positive gastritis compared to those without. Increased inflammatory cytokine levels may contribute to the pathogenesis of *H. pylori*-associated gastritis in childhood. Based on these data, it is thought that reflux-induced cytokine release may be a target for future medical treatments [59].

H. pylori and Gastric Microbiota in Children

The gut microbiota plays a fundamental role in modulating inflammatory responses. Information on the stomach microbiome and its relationship to diseases in both children and adults are very limited [108, 109]. *H. pylori* has a strong influence on the gastric microenvironment as well as on the immunological state of the host, leading to shifts in the gastrointestinal microbiome. These shifts play a role in the pathogenesis of *H. pylori*-related diseases. Differences in both diversity and community composition were observed in the stomachs of *H. pylori*-infected children [109, 110]. The presence of *H. pylori* significantly reduces the diversity of the stomach microbiota and alters the microbiome by increasing the relative abundance of Proteobacteria, Spirochetes, and Acidobacteria and conversely reducing Actinobacteria, Bacteroidetes, and Firmicutes [111, 112]. The study by Kato et al. [113] discussed that the overall rate of colonization of non-Helicobacter bacteria in the gastric mucosa is higher in adults than in children (100% vs 10%). This suggests that microorganisms rarely colonize the stomach of children [113].

According to a meta-analysis result including five studies (N. 484), it was observed that *H. pylori* eradication rates increased and treatment-related side effects decreased with the addition of probiotics to the treatment. However, not all probiotics are beneficial for the eradication of *H. pylori*. It has been reported that adding Lactobacillus supplements to the treatment of children with *H. pylori* infection reduces the side effects [114]. In an interesting adult study by Feng et al. [115], 29 studies containing 17 probiotics were evaluated (N.3122). If *H. pylori* triple therapy is supplemented with a probiotic, Lactobacillus casei was identified the best for *H. pylori* eradication rates (*P* score = 0.84), and multi-strain of Lactobacillus acidophilus and Lactobacillus rhamnosus for total side effects (*P* score = 0.93).

The effects of early acquisition of *H. pylori* on the shaping and differentiation of the microbiome, and therefore on the immune system, may produce different results. While the answer is unknown, the question is what will be the future effects of acquiring the bacterium early in life when analyzing the effects of *H. pylori* on the immune system and microbiome. Recent studies have associated different gastric microbial compositions with a high or low risk of malignancy in adults [109, 110].

Limitation

Almost all of the children with chronic active gastritis colonized with *H. pylori* can be diagnosed using endoscopy/biopsy. However, endoscopy is not a widespread application for the diagnosis of GERD in childhood. In most studies, only children who underwent upper gastrointestinal endoscopy were enrolled in the studies. In addition, while investigating the effects of *H. pylori* on GERD, the site of inflammation was not specified.

Conclusion

The effect of *H. pylori* on the esophagus varies according to the anatomical location of the *H. pylori* infection and the resulting hypoacidity or hyperacidity. Most previous studies showed that the results of eradication of *H. pylori* infection depend on the type and location of gastritis in patients with GERD. Atrophic gastritis appears to be protective against GERD because of hypoacidity. In these patients, GERD symptoms are exacerbated and RE is common after the eradication of *H. pylori*. Identifying the mechanism of the abnormalities aids in effective causal treatment. *H. pylori* infection in childhood often leads to antral gastritis and duodenal ulcer. Chronic inflammation (infiltration of lymphocytes and plasma cells) is more pronounced in children infected with *H. pylori* than in adults. According to these results, *H. pylori* may exacerbate GERD symptoms in children, and eradication of *H. pylori* does not lead to any change in GERD symptoms even in children with neurological disabilities.

In conclusion, the determining factors influencing GERD involving *H. pylori* are the location of gastritis, CagA positivity, and gastric released substances leading to TLESR in both children and adults. The reason why *H. pylori* affects the gastric corpus or antrum in different populations may be due to genetic differentiation. CagA-positive strains of *H. pylori* are associated with pangastritis leading to hypoacidity and less severe GERD. But, pangastritis and atrophic gastritis are rare in childhood. *H. pylori* infection with CagA strains is associated with less severe reflux esophagitis in children. But, antral nodularity was found more frequently in CagA-positive patients. VacA, s1b positivity was associated with a lower frequency of esophagitis rate in children.

In this section, to put this complex relationship in perspective to understand, we have updated based on recent progress in children while considering insights from research in adults. Further studies are required to explain this complex relationship between the location of gastric inflammation and CagA positivity.

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GER and Probiotic

15

Flavia Indrio and Fernanda Cristofori

Abstract

Gastroesophageal reflux (GER) refers to retrograde movement of gastric contents out of the stomach with or without regurgitation and vomiting.

Regurgitation is defined as the passage of refluxed gastric content into the oral pharynx while vomiting is defined as expulsion of the refluxed gastric content from the mouth. The frequency of regurgitation may vary largely in relation to age, and younger infants up to first month of age are more frequently affected by regurgitation. The effect of the intestinal microflora in the pathophysiology of GER and regurgitation is becoming in the last few years more evident even though the exact mechanisms of interaction between the intestinal bacteria and host are still unknown. Probiotic might play an important role in maintaining gut homeostasis by modulating intestinal barrier function, immunity, motility, and influencing the gut–brain interaction. The role of intestinal microbiota in the pathogenesis of GER could represent a promising field of research in the next future.

Keywords

Gastroesophageal reflux · Regurgitation · Gut–brain axis · Probiotic

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Gastroesophageal reflux (GER) refers to retrograde movement of gastric contents out of the stomach with or without regurgitation and vomiting.

Regurgitation is defined as the passage of refluxed gastric content into the oral pharynx, while vomiting is defined as expulsion of the refluxed gastric content from the mouth. The frequency of regurgitation may vary largely in relation to age, and younger infants up to first month of age are more frequently affected by regurgitation.

Reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response causing forceful expulsion of gastric contents. GER is a common, physiological and self-limiting process occurring several times per day in healthy infants. Most episodes of GER in healthy individuals, which last less than 3 min, occur in the postprandial period and cause few or no symptoms. GER is distinguished from gastroesophageal reflux disease (GERD) by the presence of organic complications and/or troublesome symptomatology (esophagitis, obstructive apnea, reactive airway disease, pulmonary aspiration, feeding and swallowing difficulties, failure to thrive) [1].

Regurgitation or spitting up is the involuntary return of previously swallowed food or secretion into the mouth. According to some authors, regurgitation is a form of GER. Regurgitation occurs daily in about 50% of infants <3 months of age and resolves spontaneously in most healthy infants by 12–14 months of age.

Infant regurgitation is the most common functional gastrointestinal disorder in the first year of life. Recognition of infant regurgitation avoids unnecessary doctor visits and unnecessary investigations and therapy for GERD.

In 2016, Rome IV criteria for the diagnosis of infant regurgitation (in otherwise healthy infants of 3 weeks to 12 months of age) have been published. The criteria include regurgitation two or more times per day for three or more weeks and no retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing [2].

The Infant with Uncomplicated Recurrent Regurgitation

In the infant with recurrent regurgitation or spitting, a thorough history and physical examination with attention to warning signals suggesting other diagnoses (Table 15.1) are generally sufficient to establish a clinical diagnosis of uncomplicated infant GER. The typical presentation of uncomplicated infant GER is effortless, painless regurgitation in a healthy-appearing child with normal growth—the so-called happy spitter. Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, it is not an indication for extensive diagnostic testing. An upper GI series or other diagnostic tests are not required unless other diagnoses such as gastrointestinal obstruction are suspected. Recurrent regurgitation due to GER generally decreases over the first year, resolving at 12–18 months of age. If "warning signs" for GERD or other diagnoses are present or if regurgitation is not resolving by 18 months of age, consultation with a pediatric gastroenterologist is recommended.

Table 15.1 Warning signals requiring investigation in infants with regurgitation or vomiting

Warning signals	
Bilious vomiting	Fever
Gastrointestinal bleeding	Lethargy
Hematemesis	Hepatosplenomegaly
Hematochezia	Bulging fontanelle
Consistently forceful vomiting	Macro−/microcephaly
Onset of vomiting after 6 months of life	Seizures
Failure to thrive	Abdominal tenderness or distension
Diarrhea	Suspected genetic/metabolic syndrome
Constipation	

Generally, only parental education, anticipatory guidance, and modification of feeding frequency and volume are necessary for the management of uncomplicated infant GER. Overfeeding exacerbates recurrent regurgitation and should be avoided. In some infants with persistent regurgitation, a thickened or commercial anti-regurgitation formula may help control the frequency of regurgitation. There is no evidence for the use of anti-secretory or pro-motility agents in physiologic infant regurgitation. Prone positioning is not recommended because of its association with SIDS. Since regurgitation is sometimes the sole manifestation of cow's milk protein allergy in healthy-looking infants, a 2-week trial of protein hydrolysate or amino acid-based formula or a trial of milk-free diet for the breastfeeding mother could be appropriate.

The Infant with Recurrent Regurgitation and Poor Weight Gain

The infant with recurrent regurgitation and poor weight gain should not be confused with the "happy spitter." While the history and physical examination may be identical, poor weight gain is not typical of uncomplicated infant GER and is a crucial warning sign that alters clinical management.

Since there are no well-controlled studies evaluating diagnostic or therapeutic strategies for these infants, the following approach is based on expert opinion [3]. A feeding history should be obtained that includes an estimate of calories offered and ingested per day, an estimate of calorie loss through regurgitation, a description of formula preparation and feeding schedule, an assessment of breast milk sufficiency, and a description of infant sucking and swallowing behavior. It is important to ensure with the help of a dietitian that there is no nutritional compromise to the infant secondary to inadequate caloric or fluid provision. If problems identified by history seem to explain the symptoms and can be addressed, close outpatient monitoring of weight gain will determine whether further evaluation is indicated.

If chronic regurgitation and inadequate weight gain persist after observation and despite adequate calorie intake, evaluation for causes of failure to thrive compatible with the history is mandatory. Among possible etiologies in infancy are infections (especially urinary tract), food allergy, anatomic abnormalities, neurologic

disorders, metabolic disease, and neglect or abuse. A 2- to 4-week trial of extensively hydrolyzed or amino acid-based formula could be appropriate. Depending on the results of investigations and response to dietary management, the infant should be referred to a pediatric specialist. Hospitalization for observation and testing is appropriate in some infants with persistent failure to thrive. Nasogastric or nasojejunal feeding is occasionally necessary to achieve weight gain in the infant, with no other clear explanations for poor weight gain.

The Child over 18 Months of Age with Chronic Regurgitation or Vomiting

Regurgitation, episodic vomiting, and regurgitation followed by swallowing of refluxate in the mouth are additional symptoms of GER more characteristic of children over 18 months. These symptoms are not unique to GERD, but whether of new onset in the older child or persisting from infancy, they should be evaluated as possibly secondary to GERD. The suggested evaluation includes upper intestinal endoscopy and oesophageal pH/MII to diagnose GERD, while upper GI series is sometimes needed to rule out alternative diagnoses. The verbal child can communicate pain, but descriptions of quality, intensity, location, and severity generally are unreliable until at least 8 and possibly 12 years of age.

Because individual symptoms do not consistently correlate with objective findings or response to medical treatment, parent−/patient-reported questionnaires based on clusters of symptoms have been developed. Orenstein et al. developed a diagnostic questionnaire for GERD in infants, which has undergone several revisions and has been shown to be reliable for documentation and monitoring of reported symptoms. However, in a study of infants referred for symptoms of GER and controls, the questionnaire had sensitivity and specificity of 47% and 81% for an RI >10% and 65% and 63% for a reflux index >5%. The questionnaire score failed to identify 26% of infants with GERD. The score was positive in 17 of 22 infants with normal biopsies and pH studies and in 14 of 47 infants with normal pH studies. No single symptom was significantly associated with esophagitis. In another study, the questionnaire was unable to identify a group of infants responsive to proton pump inhibitor therapy. Thus, no symptom or cluster of symptoms has been shown to reliably predict complications of GER or to predict those infants likely to respond to therapy.

Role of Probiotics

The pathophysiology of regurgitation is multifactorial, involving esophageal, gastric, and enteric nervous system abnormalities. Gastric distension and impaired fundic relaxation as a result of disturbed gastric motility might play a role in acid reflux to the esophagus. In fact, transient lower esophageal sphincter relaxations, which are one of the main pathophysiological mechanisms of GER, seem to be triggered

by gastric distension via activation of stretch receptors in the stomach. The enlarged fasting antral area and delayed gastric emptying time could be related with gastric distension and consequently provoke regurgitation.

An intrigue experimental work on colonic motility in rat showed that *L. reuteri* ameliorates the rhythmic contraction of the colon. The molecular and physiological pathways via which the commensal bacteria exert their effect on intestinal motility are far from being elucidated. Nevertheless, the mechanism of neuroimmune interaction may play a crucial role also in this age range infant.

It is reasonable to suppose that the structure responsible for the intestinal motility as enteric neurons, interstitial cells of Cajal, and smooth muscle cells could relay some of the actions that probiotic exerts, beyond the gut, on central and autonomic nervous system.

An aberrant gut microbial composition, such as an inadequate *lactobacilli* level and an increased concentration of coliforms in the first months of life, may play an important role in the pathogenesis of gastrointestinal stress-related disorders such as regurgitation and GER.

During the last few years, the role of the intestinal microflora in health and disease has become increasingly recognized, and a strong indication has been aroused that diet can influence the relative amount of microbial species and strains of the gastrointestinal flora. An approach to fortify the biological role of formula feeds has been to use probiotics as constituents. Bifidobacteria and lactobacilli are the most popular microorganism for probiotic applications, and the most effective ones are of human origin. Probiotic supplementation in infant formulas has shown that some strains may persist in the infant gut and lower stool pH.

The intestinal microflora participates in the development and maintenance of gut sensory and motor functions by the release of bacterial substances, fermentation products, and intestinal neuroendocrine factors.

Moreover, the end products of colonic microflora fermentation (i.e., the short-chain fatty acids [SCFAs] butyrate, acetate, and propionate) may affect local and distant motor events via direct and indirect (nervous) pathways.

In 2008, our group studied the effect of dietary supplementation with a probiotic on feeding tolerance and gastrointestinal motility in healthy formula-fed preterm infants. Thirty preterm newborns were enrolled; ten were exclusively breastfed, and the remaining 20 were randomly assigned in a double-blind manner to receive either *Lactobacillus reuteri* ATCC 55730 or placebo for 30 days.

Clinical symptoms of gastrointestinal function (regurgitation, vomiting, inconsolable crying, and evacuation) and physiological variables (gastric electrical activity and emptying) were recorded before and after the dietary intervention.

We demonstrated that the newborns receiving breast milk and those receiving *L. reuteri* had a significant decrease in the number of episodes of regurgitation, compared with that given placebo. We also collected the gastric emptying parameter. In particular, the fasting antral area was significantly smaller, and the gastric emptying rate was significantly faster in the newborns receiving *L. reuteri* compared with formula with placebo, and the *L. reuteri*-supplemented babies had a motility pattern resembling that of newborns fed with breast milk [4].

More recently, we confirmed our previous results studying the gastric emptying in 34 infants with regurgitation (19 infants receiving probiotics and 15 placebos for 4 weeks). At baseline, the whole group of infants was similar to the control group as regards anthropometric and physiological data. After the treatment, the median fasting antral area was significantly reduced; the delta in gastric emptying rate was significantly increased, and the median episodes per day of regurgitation were reduced in the probiotic group compared to the placebo group. The comparison with the normal value of gastric emptying in this age range allows us to define specifically the effect of probiotic on gastric motility. Actually, these children treated with *L. reuteri* had an acceleration of gastric emptying time [5].

In 2014, a prospective, multicenter, double-masked, placebo-controlled randomized clinical trial was performed on 598 term newborns.

They were randomly allocated to receive *L. reuteri* DSM 17938 or placebo daily for 90 days. At the end of the 3-month intervention, infants who received *L. reuteri* DSM 17938 showed significantly decreased regurgitation frequency compared with those who received the placebo [6].

Garofoli et al. performed another RCT on 40 breastfed full-term newborns. They were randomized to receive 10^8 colony-forming units/day of *L. reuteri* DSM 17938, or placebo for 120 days. Treated infants presented a reduction in daily regurgitations at the end of treatment ($p < 0.02$) [7].

In 2017 our group performed another randomized double-blind, controlled trial investigating the effects of a formula containing partially hydrolyzed, 100% whey protein, starch, and *L. reuteri* (DSM 17938) on regurgitation frequency and gastric emptying rate and in 72 infants with functional regurgitation. Infants with functional regurgitation were randomized to receive either a standard starter formula or the test formula for 4 weeks. Regurgitations number, feed volumes and potential adverse events were recorded in a daily diary, while ultrasound gastric emptying rate assessment was performed at baseline and at the end of treatment. Infants fed with the supplemented formula showed significant reduction of mean daily regurgitations ($p < 0.0001$) and a greater percentage of changes in gastric emptying rate (12.3% vs. 9.1%, $p < 0.01$) [8].

Aloisio et al. studied in double-blind, randomized, placebo-controlled clinical trial the effect of the administration of a probiotic formulation (two strains of *B. breve*) for 90 days to newborns. They showed that number of regurgitation episodes decreased in the probiotic group compared to placebo group ($p < 0.03$) [9].

Finally Baldassare et al. evaluated the effect of multistrain probiotic supplementation (*L. paracasei* DSM 24733, *L. plantarum* DSM 24730*, L. acidophilus* DSM 24735*, L. delbrueckii* subsp. bulgaricus DSM 24734, *B. longum* DSM 24736*, B. breve* DSM 24732*, B. infantis* DSM 24737, and *Streptococcus thermophilus* DSM 24731) to women during late pregnancy and lactation. Sixty-six women were randomized to receive the multistrain probiotic or placebo. Regurgitation was less frequent in the probiotic group. Moreover, they demonstrated a significant increase TGF-β1 and IL-10 in breast milk in probiotic-supplemented mothers compared to controls [10].

Probiotics and PPI

The proton pump inhibitors (PPIs) such as omeprazole, lansoprazole, and esomeprazole are the most widely used drug in GERD. Treatment with proton pump inhibitors (PPIs) profoundly reduces the production of gastric acid, and, moreover, prolonged PPI use can reduce gastric emptying and leukocyte activity. The inhibition of normal gastric acid secretion has important side effects, the most important being bacterial overgrowth in the stomach and duodenum with a concentration of $>10^5$ viable cells/mL. It has been demonstrated that PPI usage for 8 weeks results in a decrease of Lactobacilli and Stenotrophomonae and an increase of Haemophilus. Additionally, the relative abundances of the phyla Firmicutes, Bacteroidetes, and Proteobacteria changed significantly [11].

Harmful or even pathogenic bacteria could survive the gastric transit and colonize either the stomach itself, the duodenum, or the gut, where they could establish acute and even chronic infections with unavoidable consequences for the host's health. In other words, the strongly reduced or even disrupted "gastric barrier effect" may lead to small intestine bacterial overgrowth (SIBO).

Lombardo et al. reported SIBO, diagnosed by hydrogen breath tests, in 50% of 200 GERD patients receiving PPIs for a median of 36 months [12].

Moreover, a meta-analysis of 11 studies revealed an association between PPIs and SIBO only in a subgroup analysis of studies that used duodenal or jejunal aspirate cultures to diagnose SIBO [13].

Del Piano et al. performed a study in adults demonstrating that the administration of an association of four selected probiotic strains, namely, *L. rhamnosus* LR06, *L. pentosus* LPS01, *L. plantarum* LP01, and *L. delbrueckii*, for 10 days was able to significantly reduce bacterial overgrowth at stomach and duodenum levels while decreasing gram-negative bacteria, in the gut microbiota after 10 days of oral supplementation [14].

This result has been confirmed by a randomized, double-blind, placebo-controlled study on adult patients with typical gastro-oesophageal reflux disease symptoms receiving pantoprazole 40 mg/day for 6 months that demonstrates the protective effect of *Lactobacillus paracasei* F19 supplementation in preventing the onset of bowel symptoms in patients chronically treated with PPIs [15].

A double-blinded, placebo-controlled trial was performed in 70 children treated with 20 mg omeprazole per day for 4 weeks. *L. rhamnosus* and *L. acidophilus* were simultaneously given daily to 36 subjects (probiotic group), while 34 subjects received placebo (placebo group). They founded a high prevalence of SIBO but the probiotic tested did not prevent its development [16].

Belei et al., showed that children with GERD treated with PPI for 3 months in combination with probiotics (Lactobacillus reuteri DSM 17938) that only 6.2% ($P < 0.001$) had a positive glucose hydrogen breath test compared with 56.2% in the placebo group [17].

In conclusion, probiotics could be useful in preventing regurgitation in otherwise healthy infants and SIBO in patients treated with PPI.

Possible Effect of Probiotic Treatment

Microbiota–Gut–Brain Axis

Gut–brain interactions are well-known mechanisms for the regulation of intestinal function in both healthy and diseased states. The gut–brain axis is a complex bidirectional communication system that exists between the central nervous system (CNS) and the gastrointestinal tract [18]. A role of the enteric microbes in these interactions has only been recognized in the past few years. This has been reflected in the form of a revised nomenclature to the more inclusive brain–gut–microbiota axis, and there is now a sustained research effort to establish how communication along this axis contributes to both normal and pathological conditions.

The gut–brain axis integrates cognitive and emotional centers in the CNS with the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic arms of the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, the enteric nervous system (ENS, called also "little brain"), and the intestinal microbiota. Through this bidirectional complex network, the CNS and the gut are intimately connected: signals from the brain influence the motor, sensory, and secretory functions of the gastrointestinal tract by releasing neuropeptides and hormones, and conversely visceral messages from the gastrointestinal tract can influence brain function, mood, and behavior [19, 20].

One approach that is being utilized to study the role of microbiota on host's health is the use of germ-free animals. Germ-free mice, which are animals devoid of any bacterial contamination, offer the possibility to study the impact of the complete absence of microbiota on gastrointestinal functions and gut–brain axis-related functions. The cross-talk between the gut microbiota, the immune system, and the gut–brain axis seems also to play an important role in the modulation of the stress response. Microbiota communicates with gut–brain axis through different mechanisms and multiple routes:

- *Direct interaction with mucosal cell (endocrine message)* through the release of bacterial substances, fermentation products such as short-chain fatty acids, and indirectly stimulating production of intestinal neuroendocrine factors.
- Via *immune cells (immune message)* through recognition of pathogen-associated molecular patterns (PAMPs) by Toll-like receptors which modulate expression of factors, such as cytokines and chemokines, which recruit and change the phenotype and function of immune and inflammatory cells. Mast cells are important effectors of gut–brain axis that translate the stress signals into the release of a wide range of neurotransmitters and pro-inflammatory cytokines. Neurons, astrocytes, and microglial cells express membrane surface receptors that are specific to the molecular products of immune cells, which underlie brain cellular responses to immunological signals.
- Via *contact to neural endings (neuronal message)* through increasing expression of GABA receptors, by inducing expression of opioid and cannabinoid receptors in intestinal epithelial cells; via elevation in plasma of tryptophan, a precursor to

serotonin which is a key neurotransmitter within the gut–brain axis; and so on. Of course, multiple mechanisms are possible, and further studies will clarify both neural and humoral routes through which the intestinal communal microflora may influence ENS and CNS signalling.

Taken together, it is clear that microbiota can modulate various aspects of the gut–brain axis. However, these effects are bacterial strain dependent, and care must be taken in extrapolating data obtained from one organism to another.

A disturbance in the primary colonization or in the balance of normal intestinal microflora (or the host response to this) has been shown to play a critical role in the pathogenesis of a wide variety of intestinal and extra-intestinal disorders. Bacterial colonization of the intestine plays a major role in the postnatal development and maturation of the immune nervous and endocrine systems. These processes are key factors underpinning CNS signalling and suggest a role for microbiota in the modulation of mood and behavior [21]. Microbiota plays an important role in the modulation of hypothalamic-pituitary-adrenal axis, activated in response to a variety of physical and psychological stressors [22]. One of the important coordinators of the endocrine, behavioral, and immune response to stress is corticotropin-releasing factor (CRF). CRF has a potent effect on gut via modulation of inflammation, increase of gut permeability, contribution to visceral hypersensitivity, and modulation of the gut motility [23]. Stressors in GF mice induce an exaggerated release of CRF with an abnormal activation of HPA involved in stress response. The pituitary gland responds to CRF by releasing ACTH to stimulate adrenal gland secretion of cortisol. This abnormal stress response in GF mice is partially reversed by bacterial recolonization [24].

Other authors report in GF mice a reduction in anxiety behavior and an upregulation in the expression of brain-derived neurotrophic factor (BDNF), a protein involved in multiple aspects of cognitive and emotional behaviors through the modulation of new neuron and synapse growth and differentiation. A strategy employing antibiotic-induced dysbiosis of the microbiota resulted in mice displaying less anxiety-like behavior and altered protein levels of BDNF. The discontinuation of the antibiotic cocktail restored the normal behavioral profile of the animals [25].

Similar perturbation of the microbiota by administration of pathogen bacteria has been shown to increase anxiety-like behavior and produce stress-induced memory dysfunction, reverted by daily administration of a probiotic cocktail.

The human brain has achieved its nearly complete neuronal capacity by birth. However, brain development does not cease at birth. Rather, during infancy, the brain establishes the myriad synaptic connections that provide the essential substrate for functional brain networks that underlie perception, cognition, and action. A recent study revealed that the bacterial content of the gut can modulate brain developmental pathways [26]. This regulation has explicit time constraints with a critical developmental window in the early postnatal period, during which gut microbiota might modulate synaptogenesis through changes in the expression of genes whose products influence neurotransmitter modulation in the nervous system. The microbial colonization process modulates signalling mechanisms that affect

neuronal circuits involved in motor and sensitive control and can also influence the neural network responsible for controlling stress responsiveness.

Although the microbiota exerts a broad influence on brain functions, the converse is also true. The brain can alter the microbiota through modulation of intestinal secretion, permeability, and motility, removing excessive bacteria from the lumen and preventing bacterial overgrowth [27]. Signalling molecules released into the gut lumen from cells in the lamina propria that are under the control of the CNS can result in changes in gastrointestinal motility and secretion as well as intestinal permeability, thus altering the gastrointestinal environment in which the bacteria reside [28].

There is evidence that exposure to stress may be responsible for the dysregulation of the gut–brain axis, thus leading to the different diseases of the gut.

Changes in bidirectional interplay between the microbiota and brain have been implicated in the pathophysiology of functional gastrointestinal disorders, such as infantile colic or irritable bowel syndrome [29], and in pathogenesis of other gastrointestinal diseases, such as inflammatory bowel disease, food antigen-related adverse responses, peptic ulcer, and gastro-oesophageal reflux disease [30].

Conclusion

The effect of the intestinal microflora in the pathophysiology of GER and regurgitation is becoming in the more evident even though the exact mechanisms of interaction between the intestinal bacteria and host are still unknown. Probiotic might play an important role in maintaining gut homeostasis by modulating intestinal barrier function, immunity, and motility and influencing the gut–brain interaction. The role of intestinal microbiota in the pathogenesis of GER could represent a promising field of research in the next future.

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Diagnosis of GERD

16

Michiel van Wijk

Abstract

Despite the existence of internationally approved guidelines, the diagnosis of gastroesophageal reflux (GER)-*disease* remains difficult (Rosen et al. J Pediatr Gastroenterol Nutr. 66:516-54, 2018). GER-disease is generally considered a clinical diagnosis. However, differentiation between physiologic GER, functional regurgitation, and GER-disease in infants and between functional heartburn, hypersensitive esophagus, rumination syndrome, symptoms of esophageal dysfunction, and GER-disease in older children can be difficult based on clinical grounds alone. In addition, some patients present with extra-esophageal problems such as chronic respiratory disease, chronic cough, or ENT problems.

Many diagnostic tests have been proposed, but none of them can truly be seen as a gold standard. Upper gastrointestinal endoscopy with biopsies can show erosive esophagitis and Barrett's esophagus and is able to differentiate between reflux esophagitis and eosinophilic esophagitis, but cannot show or exclude non-erosive GER-disease. In theory, 24-h pH-impedance testing allows for detecting all GER events and establishing a temporal association between individual GER events and symptoms. However, no true normative data are available and its analysis can be difficult, especially in severe cases with low impedance baselines. Additionally, the statistical calculation of an association between GER and symptoms is dependent on sufficient symptoms and their adequate objective monitoring. A trial with acid suppression can be helpful to diagnose acid-related disease in older children, but not in patients where weakly acidic GER is predominant. The placebo effect of such a trial carries the risk of chronic over-

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treatment in functional heartburn. Several less invasive tests have been studied, but their diagnostic value is, as yet, limited.

Keywords

Gastroesophageal reflux · Gastroesophageal reflux disease · Esophagus · Motility · Eosinophilic esophagitis · Rumination · Diagnostics

Introduction

Gastroesophageal reflux (GER), defined as the effortless retrograde flow of gastric contents into the esophagus, is a normal physiologic process occurring multiple times a day in children of all ages. It usually does not lead to symptoms or complications. GER can be liquid and gaseous (belch) and can vary from alkaline (pH > 7) to acid (pH < 4). If GER leads to flow of gastric contents into the oropharynx or above, it is referred to as *regurgitation*. *Vomiting* has a different underlying mechanism and leads to forceful expulsion of gastric contents out of the mouth.

GER-*disease* is defined as GER leading to troublesome symptoms that affect daily functioning or complications [1]. In the pediatric age range, complications include, but are not limited to, esophagitis, Barret's esophagus, anemia, growth retardation, and extra-esophageal problems (e.g., recurrent pneumonia, dental erosions, cardiorespiratory events in infants and ENT problems).

Diagnosis of GER-*disease* is primarily based on clinical presentation. A thorough history and physical examination is essential in all patients, not only to differentiate between GER and GER-disease, GER-disease and rumination, and GER-disease and vomiting, but also to rule out other underlying diseases. If there is uncertainty about the diagnosis or a suspicion of complicated disease, additional testing may be necessary. Several diagnostic and therapeutic algorithms are available [1, 2]. The available diagnostic tests are outlined below.

History, Physical Exam, and Questionnaires

Typical Symptoms

Infants

GER-related symptoms, especially regurgitation and crying, are very common in infancy and not necessarily suggestive of or specific for any disease [3–5]. Regurgitation occurs at least regularly in 70% of 4 month old infants and at least daily in 13.8% of healthy children ranging from 0–12 months [6–8]. If excessive, it may simply be the result of overfeeding, which can be easily corrected [1]. Infants that regurgitate more than once daily for more than 3 weeks (without alarm symptoms) fulfil criteria for *infant regurgitation* as per Rome IV criteria for functional diseases, but do not suffer from GER-disease [8]. In physiologic GER and infant regurgitation, the regurgitation episodes resolve with age without treatment [3, 6, 9].

On the other hand, GER-disease can cause severe symptoms and complications, while infants may initially present with similar non-specific symptoms like regurgitation and crying.

To discern between physiological GER, infant regurgitation, and GER-disease, it is important to thoroughly evaluate the severity of symptoms as objective as possible and to investigate the presence of more signs and symptoms that may suggest pathology (Table 16.1) or alternative diagnoses. Alarm symptoms as shown in Table 16.2 should prompt for specific diagnostic workup and/or treatment, depending on the suspected disorder.

In addition, information about feeding type, volumes, frequency and associated problems is essential. Feeding problems may be the result of oropharyngeal dysphagia or eosinophilic esophagitis rather than GER-disease. Non-IgE mediated cow's milk allergy may also present with atypical regurgitation and irritability. Other symptoms of allergy should be asked for and eczema should be specifically looked for during the physical exam. Note that true mono-symptomatic presentation of cow's milk allergy is rare and, if present, involves dermatitis and not gastrointestinal

Table 16.1 Symptoms and complications of physiological GER and GER-disease in infants

Symptoms associated with physiological GER and/or infant regurgitation	
	Regurgitation
	Crying
	Irritability
Symptoms associated with GER-disease	
Esophageal symptoms	
Typical symptoms	Excessive regurgitation
Atypical symptoms	Excessive crying/irritability
	Feed refusal
	Choking
	Back arching
	Anemia
Extra-esophageal symptoms and complications	
General	Growth retardation/failure to thrive
	Anemia
	Hematemesis
	Sleep disturbance
	Sandifer's syndrome
	BRUE
Lungs/ENT	Recurrent pneumonia
	Laryngitis
	Stridor
	Chronic cough
	Apnea
	Desaturations
Heart	Bradycardia
Mouth	Halitosis

Symptoms of physiologic GER and GER-disease in infants. From: van Wijk MP. Pediatric gastroesophageal reflux and upper gastrointestinal tract motility. Amsterdam: University of Amsterdam; 2010. With permission from the author

Table 16.2 "Red flag" symptoms and signs that suggest disorders other than gastroesophageal reflux disease

Symptoms and signs	Remarks
General	Suggesting a variety of conditions, including systemic infections
Weight loss	
Lethargy	
Fever	
Excessive irritability/pain	
Dysuria	May suggest urinary tract infection, especially in infants and young children
Onset of regurgitation/ vomiting >6 months or increasing/persisting >12–18 months of age	Late onset as well as symptoms increasing or persisting after infancy, based on natural course of the disease, may indicate a diagnosis other than GERD
Neurological	
Bulging fontanel/rapidly increasing head circumference	May suggest raised intracranial pressure, for example, due to meningitis, brain tumor or hydrocephalus
Seizures	
Macro/microcephaly	
Gastrointestinal	
Persistent forceful vomiting	Indicative of hypertrophic pyloric stenosis (infants up to 2 months old)
Nocturnal vomiting	May suggest increased intracanial pressure
Bilious vomiting	Regarded as symptom of intestinal obstruction. Possible causes include Hirschsprung's disease, intestinal atresia or mid-gut volvulus or intussusception
Hematemesis	Suggests a potentially serious bleed from the esophagus, stomach or upper gut, possibly GERD-associated, occurring from acid-peptic disease[a], Mallory–Weiss tear[b] or reflux esophagitis
Chronic diarrhea	May suggest food protein-induced gastroenteropathy[b]
Rectal bleeding	Indicative of multiple conditions, including bacterial gastroenteritis, inflammatory bowel disease, as well as acute surgical conditions and food protein-induced gastroenteropathy rectal bleeding[b] (bleeding caused by proctocolitis)
Abdominal distension	Indicative of obstruction, dysmotility, or anatomic abnormalities

GERD gastroesophageal reflux disease, *NSAID* non-steroidal anti-inflammatory drugs
Alarm symptoms that should prompt further investigation. From: Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(3):516–54, with permission from Wolters Kluwer Health, Inc

[a] Especially with NSAID use

[b] More likely in infants with eczema and/or a strong family history of atopic disease

[c] Associated with vomiting

symptoms [10]. It is, however, not uncommon for parents of patients with cow's milk allergy to report only symptoms suggestive of GER-disease [11].

Finally, maternal depressive symptoms have been shown to be associated with a threefold higher risk of gastroesophageal reflux symptoms in the infant as compared to infants of mothers without depressive symptoms, so maternal mental health deserves attention during history taking [12, 13].

Several questionnaires have been developed to more objectively score GER-related symptoms in infants [14–20]. Although the IGERQ-R is most commonly used, was validated for symptom tracking over time [15] and a clinically meaningful difference in its total score was determined [21], it was not validated for the diagnosis of GER-disease, nor was any one of the other questionnaires. Its limited diagnostic value is likely related to the symptoms overlapping between GER-disease and pharyngeal dysphagia [22].

Older Children and Adolescents

New-onset regurgitation or increase thereof after the age of 12 months, should raise the suspicion GER-disease or other diseases that provoke GER. In infants with regurgitaion, which persists after the age of 18 months, true GER-disease should also be considered.

For other symptoms than regurgitation, it is hard to objectify a relation with GER. In toddlers and young children no data exist on the specificity or sensitivity of symptoms. A validated questionnaire exists for children up to 4 years of age, but robust testing of its sensitivity and specificity as compared to an objective reference test is lacking [20]. The same questionnaire was also adapted for, but not validated in children from 5–11 years [23].

With age, symptoms of GER-diseases tend to become more specific and they resemble adult symptomatology in adolescence. A history and physical exam by an expert gastroenterologist has a sensitivity of only 67% and a specificity of 70% for diagnosing GER-disease in adults, indicating that even with increased specificity, the clinical diagnosis of GER-disease remains similarly difficult in adolescents [24].

No diagnostic questionnaires are available for adolescents, but the Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) is available for validated symptom assessment in patients from 2 to 17 years old [25]. Some studies in adolescents have used the Reflux Disease Questionnaire, which was purposely developed to separate GER-disease from other causes of upper abdominal and lower retrosternal symptoms in adults, and was thoroughly validated [26]. Its test characteristics approach those of an expert gastroenterologist in adults, but were not tested in adolescents [26, 27].

Extra-Esophageal Symptoms

Many extra-esophageal symptoms have been linked to GER (Table 16.1).

In (premature) infants brief resolved unexplained events (BRUEs) are commonly thought to be GER related. Most studies, however, do not provide evidence for such

a relation and oropharyngeal dysphagia seems to be a larger contributing factor in the majority of these children [28–30]. Other presentations at different ages, like chronic cough, laryngitis, and wheezing, can be GER related [31, 32] but more common causes should be excluded first, especially when no typical GER-related symptoms are present. If still suspected to be GER related, history should focus on the presence of additional typical GER symptoms and on a possible temporal relation between the symptoms and feeding times. This is similarly true for older children and adolescents [31, 32].

Diagnostic Tests

Proton Pump Inhibitor (PPI) Trial

In infants, the use of PPI as an empiric diagnostic trial is not recommended. In this age group, PPI has been shown to lack additional efficacy as compared to placebo [33]. Because of the very high placebo effect observed in most clinical trials, a PPI-trial as diagnostic test additionally carries a large risk of over-diagnosing GER-disease and subsequent prolonged unnecessary treatment.

In adolescents, it seems reasonable to use a PPI-trial for 4–8 weeks as per adult guidelines, i.e., in treatment naïve patients with typical symptoms of heartburn and/or regurgitation and this test is now incorporated in pediatric guidelines too [1, 34]. Clinical improvement during such a trial has, however, poor test characteristics in adults (sensitivity 54%, specificity 65%, PPV 75% and NPV 41%) and the results should therefore be interpreted with caution, especially in younger children [24]. Unnecessary treatment of patients who respond based on a placebo effect remains a matter of concern in this age group and therapy based on the results of a PPI-trial should therefore be reconsidered regularly.

Endoscopy and Esophageal Biopsies

Endoscopy, albeit considered a relatively safe procedure, is invasive and requires sedation in children. Although clear macroscopic abnormalities during endoscopy confirm GER, negative predictive value is very low, and a normal-looking mucosa does not exclude GER-disease [35, 36]. In patients with GER-diseases, endoscopy can differentiate between erosive and non-erosive disease. Barrett's esophagus (BE) as a complication of GER-disease, is very rare in children and can be demonstrated only in 0.13% of all children and adolescents undergoing endoscopy with biopsies [37]. Approximately 70% of children with BE have an underlying disorder that predisposes to severe GER-disease [38]. Endoscopy thus has limited clinical consequences when used as a first-line diagnostic test; both erosive esophagitis and non-erosive GER-disease need treatment with acid suppression.

Endoscopy should thus be reserved for patients with therapy-resistant GER-disease, alarm symptoms such as hematemesis, or those in whom another cause of

their symptoms is suspected (eosinophilic esophagitis, Crohn's disease or infectious esophagitis). If an endoscopy is performed, biopsies should be taken to rule out eosinophilic esophagitis and examine microscopic esophagitis, even if no macroscopic abnormalities are seen [1].

Function Tests

High-Resolution Manometry

High-resolution manometry (HRM) cannot be seen as a standard diagnostic test for GER-disease and should be reserved for specific indications in refractory cases. In these children, HRM can have an important role in the diagnostic process. First, many PPI-refractory patients in fact do not have GER-disease, and HRM can help to diagnose motility disorders as described by the Chicago classification, or, when combined with impedance rumination syndrome and supragastric belching [39, 40].

Second, all patients considered for anti-reflux surgery should have a manometry test to exclude rumination syndrome and disorders of esophagogastric junction outflow obstruction (such as achalasia) [41–43], accurately show and subtype the presence of a hiatus hernia (HH) [44] and evaluate esophageal peristalsis. Although debated, patients with severe forms of hypomotility may have more post-fundoplication dysphagia, especially when a Nissen fundoplication is performed [45–48]. In children HRM in combination with impedance has shown promising results in predicting post-fundoplication dysphagia [49, 50].

HRM can accurately localize the position of the lower esophageal sphincter, which can be used to position a 24-hour pH(−impedance) catheter.

Finally, high-resolution *impedance* manometry can evaluate impedance baseline at the moment of maximal esophageal contraction (contractile segment impedance), which shows promise in augmenting the diagnosis of GER-disease [51, 52]. This metric, however, needs further validation in adults and children, before its role in the diagnostic process can be determined.

24-Hour Esophageal pH—Monitoring

24-Hour esophageal pH monitoring is able to detect pH changes at a single level in the esophagus and thus indirectly measures acid GER. Although esophageal acid exposure is an important factor in symptom generation and the development of complications, especially in older children, this test has some drawbacks, which should be considered when results are interpreted [53].

First, the cut-off value for the amount of acid exposure that is pathological is still a matter of debate, because true normal values are not available with currently used pH-sensors [1]. Early pH-metry studies that used glass electrodes, were validated using other reference standards that have severe limitations [36, 54, 55]. In addition, the most commonly used parameter, the reflux index or acid exposure time (AET), does not answer the essential question whether symptoms are related to GER.

Second, adult pH monitoring results have shown a significant day-to-day variability, which complicates its interpretation [56]. The use of Bravo wireless

capsules allows for 48–72 hours of pH recording and was used to show that the variability may be less in children [57]. Nevertheless, Bravo capsules are not widely available and seldomly used in children as they require endoscopy for their placement.

Third, pH monitoring also possesses intrinsic qualities, which limit sensitivity and specificity. First of all, GER episodes are indirectly detected by acidification of the lumen surrounding the pH sensor, which is normally positioned at 3 or 5 cm proximal to the lower esophageal sphincter. Observations have shown marked regional differences in pH levels throughout the esophagus and it is as yet unclear what position of the pH sensor gives best diagnostic results [58]. Second, for standard automated recognition of a GER episode, pH must drop by at least 1 point and to a value lower than 4. As a result, weakly acidic ($4 < pH \leq 7$) and alkaline ($pH > 7$) GER episodes are per definition not detected by standardized esophageal pH monitoring. This is especially problematic in infants, in whom frequent feeding and subsequent buffering of stomach contents causes gastric pH to be only weakly acidic during most of the day [59]. Because most GER episodes occur in the early postprandial period, when pH in the stomach is highest, it is not surprising that in infants, the majority of GER episodes is weakly acidic and therefore not detected by standardized esophageal pH monitoring [60]. Another consequence of the indirect measurement of GER is that acid re-reflux or "superimposed" acid GER (i.e., acid GER during the period in which the acid of a previous GER episode is still being cleared) is not detected. Finally, the results of pH monitoring are influenced by dietary intake during the test, because acidic food and drinks will also cause a drop in pH in the surroundings of the pH sensor. Dietary restrictions are, therefore, commonly imposed on patients, resulting in test conditions that do not necessarily reflect daily routine. Despite its limitations, esophageal pH monitoring is still performed in many centers worldwide due to the fact that it is readily available, analysis is automated and it is relatively inexpensive. A 24 h pH-metry can be considered in the suspicion of acid-related disease with/without symptom correlation (see below) and to evaluate the efficacy of acid-suppressive therapy in patients with already proven GER-disease [1].

24-Hour Esophageal pH-Impedance Monitoring

With the introduction of pH-impedance monitoring, some disadvantages of pH monitoring seem to have been overcome. Because pH-impedance detects esophageal flow directly, it is possible to detect all GER episodes and classify these into acidic, weakly acidic, and weakly alkaline GER [53]. Due to the multiple measuring sites, the direction of flow can be determined. Hence, GER can be discerned from swallowed material, making dietary restrictions unnecessary. Furthermore, this makes it possible to study the mechanisms of bolus and acid clearance and provides information on the proximal extent of a GER episode which can be helpful for determining a relation between GER and extra-esophageal symptoms [61].

pH-impedance has its limitations, too. Again, normal values do not exist in the pediatric age range, and although efforts to establish these have been made (Fig. 16.1), it is unlikely that truly normative data will ever become available

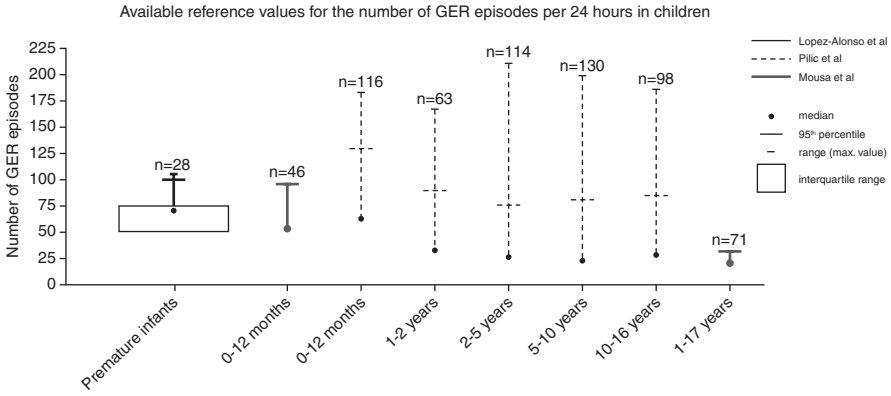

Fig. 16.1 Available reference data for the number of GER events per 24 hour and their distribution. From: Singendonk MMJ, Benninga MA, van Wijk MP. Reflux Monitoring in Children. Neurogastroenterol Motil. 2016; 28(10): 1452–9. With permission from John Wiley and Sons

because of ethical considerations preventing the study of healthy children with invasive techniques [60, 62, 63]. Although available and continuously improving, the sensitivity and specificity of the software currently used for automated recognition of MII GER patterns require further optimization and is unlikely to obviate the need for some degree of manual review of the tracing, which makes analysis time-consuming.

A clear statistical association between GER episodes and symptoms theoretically provides convincing evidence of causality. Multiple statistical measures of association have been described: the symptom index (SI), and the symptom association probability score (SAP) are the most commonly used. The SI is the percentage of symptoms related to a GER episode and is considered positive when above 50% [64]. The SI does not take the total number of GER events into account and, by chance, leaves room for a false positive result when many GER events are present. The SAP was developed to overcome these problems. It is a statistical means (Fisher exact test) of calculating the probability that the symptoms and GER episodes found are unrelated. The p-value of this test is then subtracted from 100% to reveal the SAP [65].

With the ability of pH-impedance to detect all GER episodes, symptom association scores are indeed valuable in the diagnosis of GER-disease. However, several difficulties arise. First, not all patients experience symptoms during a 24-h study period and if they do, reporting is not always accurate [66]. Second, clear criteria defining a temporal association are lacking and are a matter of debate [67].

Apart from detecting GER episodes, pH-impedance tests can be used to evaluate other parameters. Baseline impedance is a marker for mucosal integrity and was shown to be low in infants and children with esophagitis [68, 69]. Its calculation is time-consuming and there is no consensus on which method should be used. Mean nocturnal baseline impedance is a simplified means of calculating baseline impedance and was shown to correlate with AET and esophagitis in adults [70] and with AET in children and could be supportive of a diagnosis of GER-disease [34]. Where the MNBI measures mucosal integrity, another novel metric, the post-reflux

swallow-induced peristaltic wave (PSPW) index, is a measure of esophageal clearance. Although not studied in children yet, it was also included in adult guidelines as a measure that can support the diagnosis of GER-disease [34].

In clinics, pH-impedance testing can be used to correlate symptoms with GER episodes in all age groups; to discriminate between the different phenotypes in patients with typical GER symptoms and without esophagitis [71]:

(1) patients with abnormal esophageal acid exposure (non-erosive reflux disease (NERD)); (2) those with a positive symptom association to acid or non-acid reflux but without abnormal AET (reflux hypersensitivity), and (3) patients with normal esophageal acid exposure and a negative symptom association (functional heartburn).

In addition, it can also be used in a patient with persistent symptoms despite acid suppression. Both the efficacy of the medication can be checked and a relation between GER and the persisting symptoms can be found, if present [72].

The role of pH-impedance in confirming supragastric belching, aerophagia, and rumination is beyond the scope of this chapter.

Function Testing in Extra-Esophageal Symptoms

If infants or children present with atypical or extra-esophageal symptoms, other, more common causes of these symptoms should be excluded, before any diagnostic tests for GER-disease are performed. To identify GER as a cause of such symptoms, very few diagnostic tests are available. If a temporal relation between single GER episodes and symptoms can be shown, a causative relation is likely. This can be done using pH monitoring when symptoms are related to acid GER. However, it is likely that especially these symptoms can be related to weakly acidic GER, so symptom association scores using pH-impedance tests can be helpful.

It should be noted that, especially in infants with atypical GER symptoms, functional testing is only appropriate when symptoms are thought to be directly related to bolus GER episodes, and not so much to the cumulative effect of excessive GER. Furthermore every effort should be made to obtain symptoms as objective as possible [66].

Other Tests

Imaging

Barium contrast studies, ultrasound and real-time MRI can be used to show single reflux events. Because reflux episodes in itself are not pathologic, study time is short and it is unlikely that a patient has typical symptoms during the investigation, their diagnostic value is very limited.

However, barium contrast studies and ultrasound have a important role in ruling out anatomical abnormalities and other diseases [1].

Non-invasive Tests

The non-invasive test that is most thoroughly studied, is the presence of pepsin in different body secretions (tracheal fluid, ear effusion, exhaled breath and saliva). Pepsin is the main human digestive protease and is excreted by gastric chief cells as a zymogen, pepsinogen. Salivary pepsin was proposed to be a potential biomarker of GERD in adults and children [73–76]. Although some adult studies report promising sensitivity and specificity of a salivary pepsin assay as compared to pH-metry or pH-MII [73], it was shown that current test characteristics limit its clinical use [77].

Conclusion

GER-disease is primarily a clinical, yet difficult diagnosis. A PPI-trial may be considered in older children but its limited sensitivity and specificity should be considered when interpreting improvement. If additional testing is required, endoscopy and pH-impedance are the most useful tests and together allow for excluding GER-disease or phenotyping it.

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Contribution of Histology to the Diagnosis of GER

17

Chloé Girard and Christophe Faure

Abstract

The presence of endoscopically visible breaks in the mucosa at/or immediately above the gastroesophageal junction is a sign of reflux esophagitis, but the presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of non-erosive reflux disease. Reflux esophagitis may affect the mucosa in a patchy fashion, and, as such, multiple biopsies are warranted to document histologic abnormalities. At least two biopsies at 2–3 cm above the gastroesophageal junction appear to be the most relevant to identify esophagus lesions. In infants and children, the correlation between histopathologic features, clinical symptoms, and pH monitoring is poor, whereas basal esophageal impedance and contractile segment impedance measurements appear to be predictive of peptic esophagitis.

In the context of gastroesophageal reflux, the roles of esophageal biopsies in children are to rule out other diagnosis such as eosinophilic esophagitis, Crohn's disease, Barrett's esophagus, or infection, to screen for Barrett's esophagus, and to follow complications related to specific pediatric populations such as esophageal atresia, neurologic impairment, or cystic fibrosis.

Keywords

Histology · Esophagus biopsy · Reflux esophagitis · Epithelial hyperplasia · Dilated intercellular spaces · Barrett's esophagus · Pediatric

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Introduction

Upper gastrointestinal (GI) endoscopy allows direct visual examination of the esophageal mucosa. The presence of endoscopically visible mucosal breaks at/or immediately above the gastroesophageal junction is a sign of reflux esophagitis, but the presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of non-erosive reflux disease (NERD). Even if histological lesions related to reflux esophagitis are well characterized, their sensitivity and specificity are poor, and they are not correlated with symptoms in infants and children.

In this chapter, we will review the histopathological description of the normal esophagus and of the lesions of reflux esophagitis as well as the technical aspects related to the esophageal biopsies. We will then discuss the correlation between histology and symptoms, pH monitoring, impedance measurements and finally consider the contribution of histology in patients with gastroesophageal reflux disease (GERD).

Histology of the Esophagus and Reflux Esophagitis

Normal Esophagus Biopsies

The esophagus has four concentric layers, similar to other parts of the gastrointestinal tract: mucosa, submucosa, muscularis propria, and adventitia/serosa [1, 2].

The esophageal mucosa consists of a non-keratinized stratified squamous epithelium, lamina propria, and muscularis mucosae.

The epithelium is composed of basal, intermediate, and superficial cell layers. The basal cell layer is comprised of smaller cells with round nuclei and basophilic cytoplasm, and it is less than 15% of the mucosal thickness with usually no more than two to three cell layers. It typically represents the reserve stratum from which the epithelium regenerates.

The lamina propria is the nonepithelial portion and consists of areolar connective tissue, which contains vascular structures, scattered inflammatory cells and mucous-secreting glands. Infoldings of the lamina propria form papillae, which are generally evenly spaced and usually extend one-third to one-half of the thickness of the epithelium.

The muscularis mucosae separates the mucosa from the submucosa and is composed of fibers of smooth muscle that are oriented longitudinally.

The submucosa is composed of loose connective tissue containing nerves, lymphatic channels, blood vessels, and submucosal glands. The submucosal glands are scattered throughout the entire esophagus but are more concentrated in the upper and lower segments. They contain mucous cells surrounding a central lumen in a radial fashion, and open to the lumen of the esophagus via squamous-lined ducts through the muscularis mucosae and epithelium.

Histological Lesions in Gastroesophageal Reflux Disease

Epithelial hyperplasia is the feature most often used for the diagnosis of reflux esophagitis and is related to epithelial proliferation after the initial injury. Ismail-Beigi et al. were the first to describe it in 1970 after finding that some patients with clinical symptoms suggesting reflux, and normal or minimally abnormal endoscopic appearances had basal cell hyperplasia and elongation of the lamina propria papillae [3].

- Basal cell hyperplasia is defined as the basal layer occupying >15% of the total thickness of the mucosa [2]. This feature can be seen in squamous epithelial injury of many forms and thus is not specific to reflux. The upper limit of the basal layer can be difficult to define. One useful definition of the uppermost limit of the basal zone is the point where the nuclei are separated by a distance equal to their diameter. The specificity can be as low as 45% because similar changes have been described in patients without evidence of GERD [4].
- Papilla elongation is defined as papillae of the lamina propria extending >67% of the total thickness of the mucosa. As with basal cell hyperplasia, assessment of papilla elongation requires well-oriented specimens in which the entire epithelial thickness and the length of the papilla are visible. The specificity is up to 80% according to Zentilin et al. [4].

Inflammatory cell infiltrate is also a histologic component of reflux esophagitis. Before the description of epithelial hyperplasia in 1970, inflammation was the most important criterion for the diagnosis of GERD. The sensibility is very low (10–30%) but the specificity is high (90%) [5]. The principal inflammatory cells include neutrophils, eosinophils, and lymphocytes. Contrary to epithelial hyperplasia, which requires well-oriented biopsy to be identified, inflammatory cells can be counted even in improperly oriented specimens.

- Eosinophils: The accepted number of normal intraepithelial eosinophils in the esophagus has been debated. Currently, in adult patients, intraepithelial eosinophils are considered abnormal when there are >6 eosinophils in a biopsy section (some studies have demonstrated rare intraepithelial eosinophils in the distal 3 cm of approximately one-third of control patients) [6, 7]. In children, any degree of eosinophilia is considered to be pathological because intraepithelial eosinophils are not normally present in the esophageal mucosa of pediatric patients [8]. Increased intraepithelial eosinophils can be a useful criterion with high specificity (up to 90%), although it is not sensitive, as only 20–50% of patients with reflux esophagitis will show this feature [2, 4]. However, GERD is not the only diagnosis possible in case of intraepithelial eosinophils: eosinophilic esophagitis, infections, and pill-induced esophagitis typically are present with increased eosinophils.

- Neutrophils: Intraepithelial neutrophils are present in less than 30% of patients with GERD but most often are not found in control patients. This histologic feature lacks GERD specificity because anything that causes erosion or ulceration in the esophagus, such as infections or pill-esophagitis, can result in neutrophilic infiltration.
- Lymphocytes: Scattered lymphocytes, particularly T-lymphocytes, are normal within the esophageal squamous mucosa with a mean number of 20 in Z-lines biopsies of healthy controls and less numerous in more proximal sites [2]. In the case of GERD an increased number of lymphocytes are frequently seen, but this finding is not specific, because biopsies of normal control subjects may also reveal increased numbers [9].

Dilated intercellular spaces (DIS) has been described in patient with GERD and was a significantly relevant data to diagnose an erosive or non-erosive GERD of a functional heartburn [10]. This feature is defined as an increase in the spaces between squamous cells, predominantly in the basal layer. Initially, the spaces were measured using transmission electron microscopy [11, 12]. To create a more practical approach using light microscopy, DIS has been characterized by irregular intercellular spaces with an uneven separation of cell membranes [13]. This feature is secondary to the loss of tight junctions between squamous cells resulting in increased paracellular permeability, which may facilitate leaking of the acid through the mucosa allowing for direct contact with terminal dendritic processes of underlying sensory neurons in the epithelium [12, 14]. Slight acidification of intercellular spaces can trigger symptoms, potentially explaining the occurrence of typical GERD symptoms in the absence of an endoscopic lesion. The prevalence of DIS in GERD varies from 67% to 94% [4]. A pediatric study confirmed that DIS is a morphological feature in GERD and esophagitis also in infancy and childhood. However, DIS was also increased in case of esophagitis unrelated to GERD (eosinophilic, Candida, food allergy) [15].

Dilatation of capillaries within the mucosa has been described in reflux esophagitis, but it also occurs frequently in normal controls, probably as a traumatic artifact of obtaining the biopsy that we are reluctant to assign diagnostic value to it [7, 16].

Erosions are characterized by the presence of necrosis with granulation tissue and/or fibrin with neutrophils. These lesions are mainly seen in erosive esophagitis, among less than 20% in GERD patients, with a high specificity but a low sensitivity and they represent the most severe lesion in the spectrum of microscopic esophagitis [4].

To date, there is no standardization of a histological scoring system. Many studies have used their own score combining the number and the severity or intensity of histologic findings to obtain a final score. Fiocca et al. proposed the *Esohisto score*, wherein individual lesions were assessed: basal cell hyperplasia, papillary elongation, DIS, intraepithelial eosinophils, neutrophils, and mononuclear cells [17]. After that, a combined histological severity score was obtained by summing up lesion scores for each of the parameters. Evaluation of the score showed good correlation

with adult patients' reflux symptoms as well as strong interobserver agreement [18, 19]. Finally, a good distinctive value for separating GERD patients from controls or functional heartburn patients seems to be the association of several types of histological lesions, their severity (≥two mild histologic lesions or ≥ one severe lesion) and the presence of erosions, healed erosions and/or intraepithelial neutrophils [4, 20].

Where to Take Biopsies? How Many Biopsies?

Nowadays, the majority of pediatric centers use endoscopic biopsies to study esophageal histopathology. Others use esophageal suction biopsies which also allow reliable measurements of quantitative esophageal histological morphometric parameters [21].

Zentilin et al. conducted a study comparing a group of adult patients with GERD and a control group by taking biopsies at the Z-line, 2 cm and 4 cm above the Z-line [4]. The prevalence of lesions increased as got closer to the junction: from 4 cm, 2 cm to Z-line, basal cell hyperplasia ranged from 57%, 72 to 88%, respectively; papillae elongation from 14%, 32 and 58%, and DIS from 54%, 67 to 72%. They also described frequent mild changes, especially at the Z-line in controls with basal hyperplasia (55%) and papillae elongation (20%). In 1975, Weinstein et al. had already described minor histologic alterations in the most distal 2–3 cm of the esophageal mucosa, presumably related to "physiologic" episodes of reflux in asymptomatic adults [22]. Above 4 cm, the specificity of the lesion increases (>90%) but the sensitivity decreases (<10–30%) [20]. Therefore sensitivity in identifying lesions linked to GERD is higher on distal biopsies. In order to avoid misinterpretation of a simple physiological variant as being pathological Zentilin et al. used higher cutoffs at the Z-line: less than 20% vs. less than 15% for basal cell thickness and less than 66% vs. less than 50% for papilla elongation. According to them, the data provided by four biopsies (two at the Z-line and two at 2 cm above) are sufficient to discriminate a patient with GERD from a control patient with a sensitivity and specificity of more than 80% [4, 23].

Based on these adult studies and because most pediatric studies report esophageal biopsies obtained at/or 3 cm above the gastroesophageal junction [24, 25], we recommend at least two biopsies at 2–3 cm above the gastroesophageal junction.

Correlation of Histology to GERD in Children

Symptoms

Infants

In several studies, less than 50% of infants (<18 months) with clinically GERD had biopsy abnormalities, mainly mild lesions [24–28]. Chadwick et al. described age-related changes in histological features, intraepithelial lymphocytes being the

earliest histological lesion noted being present prior to 4 months. The number of intraepithelial eosinophils and lymphocytes and the presence of papillary elongation increased with age [26]. Conversely Orenstein et al. described ten patients (<12 months) with GERD and esophagitis whose symptoms improved after 1 year without treatment (placebo group), although the histology remained abnormal for some of them [25]. Heine et al. reported that esophagitis occurred in 25% of infants with persistent distress [27]. Salvatore et al. showed that questionnaires did not correlate with esophageal histology and that histology did not predict symptoms severity in infants [24]. Therefore symptoms suggestive of GERD are frequent within the first year, but there is no correlation between symptoms and histological lesions.

Child and Adolescent

In older patients, the correlation is also poor, as symptoms are not predictive of the presence of histological lesions [29–31]. In the study of Quitadamo et al., in 164 children with typical GERD symptoms, 37% had a normal mucosa, 28% mild histologic esophagitis, and 35% severe histologic esophagitis. There was no correlation between patient reported symptom severity and the histological grade of the esophageal mucosa [31]. Even adolescent patients whose main symptoms were heartburn and chest pain did not show any positive correlation with histological lesions [30, 31].

Endoscopy

A significant discordance between endoscopic and histologic findings exists. Reflux esophagitis may affect the mucosa in a patchy fashion, therefore, depending on the biopsy site, the lesions may go unnoticed. Gupta et al. showed that reflux symptoms were not predictive of the presence or lack of mucosal damage on histology [30]. Cui et al. found the mean DIS in the erosive esophagitis group was significantly wider than the others groups, including non-erosive reflux, functional heartburn or healthy patients [32]. In cases of visible erosive esophagitis, biopsies are primarily useful to rule out other conditions rather than to diagnose GERD or to determine the severity of the esophagitis.

pHmetry

In the literature, the association between abnormal pH monitoring and histologic esophagitis is controversial. A concordance between acid exposure and esophageal histology was found in only 25–42% in pediatrics studies [24, 27, 29]. According to Cui et al. DIS was found significantly wider in case of abnormal acid reflux than in the subject with weakly reflux or without abnormal reflux [32]. Therefore a normal biopsy does not rule out a pathologic acid reflux, most likely because the esophageal lesion might be patchy.

Esophageal Impedance

Baseline Impedance

Impedance baseline measurements may be used to evaluate the status of the esophageal mucosa with good correlation in the case of erosive esophagitis having mucosal breaks visualized on upper GI endoscopy. Farré et al. found patients with NERD had lower impedance baseline values in the more distal esophagus as compared to healthy volunteers [33]. However, Salvatore et al. and Borrelli et al., did not find any significant association between esophageal basal impedance and esophageal mucosa injury in children [29, 34]. Cohen-Sabban et al. described children with macroscopic (n = 8/87) or severe microscopic (n = 10/87) esophagitis having lower baseline impedance <900 Ohms (Positive predictive value and Negative predictive value 100%) at the most distal channel (number 6) ($p < 0.001$) suggesting that the correlation of baseline impedance in case of microscopic esophagitis is not as obvious as in the case of erosive esophagitis [35].

Contractile Segment Impedance

Contractile segment impedance (CSI) is the impedance value at the peak of the esophageal contraction. It is a suggestive marker of mucosal integrity [36]. To date there are few data correlations between histology and contractile segment impedance [37]. In the study of Courbette et al., a CSI <800 Ohms predicted the presence of histopathological findings with sensitivity of 80% and specificity of 57% in esophageal atresia patients [38].

Contribution of Histology to Diagnostic of GERD

Among all of the histological lesions found in cases of GERD esophagitis DIS seems to be the most distinguishing histologic feature between GERD and functional heartburn. As described above, histological features are numerous and have a poor sensitivity and specificity in identifying NERD because abnormalities resulting from GERD can be similar to those noted with any inflammatory process of the esophagus. Finally, histology appears to be insufficient for the diagnosis and treatment of GERD. Diagnosis remains a correlation between clinical, endoscopic, histological, and/or pH-impedance characteristics.

However, biopsies have a role in the management of GERD patients, especially in the following situations:

Identifying the Differential Diagnosis

One of the main reasons to perform esophageal biopsies is to rule out other diagnosis, such as eosinophilic esophagitis, Crohn's disease, Barrett's esophagus (BE), infection, etc.

Screening for Barrett's Esophagus

BE is a complication of chronic GERD, mainly in adults. In 2016, the American College of Gastroenterology (ACG) guidelines defined it as a change in the distal esophageal epithelium at least 1 cm in length that can be recognized as columnar "salmon-colored" mucosa during endoscopy and is confirmed by gastric or intestinal metaplasia on biopsy of the tubular esophagus [39]. The prevalence of BE in the general population is 1.6% in the western world. BE is rare in children and is usually seen in those with congenital neurodevelopmental disorders or tracheoesophageal abnormalities. Obesity appears to be an independent risk factor for BE in children [40]. El-Serag et al. reported a low prevalence rate (0.25%) of endoscopically suspected BE in 6731 children and adolescents who underwent upper endoscopy. Histologically proven intestinal metaplasia was reported only in 0.13% of their cohort [41].

The importance of diagnosing BE is related to its association with the development of esophageal adenocarcinoma. According to the ACG guidelines, the endoscopist should obtain at least eight random biopsies from the columnar mucosa to maximize the yield of intestinal metaplasia on histology [39]. In the adult population, the risk of developing high-grade dysplasia or esophageal adenocarcinoma is approximately 0.66% per year, but the risk of BE appearing in child age is not known, and there are only a few isolated cases report of esophageal adenocarcinoma in children the literature [42, 43]. The ACG guidelines recommend an endoscopic surveillance at intervals of 3–5 years for BE patients without dysplasia. To date, there are not specific guidelines for children [39].

In Specific Situations

Esophageal Atresia (EA)

Esophageal mucosal abnormalities can be observed in up to 35% of EA patients during endoscopy despite the absence of symptoms, therefore, the recommendation for endoscopic assessment based solely on symptomatology is inappropriate [44]. The aim of surveillance biopsies is to detect early esophagitis, with the opportunity for subsequent intervention, before the development of late complications such as strictures, BE, which is ten times more frequent in this population [45, 46], and cancer [47]. Multilevel esophageal biopsies are recommended for screening for peptic and eosinophilic esophagitis [48]. ESPGHAN-NASPGHAN guidelines recommend three systematic surveillance endoscopies throughout childhood; one after stopping PPI therapy, one before the age of 10 years, and one at transition to adulthood. Endoscopy is additionally useful in children post-fundoplication because the recurrence of GERD and peptic esophagitis is possible [49].

Neurologically impaired Children

Neurologically impaired patients suffer a high incidence of GERD though they are often unable to complain of GERD-related symptoms. They are at risk of

developing BE with an increased risk of adenocarcinoma compared to the general population [50]. To date, there are no specific guidelines about the role of endoscopy and biopsy for this patient, each case should be discussed individually, considering the risks and benefits of performing endoscopy and biopsies.

Cystic Fibrosis (CF)

GERD is one of the most common gastrointestinal manifestations of CF, with a prevalence of 27–87% in children and it likely plays a role in the pathogenesis of the respiratory disease. In the presence of alarm symptoms, upper GI endoscopy and biopsies are indicated to detect complications of GERD, diagnose GERD predisposing conditions such as hiatal hernia, or to diagnose conditions that might mimic GERD, such as eosinophilic esophagitis and infectious esophagitis [51].

Conclusion

Esophageal biopsies provide information that can help the gastroenterologist to manage his or her patients, especially in particular pathological situation or when suspecting a differential diagnosis other than GERD. The histological features are not sufficient in diagnosing GERD due their lack of specificity and sensitivity, and most of the time they do not change the treatment. We do not recommend performing upper gastrointestinal endoscopy and esophageal biopsies for all patients with suspected GERD. Every case is different, therefore before scheduling an endoscopic exam one should ask, “Is endoscopy with esophagus biopsies relevant for the patient? What is the expected histological result? Are there any therapeutic changes to be made afterwards?” Therefore, biopsies should be primarily recommended for patients with atypical GERD, with suspected differential diagnosis other than GERD, or in specific pathologies, particularly esophageal atresia or cystic fibrosis and while screening for Barrett’s esophagus.

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How to Position pH-Impedance Probes in Pediatric Patients

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Abstract

Background: Multichannel intraluminal-impedance (MII)—pH recording is used frequently for the diagnosis of gastroesophageal reflux disease in children. The location of the pH-sensor is essential to obtain a reliable recording. Positioning of the electrode through radiologic control is recommended as standard. In order to decrease radiation, different attempts have been made to develop equations to obtain a correct positioning of the probe without radiation.

Methods: We prospectively compared the location of the pH-sensor in 212 children according to a formula developed by our nurses ("distance (nose tip to ear canal) + (nose tip with head in neutral position to nipple line) in cm") to the location determined by fluoroscopy at the seventh posterior rib, which is considered the gold standard. The probe was considered malpositioned if the distance of the formula differed more than 1 cm compared to fluoroscopic control. Statistical analyses were done using R version 4.0.3. Spearman correlation coefficients, mean error and 95% limits of agreement of Bland–Altman plots were calculated. A p-value of <0.05 was considered statistically significant.

Results: According to the overall results, the spearman correlation between the formula and fluoroscopic control was excellent (ρ = 0.91). In 67% of the patients, the location according to the formula was correct, if a difference of 1 cm above or below the exact location is accepted.

Conclusions: The formula adequately predicts the location of the MII-pH probe in 67% of the children (exact distance ±1 cm). In 9% of the children the

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difference was over 2 cm. Each center should decide: accept about 10% of dislocations of the pH-sensor of 2 cm or more or continue with the radiologic control.

Keywords

Electrode positioning · Equation · Multiple intraluminal impedance · pH-impedance monitoring; pH metry · Probe · Gastroesophageal reflux

Introduction

Multichannel intraluminal impedance (MII)-pH recording is a recommended investigation for the diagnosis of gastroesophageal reflux disease [1]. The procedure can be performed in all age groups.

The correct location of the MII-pH probe is of major importance for an accurate interpretation of the result of the investigation [1]. The catheter is inserted transnasally. The current guidelines of the European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) recommend that the pH electrode must be placed at a distance of two vertebral bodies above the diaphragm, and that this position should be confirmed by X-Ray or fluoroscopy [1]. Two vertebral bodies above the diaphragm correspond with the posterior seventh rib, which is used as reference by the nurse staff of our unit.

The aim of this study was to evaluate a formula developed by the nurses of our team to predict a correct placement of the pH-sensor. A good performing formula would be of benefit for the patient and nursing staff, and simplify the manipulations related to the investigation if no radiologic control would be needed.

Formulas Proposed in Literature

Historically, different formulas to estimate the correct location of the probe were developed with the goal to avoid radiology and thus decrease exposure to radiation.

The Strobel formula (0.252 × length in centimeter + 5) was 40 years ago the first attempt to avoid radiologic control [2]. However, this formula was considered inadequate as it was shown to overestimate esophageal length; the older the child, the greater the inaccuracy [2]. Moreau et al. developed a different formula ($L = 0.216$ (length in cm) + 7.13) based on measurements in only 116 children, resulting in a correlation coefficient of 0.85 with the radiologic control [3]. Increasing length of the children was related to a greater difference between the location according to the formula and the correct location [3].

In 1991, Staiano and Clouse evaluated in 213 children and adults if anthropometric variables could be used to accurately predict the lower esophageal sphincter location according to manometry across all age ranges [4]. The upper margin of the lower esophageal sphincter was determined with a nasally placed manometry

catheter. Lower esophageal sphincter location differs of course from the determination of pH-sensor location. The regression equation that best predicted the location in children younger than 2 years of age was "L = 0.22[H] + 4.92," where L is the location in centimeter from the nares and H is the height of the child in centimeter [4]. The formula resulted in an error of more than 1 cm in 10% of the children younger than 2 years [4]. In the older patient groups, the error of the predicted lower esophageal sphincter location was greater than 2 cm in more than 25% of the children, even when more age-specific equations were used [4]. The predictive ability of height remained significant but progressively decreased in the older subject groups (>2 and < or = 10 years of age, $r2 = 0.74$; >10 and < or = 20 years of age, $r2 = 0.66$; >20 and < or = 40 years, $r2 = 0.58$; and >40 years, $r2 = 0.49$) [4].

A Spanish group tested different formulas which were used in their institutions to estimate the best pH-probe positioning in adults according to formulas used in children [5]. The tested equations were: "9.31 + height in cm × 0.197" (Hospital de Navarra) and "9.31 + height in cm × 0.179" (Hospital Infantil Vall d'Hebron, Barcelona) [5]. The formula from Barcelona came out as the best, but differences up to 6 cm in adults were observed [5].

Colleagues from the Great Ormond Street Hospital developed a table (GOSH-Table) based on height intervals of 144 children and showed a correlation between desired pH-sensor position ("approximately two vertebral bodies above the diaphragm") for the whole group of 0.95 [6]. For the same group of children, these authors also calculated the correlation between desired catheter position and Strobel, which was 0.84, and Moreau, with a correlation of 0.85 [6]. However, the use of such a table in daily clinical routine is not very practical and a good correlation does not necessarily mean that the predictions are good.

A Polish group reported that according to observations from 353 children aged 0–18 years in whom the position of the pH-sensor was determined radiographically, that the following mathematical formula ("3.2 + 0.2 × body length or height in centimeter") could guide to the best location of the probe [7]. The desired location was obtained in 71.7% of the patients [7]. The mean absolute error of prediction of catheter placement depth was 1.30 cm [7].

The KidZ Health Castle Formula

In 212 consecutive children, prior to the fluoroscopic control, the nursing staff locates the pH-sensor at a distance calculated according to a simple formula developed by the KidZ Health Castle nursing team: "distance (nose tip to ear canal) + (nose tip with head in neutral position to nipple line) in cm." Children with scoliosis or other anatomic problems were excluded. A ZepHr® Impedance/pH Reflux Monitoring System (Sandhill Scientific, Inc.; Highlands Ranch, CO 80129 USA. US Patent #7,493,158) and BS01, BS46 and BS51 catheters were used. Impedance rings are 1.5 cm or 2 cm apart from each other in infant and pediatric catheters, respectively. Catheters were placed trans-nasally, with no sedation, with a 4-h fasting and lubrication of the catheter with gel.

When the pH-sensor was located according to the previously described formula, the position was controlled by fluoroscopy, which should be on the seventh posterior rib. This position corresponds to the second vertebra above the diaphragm but is easier to recognize [1]. A difference of 1 cm or less between the anticipated pH-sensor location and the fluoroscopic control was not considered to be of any clinical relevance since head movements and respiration cause at least a similar of greater displacement.

Five well-trained nurses inserted the MII-pH catheters in 212 consecutive children (102 girls, 110 boys) referred for a pH-MII. Patient characteristics are listed in Table 18.1.

Since the data were not normally distributed, Spearman correlation coefficients were calculated, which was 0.91 for the formula vs. fluoroscopic control ($p < 0.00001$). In 66% of the children, the location according to the formula was exact (≤1 cm difference with radiologic control), independent of the age or length of the children (<1 year: 70%, <1 m: 68%). A Bland–Altman plot (Fig. 18.1) was developed as well, showing that that the pH-sensor was as a mean 0.39 cm to deep according to the formula if the radiologic control is used as golden standard. In 19 (9.0%) children, the difference was larger than 2 cm, and in 7 (3.3%) the difference was 4 cm or more. The 95% limits of agreement are between 2.92 cm to deep and 2.14 cm to high. The figure suggests that when the pH-sensor was dislocated compared to radiology, the pH-sensor tended to be too high in young children and too deep in older children. This is shown nicely in Fig. 18.2**,** when age is as well considered. Figure 18.3 shows that the difference in location is associated to the length of the child.

Little is known about the growth of the ribs in children [8]. The width of a rib is about 0.5 cm in a newborn, 0.75 cm in a 3 year old and 1 cm in a 15 year old. In an adult, the esophagus is a 25-cm long muscular tube that connects the pharynx to the stomach. The length of the esophagus correlates with an individual's height and is usually longer in men than in women. The length of the esophagus at birth varies between 8 and 10 cm and measures about 19 cm at age 15 years. Therefore, an additional post-hoc analysis was done, considered the length of the children. If a difference of ≤1 cm is accepted for children <75 cm, ≤ 1.5 cm for children with a length between ≥75 and <125 cm, and ≤2 cm for children ≥125 cm length, the correct positioning of the pH-sensor increased from 66% up to 72.2%.

Considering that according to the radiologic control the formula was located 0.39 cm to deep, another post-hoc analysis was done considering this difference. Of course, the mean difference dropped to 0.01 cm, with a lower and upper limit of agreement of −2.5 and +2.5 cm (original analysis: −2.92 cm (to deep) and +2.14 cm (to high)).

Table 18.1 Patient characteristics

	Median	Q1 to Q3	Mean	SD
Age (months)	6.46	2.77 to 15.58	25.17	44.81
WFA *z*-score	−0.23	−0.97 to 0.54	−0.36	2.03
HFA *z*-score	−0.36	−1.13 to 0.47	−0.41	1.30

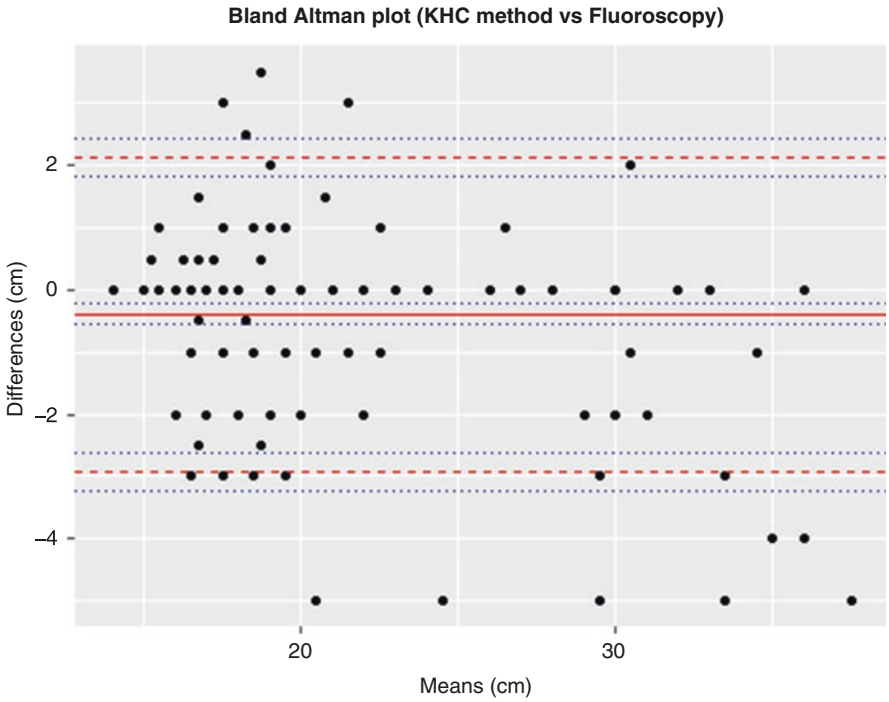

Fig. 18.1 Differences between radiologic location and KHC formula. Means: mean of the KHC formula and radiologic control

It is probable that the differences are the consequence of incorrect measurements by the nursing staff, but it does reflect clinical reality.

Due to the increased radiation sensitivity of children, the potential risk of multiple radiographic examinations should be minimalized as much as possible. If a radiologic control could be avoided, it would also simplify the methodology of the MII-pH recording and decrease the burden for the patient and health care professionals.

The formula proposed should be used for estimating the MII-pH catheter insertion length as the predicted distance was exact in 66% of all children, increasing up to 72% if 0.4 cm is deducted from the original formula. 95% of all probes are placed within a difference of 2.5 cm; however, length of the patient was not considered for the original Bland–Altman analysis. While a difference of 2 cm might be considered acceptable for a child measuring 150 cm, it is a clinically relevant difference for a child measuring 75 cm. Adequate initial positioning of the catheter will avoid its subsequent displacement and the related discomfort thereof. However, the formula does not replace the need for radiologic control.

Further research is needed. We will prospectively evaluate the new formula: "distance (nose tip to ear canal) + (nose tip with head in neutral position to nipple line) in cm − 0.4 cm."

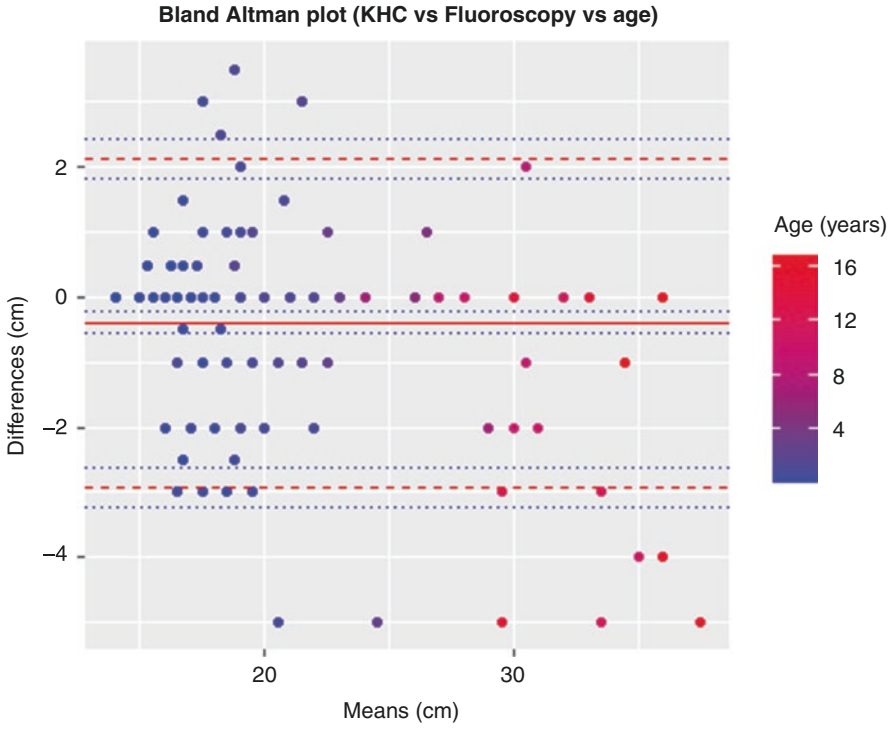

Fig. 18.2 The influence of age on positioning of the pH probe t

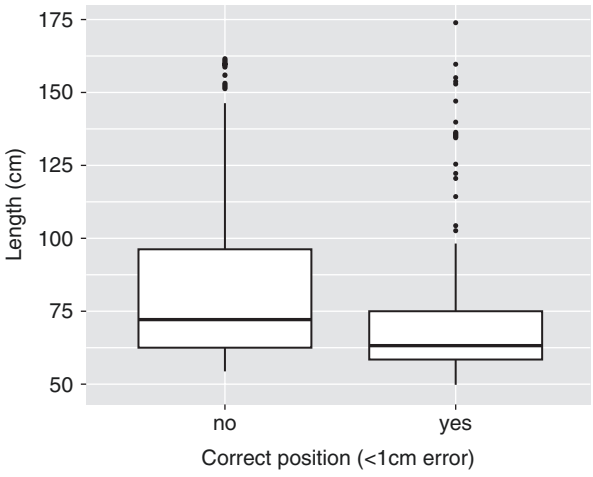

Fig. 18.3 The influence of length of the patient on correct positioning of the pH probe

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Esophageal Clearance in GERD

19

Stefano Nobile and Giovanni Vento

Abstract

Gastroesophageal reflux is a frequent condition in childhood, particularly among infants. Gastroesophageal reflux disease (GERD) is defined as when the reflux leads to troublesome symptoms and/or complications. However, as symptoms are often non-specific and vary with age, it may be difficult to differentiate GER from GERD in children. Esophageal clearance is involved in the pathogenesis of GERD. It consists of two different phases, volume and chemical clearance. Volume clearance allows bolus transfer into the stomach by swallowing and peristalsis. Thanks to chemical clearance, the residual acid content in the esophagus is neutralized by bicarbonate contained in the swallowed saliva and in submucosal esophageal gland secretions. Esophageal clearance is typically evaluated by pH-impedance (MII-pH) monitoring and high-resolution manometry (HRM); the addition of impedance to HRM is useful to assess motility and its disorders. Esophageal clearance is influenced by a variety of physiologic factors, including age, sleep, body positioning, feeding modalities. Moreover, several pathologic conditions have been linked to alterations in esophageal motility and clearance in childhood, including esophageal atresia, achalasia, eosinophilic esophagitis, neurological impairment, systemic sclerosis, cystic fibrosis, rumination syndrome, prematurity and its complications.

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Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus with or without regurgitation and/or vomiting [1]. GER is considered to be pathologic and referred to as gastroesophageal reflux disease (GERD) when the reflux leads to troublesome symptoms and/or complications, such as esophagitis or structuring [2]. However, as symptoms are often non-specific and vary with age, it may be difficult to differentiate GER from GERD in children. Moreover, to date, no gold standard diagnostic tool exists for the diagnosis of GERD in infants and children.

The major mechanism of GER in children and infants is transient lower esophageal sphincter LES relaxation (TLESR) [3, 4]. TLESR is an abrupt decrease in LES pressure to levels at or below intragastric pressure, unrelated to swallowing and triggered by gastric distention [5]. Mechanoreceptors located in the proximal stomach and cholecystokinin trigger TLESR via a vago-vagal pathway.

Besides TLESR, several factors are involved in the pathogenesis of GERD, including esophageal dysmotility, esophageal hypersensitivity, impaired esophageal mucosa defense against different types of refluxed contents (e.g. pH, bile, pepsin, pancreatic enzymes), dysfunction of the esophagogastric junction. Some of these factors have been also associated with the severity of symptoms and response to therapy [6].

For example acid content, proximal migration of reflux, and gas in the refluxate were associated with symptomatic GER [7]. The proximal extent of GER events has been associated with the stimulation superficially localized mucosal afferent nerves in the proximal esophagus [8]. Enhanced sensitivity might be associated with impaired mucosal integrity [9]. Moreover, bile reflux in an acidic esophageal environment has been associated with significant heartburn, scarce relief from proton pump inhibitor therapy, impairment of esophageal mucosal integrity, and less effective chemical clearance [10].

Upper gastrointestinal tract motility involves multiple factors such as swallowing frequency, esophageal primary and secondary peristalsis, LES tone and relaxation, gastric emptying, and duodenal motility. Alterations in these parameters have been associated with GERD, and conversely, these parameters may be altered secondarily to GERD, as observed in severe esophagitis [4]. Recent techniques, such as multichannel intraluminal impedance (MII), esophageal manometry, and high-resolution manometry (HRM), are useful to assess esophageal motility and clearance.

Clearance of Gastroesophageal Reflux

Esophageal clearance consists of two different phases, volume and chemical clearance. During the first one, volume clearance, the bolus is transferred into the stomach by swallowing and peristalsis [11]. Following volume clearance, the residual acid content in the esophagus is neutralized by swallowed bicarbonate-rich saliva and submucosal esophageal gland secretions [12, 13]. Thus, the process of esophageal clearance may be prolonged by either abnormal esophageal peristalsis or altered salivation. Efficient clearance of refluxed material from the stomach is a major defense mechanism against esophageal mucosal damage.

The duration of exposure of the esophageal mucosa to the refluxate depends on the effectiveness of the reflux clearance mechanisms. The presence of a hiatal hernia is associated with re-reflux (reflux of liquid from the hernial sac during swallowing) and can therefore alter esophageal clearance mechanisms [14].

An impaired bolus transit may affect esophageal emptying and clearance of saliva which can result in prolonged acid contact, and ultimately the emergence of reflux-related symptoms. In adults, the transitioning zone of striated muscles to smooth muscles was identified as the most common site at which impaired bolus transit occurs [15].

Volume Clearance

Volume clearance depends on effective swallow-induced primary peristalsis and distension-induced secondary peristalsis. The integrity of the peristaltic sequence is important, since abnormal fragmentation of peristalsis is associated with poor clearance [16].

Primary esophageal peristalsis is mainly responsible for bolus transport whereas secondary peristalsis clears the refluxate and swallowed food residuals from the esophagus. Following a swallow, pharyngeal contractions transfer the bolus through the upper esophageal sphincter in the esophageal body. Then, primary esophageal peristalsis transfers the bolus to the stomach; nonetheless, food residuals may remain in the esophageal lumen, triggering secondary peristalsis.

Secondary peristaltic waves are elicited by esophageal stretch receptors and remove residuals of the refluxate, determining the end of a reflux event and the transfer of the refluxate to the stomach [17]. Bolus-induced peristalsis can be initiated by intrinsic neural programs but is also influenced by vagal activity [18]. Proximal esophageal innervation is more superficial than in the distal esophagus, suggesting that the proximal esophagus is more sensitive, and thereby prone to trigger reflexes when stimulated [8].

Secondary peristalsis can be also impaired in patients with GERD and is more important during sleep when the rate of swallowing is reduced [19].

Chemical Clearance

After initial volume clearance due to peristalsis, the distal esophageal mucosa may remain acidic and also be damaged by gastroduodenal debris containing pepsin and bile acids. However, reflux events elicit an esophago-salivary vagal reflex which triggers a salivary swallow, resulting in the delivery of bicarbonate and epidermal growth factor to the esophagus. This process represents chemical clearance and allows an increase in distal esophageal pH and the repair of reflux-induced mucosal damage [20]. Chemical clearance also requires the secretion of adequate amounts of bicarbonate-rich saliva and rhythmic pharyngeal and proximal esophageal contractions. Healthy adults swallow around once/minute and the latency period of salivary glands to secrete saliva in response to esophageal acidification is reported to be 10–15 s. Moreover, bicarbonate secretion from esophageal submucosal glands helps acid neutralization in the esophagus. Chemical clearance is much slower than volume clearance, and, in infants, chemical clearance can persist up to six times longer [21].

Esophageal Motility Disorders

Esophageal manometry remains the gold standard to confirm the diagnosis of motility disorder of the esophagus. The Chicago classification version 4.0 proposed a hierarchical classification scheme of motility disorders based on manometric findings [22]. The two main groups of alterations are disorders of the EGJ outflow (type 1, 2, and 3 achalasia and EGJ outflow obstruction) and disorders of peristalsis (absent contractility, distal esophageal spasm, hypercontractile esophagus, ineffective esophageal motility-IEM).

Bolus transport can be measured by multichannel intraluminal impedance monitoring (MII) and manometry. Patients with GERD often show abnormal bolus transport, either invalid or extended. Abnormal peristaltic reserve, assessed by multiple rapid swallows and rapid drink challenge during manometry, are useful parameters to assess dysmotility [23, 24]. In subsets of GERD patients with dysmotility, some show improvement with resolution of acid exposure, while others maintain a stable IEM over time, and yet others either develop or worsen IEM over time [25]. In contrast, non-erosive reflux disease, and syndromes with physiologic esophageal acid exposure (reflux hypersensitivity, functional heartburn) may have increased distal esophageal contraction vigor compared to syndromes with elevated acid exposure [26].

IEM is frequently associated with GERD, which suggests that it may be a consequence of inflammation associated with GERD or a primary motor disorder leading to GERD. Patients (children in particular) with IEM and GER-like symptoms often do not have an adequate response to acid suppression treatment may thus receive repeat esophagogastroduodenoscopy and upper gastrointestinal barium contrast tests [27]. The impact of ineffective esophageal motility (IEM) on chemical clearance was examined in a study with 57 adults [28]. Esophageal chemical clearance

capability was evaluated by means of postreflux swallow-induced peristaltic wave (PSPW) index and acid clearance time (ACT). The authors found that the PSPW index was significantly lower in the IEM group than in the normal esophageal motility group and that the ACT was significantly longer in the IEM group than in the normal esophageal motility group.

Measuring Esophageal Clearance

Esophageal clearance is typically evaluated by MII-pH monitoring and manometry (particularly high-resolution manometry-HRM); the addition of impedance to HRM is useful to assess motility and its disorders. Combining esophageal pressure patterns by HRM with bolus flow measured by intraluminal impedance can assess bolus transport throughout the esophageal lumen and across the EGJ. Other techniques, such as magnetic resonance imaging, have recently been proposed [29].

In children, high-resolution manometry and 24-hour pH impedance measurements with and without ambulatory manometry are usually performed using protocols derived from adults. The use of HRM-MII is appealing in pediatrics because the study can be performed over an hour, it does not require anesthesia, and the patient/family can visualize some features and be persuaded about the diagnosis [30].

Pressure-flow analysis can detect abnormalities in esophageal motility using integrated analysis of bolus propulsion and bolus flow during swallowing. Pressure-flow parameters can distinguish the cause of dysphagia in children and differentiate patients from weak peristalsis (poor bolus clearance) or over-pressurization (abnormal bolus flow resistance) [31].

It has been reported that nearly 80% of these kinds of tests may contain patient-related imperfections; however, in a retrospective study, nearly all 24-h MII-pH measurements with and without ambulatory manometry and HRM performed in children aged 4 years and older led to interpretable results. In infants and toddlers, two-thirds of high-resolution manometry examinations were interpretable [32].

Several factors limit the interpretability of these tests: for example, discomfort and fear of the nasogastric catheters may lead to refusal or premature termination of the measurement. Moreover, younger children and infants may not be able to swallow on command as required for HRM. Artifacts due to crying, movements among others may interfere with the tracings. Also, objective symptom association during MII-pH may be difficult in infants and young children. In our experience though, the latter limitation can be at least in part overcome by the continuous, synchronized recording of vital signs during 24 h MII-pH [33]. In a study with 47 neonates, 3341 GER events and 4936 cardiorespiratory events, a median time period of 87.7 min per patient, corresponding to 6.1% of the recording time, contained inaccurate heart rate/pulse oximeter data. We used a cardiomonitor and a pulse oximeter to record cardiorespiratory events (heart rate, HR; and peripheral oxygen saturation, SpO2) among infants who underwent MII-pH; we then analyzed and filtered data and discarded SpO2 data acquired during limb movements and/or SpO2 probe detachment,

with concomitant differences in heart rate above six beats per minute between pulse oximeter and electrocardiogram [34]. The SAP index calculated considering the computerized HR/SpO2 recording was significant in 10.6% of patients. Overall, 609 CRE (12.3%) were temporally related with GER, 44% preceding and 56% following GER episodes.

Esophageal clearance can be evaluated using **MII-pH** by means of several indices, including bolus clearance time, acid clearance time, bolus head advancing time (absolute and corrected for esophageal length) and post-reflux swallow-induced peristaltic wave (PSPW) index.

Bolus clearance time (BCT) is the median time (in seconds) from the initial drop in impedance, when the liquid bolus enters the impedance-measuring segment, to the rise in impedance as the bolus is cleared from this segment by a peristaltic wave, thus returning to baseline. In a study by Zerbib and colleagues [35], using combined high-resolution manometry and impedance in asymptomatic controls, the normal range of complete bolus clearance was equal or more to 50% of swallows. The authors then assessed the motility patterns which predict abnormal bolus clearance in patients with esophageal symptoms; they found that ≥30% of failed contractions and ≥70% of ineffective contractions have the best sensitivity and specificity to predict altered bolus clearance.

Acid clearance time (ACT) is calculated by dividing the total acid exposure duration by the number of reflux episodes at each site [28]. Hypersensitive esophagus can be diagnosed when the acid exposure time is normal, but the symptom index is positive (≥50%). In a study with 60 preterm and term infants aimed at assessing predictors of sustained clinical response to anti-reflux therapy, Nobile et al. found that more efficient (faster) ACT was associated with clinical response to therapy in the whole population and in subgroups of preterm infants, infants with pathological acid exposure time (acid index >10%), and those on omeprazole therapy [36]. The results support the hypothesis that less efficient esophageal bolus clearance and persistence of potentially noxious refluxate in the esophageal lumen may trigger the onset of symptoms in newborns.

Bolus head advancing time (BHAT) is the time between the bolus entrance recorded in the proximal channel and the bolus entrance recorded in the distal channel, measured in seconds. In infants, BHAT should be corrected for esophageal length (BHATc), where esophageal length is the distance between proximal and distal impedance channels, measured in cm [37]. **Bolus presence time (BPT)** is the time between bolus entrance and exit recorded in the distal channel, measured in seconds. Cresi et al. [37] compared BHATc data from newborns to those obtained from children aged 5–10 years with GERD symptomsand observed a slower average total propagation velocity (1/BHATc) of the bolus in newborns (2.06 cm vs. 2.35 cm) confirming the presence of immature esophageal peristalsis in these patients. Moreover, they found prolonged BPT and BHATc in preterm compared to term newborns, suggesting an impaired esophageal bolus transit in preterm newborns.

*Chemical clearance***,** defined as the duration of esophageal acidification (determined by pH monitoring) that immediately followed the end of volume clearance

(determined by impedance) was studied in symptomatic infants (0–12 months) by Woodley and Mousa, who showed that this parameter is significantly prolonged during fasting in infants [21]. The same group also calculated reference values for acid neutralization during chemical clearance for infants and children [38].

*Post-reflux swallow-induced peristaltic wave (PSPW)***:** it is defined as an impedance drop originating in the upper esophagus and reaching the lower part of the organ after the end of a reflux event, signaling the peristaltic transit of saliva. PSPW index is obtained by dividing the number of reflux episodes followed within 30 s by a PSPW by the number of total reflux episodes [39]. The greater the PSPW index, the greater the chemical clearance efficiency. To limit overlap with spontaneous swallowing, only PSPWs occurring within 30 s from the end of reflux episodes are considered. In clinical studies in adults, the PSPW index has been shown to efficiently discriminate between erosive and non-erosive reflux disease. Some authors found that reflux episodes followed by a PSPW were associated with a significantly higher proximal extent, contained gas and occurred while awake than those without a PSPW [40]. After reflux events, higher volume clearance time and larger volume burden were more likely to trigger a PSPW [41, 42]. The calculation of the PSPW index in the presence of multiple successive reflux episodes is a limitation of this parameter. The same limitation occurs when calculating SAP. According to a recent study with combined MII-pH and HRM in patients with persisting reflux symptoms, PSPWI correlates with esophageal hypomotility and reflux burden and is useful to assess esophageal clearance and confirm GERD [43].

The PSPW index is considered a good indicator of chemical clearance. The PSPW index efficiently separated GERD from non-GERD subjects and erosive reflux disease (ERD) from non-ERD patients who were off-and-on proton-pump inhibitor (PPI) therapy [39]. In addition, the PSPW index was significantly lower in patients with PPI-refractory GERD symptoms compared to those with PPI-responsive symptoms [44]. Also, the PSPW index has been reported as the only impedance–pH parameter associated with PPI-refractory mucosal damage [45].

Delayed esophageal clearance is observed more often in pathological GERD, and bolus clearance time on impedance monitoring is longer in adults with severe esophagitis compared to those with non-erosive reflux disease [46]. In a study with combined HRM and pH monitoring, acid GER events were more common, esophageal acid clearance was much slower in patients with severe GERD or Barrett's esophagus compared to mild-moderate esophagitis. Postprandial exercise increased TLESR resulting in increased acid reflux [47].

High-resolution manometry (HRM) is the gold standard for the diagnosis of esophageal motility disorders. Current indications for esophageal manometry in children are suspected achalasia, chronic intestinal pseudo-obstruction syndrome, treatment-resistant GERD, dysphagia, noncardiac chest pain, and identification of the lower esophageal sphincter (LES) before pH monitoring [30]. However, clinical signs associated with these disorders are nonspecific, and it is difficult to correlate clinical signs with HRM data. HRM is well tolerated in pediatric patients. In a large retrospective pediatric study conducted in France, weight loss has been found predictive of abnormal HRM results in children with esophageal symptoms [48].

Patients with GERD can show different motility patterns, from normal to hypotensive esophagogastric junction (EGJ) barrier function (with or without hiatus hernia) and/or from fragmented esophageal body peristalsis to absent contractility. Esophageal contraction reserve can be evaluated by provocative tests such as multiple rapid swallows and rapid drink challenge [24]. The Chicago classification version 4.0 proposed a hierarchical classification scheme of motility disorders based on manometric findings [22]. The two main groups of alterations are disorders of the EGJ outflow and disorders of peristalsis, as discussed above.

Esophageal peristalsis comprises a specific chain of sequential pressure segments. These segments, one in the striated-muscle region and two in the smooth-muscle region, appear as concentrated pressure loci separated from each other by lower amplitude pressure troughs on the three-dimensional maps. This peristaltic chain can be also detected in healthy preterm and term neonates [49]. The first segment likely represents the striated esophageal region, although a direct anatomico-physiological relationship has not been established. The mechanisms responsible for the two smooth-muscle segments (second and third segments) are less secure. The second segment develops early and is most consistently present, even in preterm neonates. Control mechanisms for this segment are best developed in the preterm and term neonate. In contrast, sporadic representation of the third segment could reflect immature central or intramural control. The fact that only half of the swallows show completely intact segmental architecture at term, however, indicates that development of esophageal peristalsis continues into infancy.

Motor and structural integrity of the esophagogastric junction (EGJ) and esophageal body motor function influence esophageal reflux. HRM parameters describe EGJ morphology and esophageal body peristaltic patterns. Vigor of the EGJ barrier (esophagogastric junction contractile integral) and esophageal body contraction reserve (assessed using multiple rapid swallows) are novel motor parameters introduced through HRM.

Studies evaluating **secondary** peristalsis often involve injecting gas or liquid, first slowly then quickly, into the esophagus. During rapid injection of gas or liquid, most patients with GERD have an initiation deficit for secondary peristalsis. Patients with IEM and abnormal bolus transport require more gas to induce secondary peristalsis and experience higher incidence of failed secondary peristalsis compared with healthy individuals [50]. This higher requirement may be caused by disturbances in sensory vagal pathways affecting motor function.

Modifiers of Esophageal Clearance

Esophageal clearance is influenced by a variety of physiologic factors. Moreover, several pathologic conditions have been linked to alterations in esophageal motility and clearance, including esophageal atresia [51], achalasia, eosinophilic esophagitis, neurological impairment, systemic sclerosis, cystic fibrosis, rumination syndrome [52].

Age is one of the main modifiers of esophageal clearance features. In a pediatric study with 226 patients who underwent esophageal manometry among other tests, a significant inverse correlation was found between age and resting LES pressure, velocity of propagation, and proximal velocity of propagation [51]. The prevalence of peristaltic wave progression also tended to increase with age. This could reflect an aging and maturation effect. However, given the high prevalence of GERD in infants, it is also possible that the observed manometric features might reflect the impact of long-standing GER on esophageal motor function.

Prematurity and related morbidities are other important factors to consider. Esophageal motility and clearance are impaired in preterm infants below 34 weeks of gestation, who are physiologically unable to feed effectively and experience frequent choking and fatigue during feeding. Preterm infants undergoing high-resolution manometry had poor pharyngeal pressures at the laryngeal inlet coupled with poor coordination of pharyngeal propulsion with UES relaxation. Developmental changes in these parameters, explained by the immaturity of neural or myogenic mechanisms regulating pharyngo-esophageal contractile strength, and/or anatomical changes were suggested by the authors [53].

Other authors studied preterm and term infants using HRM and found that the second pressure segment in the midesophagus (proximal smooth-muscle region) is well developed before term. They observed that the presence of other segments significantly improves at term, but peristalsis remains incomplete in nearly half of swallows. Control mechanisms for both striated- and smooth-muscle esophageal regions are incompletely developed in neonates, thus influencing the development of GER [49]. The percentage of completed peristaltic waves increased with development, nearly doubling from preterm to full-term age. The authors suggested a potential role of inadequate esophageal body motor function in the presentation or manifestations of GERD in infants.

In newborns, swallows observed during mealtime are characterized by multiple rapid drops in impedance in the proximal channels, which merge into a single prolonged drop of impedance in the distal channel [37]. This pattern results from multiple swallows of small boluses that occur in quick succession and flow together in a single bolus of greater volume distally in the esophagus. This is typically observed during neonatal sucking and is the reason for the prolonged bolus presence time observed during mealtime. The authors observed that BHATc during mealtime was lower than during the postprandial period.

Bronchopulmonary dysplasia, a frequent complication of prematurity, has been associated with an increased risk of GER because of respiratory effort and transient increases in intra-abdominal pressure related to coughing, crying, and airflow obstruction, which can lead to a decrease in LES tone and an increased occurrence of transient LES relaxations. In a prospective study with 46 preterm infants who underwent 24-h esophageal MII-pH, Nobile et al. showed that infants with BPD had an increased number of (and sensitivity for) pH-only events, which could be explained by several factors, including lower milk intake, impaired esophageal motility, and a peculiar autonomic nervous system response pattern [54].

Esophageal clearance may be prolonged during **sleep** state compared to the awake state; however, the relationship between sleep and esophageal clearance, particularly in infants, is still controversial [55–57]. Factors influencing this relationship might be reduced swallowing rate, reduced production of saliva, decreased pharyngeal muscle activity; [56] however, clinical implications are still unclear.

It is widely presumed that **body positioning** may influence esophageal clearance, even if controversies exist. Some authors reported that, in symptomatic preterm infants undergoing esophageal MII-pH study, the left side position showed the lowest esophageal acid exposure in the early postprandial period, and the prone position showed the lowest esophageal acid exposure in the late postprandial period. They suggested that placing premature infants in the prone or left lateral position in the postprandial period is a simple intervention to limit GER [58]. Other authors studied ten preterm infants with combined esophageal impedance-manometry and showed that a strategy of right lateral positioning for the first postprandial hour with a position change to the left thereafter promotes gastric emptying and reduces liquid GER in the late postprandial period [59]. To fill the knowledge gap in older children, other authors performed a retrospective study in which they assessed the influence of upright and recumbent body positions on reflux features through MII-pH. They showed that most children experienced reflux in the upright rather than recumbent position, probably as a result of frequent transient lower esophageal sphincter relaxations while they were awake [60].

Finally, **feeding** and its modalities may influence GER and esophageal clearance. In a small study with symtomatic infants undergoing MII-pH [21], median durations of volume clearance and chemical clearance during feeding, the first hour postprandial, the second hour postprandial, and fasting were assessed. The authors reported that volume clearance remained unchanged over the course of the study, whereas chemical clearance became increasingly less efficient the further the patient was from feeding. In preterm infants, gastric tube feeding may influence GER. According to some authors, the presence of a gastric tube is associated with increased total acid reflux events and decreased gaseous GER events [54]. However, since the influence of the pH-MII probe itself may theoretically promote reflux; however, it is an intrinsic, unavoidable feature of the pH-MII method. The clinical significance of these observations is not completely understood.

In conclusion, esophageal clearance is involved in the pathogenesis of GER in children. Esophageal impedance and manometry are useful tools to assess various features of esophageal clearance. Modifiers of esophageal clearance are increasingly being recognized in clinical studies.

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Manometry

20

Taher Omari

Abstract

Esophageal manometry has been in use for physiological measurement and diagnostics for many years. Solid-state esophageal high-resolution-manometry (E-HRM) offers the ability to record pressures from the upper esophageal sphincter to stomach with fidelity and high spatial resolution, and this has led to the definition of new objective biomechanical measures of esophageal function. For pediatric patients with typical gastroesophageal (GER) disease symptoms, E-HRM may help to guide clinical decision-making, the most important application being the pre-operative investigation of children undergoing workup for anti-reflux surgery. While performing E-HRM can be challenging in younger children, it can be used to exclude achalasia as a cause of typical symptoms and can provide a range of information on esophageal physiology and mucosal integrity that may be informative for determining disease severity. This includes characterization of esophageal peristalsis and esophago-gastric junction (EGJ) barrier function, based upon EGJ hiatus hernia subtype morphology and EGJ contractility. E-HRM may potentially have a role in the investigation of recurrent transit hold-up symptoms following anti-reflux surgery. Finally, E-HRM may detect and differentiate patterns consistent with rumination syndrome.

Keywords

Gastroesophageal reflux · Esophageal motility · High-Resolution Manometry Impedance · Diagnosis · Dysphagia

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Introduction

Esophageal manometry, involving the placement of a flexible catheter to record esophageal and lower esophageal sphincter (LES) pressures, has been in use for physiological measurement and diagnostics for over 50 years. The now widely available paradigm of large array solid-state high-resolution-manometry (HRM) offers the ability to record pressure and bolus flow with high fidelity and spatial resolution that has led to the definition of new objective biomechanical measures that describe anatomical features, flow resistance, and muscle contractility. These phenomena can enable the assessment of pathophysiology and may guide clinical decision-making in relation to patients with upper GI symptoms that may be due to gastroesophageal reflux (GER) disease and/or other upper gastrointestinal motility disorders.

This chapter will discuss E-HRM in children with GER disease; however, it should be read with the knowledge that the current expert consensus is that it is *not recommended* to diagnose GER in children [1, 2]. Nevertheless, E-HRM may provide a useful adjunct tool to diagnose disorders that may "masquerade" as reflux [2]. This chapter will focus predominantly on the evaluation of children with typical signs and symptoms of primary GER disease drawing on evidence available in the adult and pediatric reflux literature. The role of E-HRM for the assessment of GER that may be secondary to other pathology (e.g., esophageal atresia) and in relation to the atypical symptoms (e.g., supra-esophageal reflux) will not be discussed.

Practicalities of Performing Esophageal HRM Studies in Children

The standardization of E-HRM procedures allows the measurements made to be compared against reference ranges for diagnostic purposes. In pediatric patients, standardization is a significant challenge due to differences in patient size and ability to swallow boluses of the same volume and consistency. This impacts on E-HRM recordings and changes optimal reference range thresholds [3, 4].

The E-HRM procedure needs to be performed in a calm quiet environment, by experienced staff and with a supportive parent/guardian at hand. Esophageal manometry is usually a short, outpatient, investigation. Patients should be studied in a fasted state (optimally a minimum of 4 h) and medications that alter esophageal motility should be withdrawn.

Neurologically normal children of toddler age are the most challenging group to study; being ambulant, communicative, and aware but usually unable to comprehend the need for this invasive test. Catheter size can have a significant impact on tolerance; a catheter size of 8Fr or less is optimal for children. Local anesthetic-containing gels can be applied to the catheter tip and shaft to reduce discomfort aiding tolerance. Once the catheter is in position, children will usually (within 5–10 min) become accustomed to the catheter. However, they may resist swallowing of boluses or may not swallow on request.

Older children who can understand the need for the procedure and are able to follow instructions will usually tolerate the procedure very well. Local anesthetic spray can be used to reduce nasal discomfort. Essentially the procedure can be performed an adult patient. Supine body positioning, a standard component for adult E-HRM investigation protocols, is often impractical particularly for young children of toddler age.

When optimally positioned, the catheter pressure sensor array should straddle the region from upper esophageal sphincter (UES) to stomach. Swallowing of a bolus typically reveals manometric features such as the UES pressure and relaxation, proximal esophageal and distal esophageal propagated contraction, and the esophago-gastric junction pressure and relaxation (see Fig. 20.1).

A typical full swallow protocol consists of ten repeat bolus swallows of thin liquid, then viscous liquid and solids (e.g., bread) as tolerated. When conducted by an experienced team, a full and meaningful swallow protocol, including all bolus consistencies, can be achieved in most children of 7 years and older. Younger children are less likely to complete the full protocol which may require tapering to assess thin liquids only, and food types/flavors that the child may be more familiar with. In a recent audit of esophageal function tests in children [5], 90% were considered interpretable; however, no child under the age of 4 years completed a perfect HRM and ~40% were uninterpretable for this age group.

Typically, liquid and viscous boluses should be administered to the mouth via a syringe and then the patient is asked to swallow on command, hence the delivery method is standardized, and only volitional swallowing is tested. Boluses should ideally be administered no more than every 20–30 s. In older adolescent patients' provocative maneuvers, such as *multiple rapid swallows* (MRS), can also be performed. However, in many pediatric patients, the protocol may be too demanding and will need to be reduced in terms of the number of swallows and/or number of different consistencies tested. This decision needs to be made on a case-by-case basis. Liquid bolus swallows are sufficient to characterize motor patterns clinically relevant to the severity of GER disease and to exclude a primary motor disorder (i.e., achalasia) based on the current *Chicago Classification* for diagnosis of swallowing disorders [6]. Although it should be recognized that problems with some diagnoses, most notably, false-positive diagnosis esophago-gastric-junction outflow obstruction (EGJOO), have been addressed by adding positional change to upright and requiring adjunct investigations to confirm EGJOO [7]. The full implications of these recommendations in the pediatric setting have not been fully resolved. However, when dysphagia symptoms are being investigated, the semi-solid and solid consistency bolus is helpful as more challenging to swallow and more likely to provoke symptoms during the test which can be correlated with the motor patterns seen.

An E-HRM study may provide a range of information on esophageal physiology and biomechanics that may be informative for further confirming disease severity in a pediatric patient with GER disease symptoms, particularly when pH-impedance probe and endoscopy evidence of GER may be equivocal. The most important reason for the extra step of performing E-HRM in a GER disease patient is for the

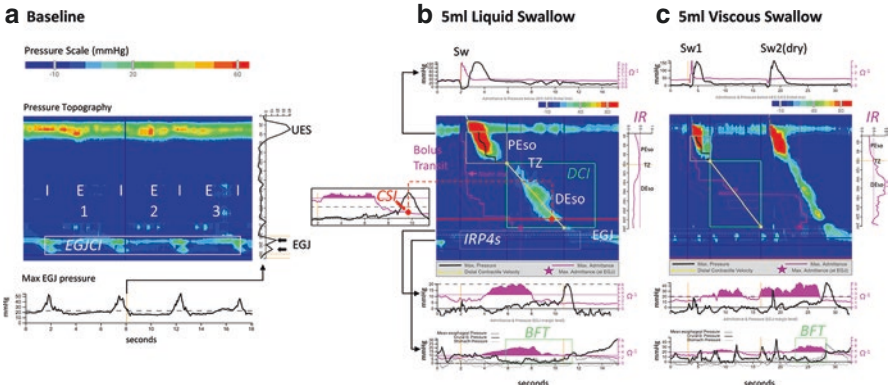

Fig. 20.1 Esophageal HRM-Impedance Measurements Relevant to GER disease. (**a**). Recording of baseline esophageal pressure topography showing two pressure zones; upper esophageal sphincter (UES) and esophago-gastric junction (EGJ). Resting pressure of the EGJ is measured over three respiratory cycles (1–3; I, inspiration; E, expiration) within the margins of the EGJ complex (white box). The line plot below shows the maximum EGJ pressure over time and line plot right shows axial pressure during inspiration which reveals an intermittent, double-peaked, EGJ pressure zone (arrows) with the inter-peak nadir pressure greater than gastric pressure and a range of LES-CD separation of <3 cm in length, fulfilling the criteria for hiatus hernia with a Type II EGJ morphology. (**b**). Recording of a 5 mL *thin liquid* bolus swallow. Anatomical locations of proximal esophagus (PEso), transition zone (TZ), distal esophagus (DEso) and EGJ are shown. Pharyngeal swallow (Sw) propels the bolus into the esophagus and initiates a peristaltic contraction of the esophageal body as well as relaxation of the EGJ. The transit of the bolus distension wave is identified by mapping the time of nadir impedance (Nadir Imp pink line). Esophageal body contractility is measured using the *Distal Contractile Integral* (DCI), EGJ relaxation is measured using *Integrated Relaxation Pressure* (IRP4s; the lowest EGJ pressures over 4 s). For this patient, all liquid swallows had DCI < 450 mmHg.cm.s, consistent *Ineffective Esophageal Motility*. Completeness of bolus transport is defined using *Impedance Ratio* (IR, right side of topography). Mucosal integrity can be inferred using *Contractile Segment Impedance* measured at peak of the contraction wave (CSI, inset left of topography). Associated line plots show pressure (black) and bolus distension based on impedance (pink) in UES distal margin (top), the most distal esophagus (below) and within the EGJ (bottom) showing the timing of esophageal emptying defined by *Bolus Flow Time* (BFT, within green box). (**c**). Recording of a 5 mL *viscous liquid* bolus swallow with delayed bolus transit. Pharyngeal swallow (Sw1) propels the bolus into the esophagus. However, the swallow fails to initiate primary distal peristalsis (DCI 0), transit is therefore paused until a secondary dry swallow (Sw2) initiates distal peristalsis completing bolus transfer across the EGJ. Note: Elevated reading of Impedance Ratio and delayed timing trans-EGJ bolus flow
Patient and Investigation Details: A 13-year-old female with symptoms of heartburn and regurgitation and nil dysphagia. Abnormal pH probe (24 h esophageal acid exposure 5.2% [normal<4.2%], 93 reflux episodes [normal <73/24 h] and positive symptom associations). Testing was performed with SBMkit, a standardized conductivity bolus media for HRM [78] (Trisco Foods, Australia). Pressure and impedance signals were recorded using Solar GI system and solid-state catheter (MMS, The Netherlands). Plots generated using www.swallowgateway.com (Flinders University, South Australia)

pre-operative workup of children being considered for anti-reflux surgery. In the right patient, anti-reflux surgery can be highly effective for reducing gastroesophageal reflux and related symptoms [8] and may obviate the need of long-term PPI

therapy. However, in the wrong patient, anti-reflux surgery can be disastrous in the long term with patients continuing to be symptomatic and requiring ongoing PPI therapy and potentially leading to revisional surgery and EGJ dilatation.

From a practical standpoint, manometry may inform the optimal placement of a reflux monitoring probe; however, it would be inconceivable to place an HRM catheter for this purpose without also capturing bolus swallows to at least characterize the dominant esophageal motor pattern and exclude a primary motor disorder which may alternatively explain symptoms of regurgitation, heartburn, chest pain or dysphagia. Furthermore, E-HRM offers the opportunity to assess features of peristalsis and to characterize the gastroesophageal barrier function. As peristalsis is often weak and the EGJ function is known to be disrupted in GER disease patients, E-HRM may provide additional information that may inform and support a diagnosis of GER disease. Figure 20.1 is illustrative for the commentary that follows.

What Can Esophageal HRM Measure That Is Relevant to GER Disease?

Many GER disease patients who happen to undergo E-HRM will have either *Normal* motility or evidence of a hypo-contractile esophagus, where *Ineffective Esophageal Motility* (IEM) or *Absent Peristalsis* may be diagnosed. The clinical relevance of IEM in non-reflux patients reporting dysphagia symptoms is not always clear because healthy asymptomatic controls can also show IEM; this has led to a recent revision of IEM criteria [6]. However, amongst reflux patients, the degree of IEM may be a marker of disease severity [9]. Esophageal HRM also allows dynamic characterizations of the anti-reflux function of the esophago-gastric junction (EGJ), comprising lower esophageal sphincter (LES) and crural diaphragm (CD). This is by determining high-pressure zone length, respiratory pressure augmentation of CD squeeze pressure and hiatus hernia subtype morphology based on CD-LES separation.

If E-HRM is combined with intraluminal impedance, then it is also possible to define additional aspects of esophageal transport function not directly detectable by pressure measurement alone. These include evidence of bolus residual and emptying time across the EGJ as markers of impaired bolus propulsion that may be secondary to reflux and/or may contribute to reflux-related symptoms of esophageal bolus hold up [10]. Finally, E-HRM may potentially have a role in the investigation of new-onset dysphagia symptoms consistent with transit hold up or suspicion of fundoplication failure due to recurrent symptoms following anti-reflux surgery.

Excluding Achalasia

The incidence of undiagnosed achalasia in adult patients undergoing diagnostic workup for anti-reflux surgery is 1% [11], equivalent data for children is currently unavailable. Esophageal HRM is now considered the optimal method for diagnosis and subtyping of achalasia [6, 12]. Multiple reviews highlight the need for careful

selection of patients for anti-reflux surgery, and that manometry is an important part of the mix of tests required during pre-operative workup [11, 13–16]. Typical symptoms, such as heartburn that are refractory to PPI therapy, have been documented in up to one-third of adult patients with achalasia [17]. In patients with refractory GER disease symptoms without esophagitis, other diseases, such as achalasia need to be considered [16, 18] and there is at least one case study of a child (9 years), with troublesome symptoms consistent with GER disease and significant non-acid reflux on MII-pH monitoring, receiving anti-reflux surgery only to be discovered subsequently to have achalasia [19].

Manometry to exclude achalasia can be achieved in almost every child undergoing E-HRM, however meaningful manometry to diagnose other primary esophageal motor disorders, IEM and/or EGJ features requires a co-operative patient who is able to swallow boluses on command. Caution is required when attempting to report on studies of unsettled children who are unable to swallow on command or who demonstrate repetitive swallowing following bolus administration.

Ineffective Esophageal Motility

The diagnosis of IEM indicates that the esophageal body is poorly propulsive often leading to failure of bolus transport and delayed reflux volume clearance. The definition of IEM has changed in line with the evolution of manometry [20]. Currently, IEM is defined by the *Chicago Classification* based on a Distal Contractile Integral (DCI) of <450 mmHg.cm.s during >70% peristaltic sequences [6]. In GERD patients, IEM has been associated with increased acid exposure time and delayed bolus clearance [21, 22] and is more likely to be associated with typical symptoms of heartburn and regurgitation, than dysphagia [23, 24]. Example swallows from a pediatric GER disease patient with IEM are shown in Fig. 20.1b, c.

There is evidence that IEM is a primary disorder leading to GER disease, rather than the consequence of pathologic acid exposure [24–26]. The processing of afferent stimuli may contribute to the disorder whereby a normal bolus presence or distension fails to initiate peristalsis [27] (see example in Fig. 20.1c), however a recent study comparing IEM vs. Normal amongst patients with refractory GER disease was unable to detect a difference in sensory afferent ending location or mechanoreceptor mRNA expression [28].

The reported prevalence of IEM, or other evidence of hypomotility, in patients undergoing anti-reflux surgery workup ranges from 9% to 50% [11, 20, 21, 29, 30]. However, the prevalence of IEM in pediatric GER disease is not well characterized, the incidence of IEM appears to increase in relation to patient age [30, 31]; however, age- and size-related differences in the key DCI parameter [32] may complicate diagnosis.

Postoperatively, the incidence of IEM is reported to not change overall [30]. However, amongst individual patients, IEM may persist, or new IEM may emerge despite an improvement in GER disease symptoms [30]. It is suggested that the presence of IEM or other evidence of diminished esophageal contractile force could

inform the surgical approach (i.e., partial fundoplication approaches rather than full fundoplication). Objective evidence underpinning "tailoring" the degree of fundoplication based on pre-operative esophageal findings is variable [15, 20]. A study by Andolfi and colleagues [29] employed a strategy of partial fundoplication when IEM patients complained pre-operatively of dysphagia however outcomes showing the advantage of this specific choice were unclear. More recent studies suggested that most patients with IEM can safely undergo a complete Nissen fundoplication [33, 34] and only recommend partial fundoplication in circumstances of severe IEM [34].

Mucosal Impedance

Direct measurement of esophageal mucosal impedance [35] appears to indicate an inflamed or impaired epithelial barrier with features such as dilated intercellular spaces [36] consistent with GER disease. The clinical diagnostic potential of measuring esophageal mucosal integrity with impedance during E-HRM, called Contractile Segment Impedance (CSI, see Fig. 20.1b), has been recently confirmed in adult datasets [37, 38]. CSI has been shown to correlate with mean nocturnal baseline impedance (MNBI) on 24 h pH-impedance monitoring [38, 39]. Pediatric data are limited to a single report showing an association of low CSI with histopathological findings in a limited dataset of patients with esophageal atresia [40].

Additive Value Multiple Rapid Swallows

Multiple rapid swallows (MRS) is a provocative test performed during an E-HRM procedure which, during pre-operative workup, is designed to reveal the dysfunction of inhibitory-excitatory neural pathways which govern esophageal bolus transport. MRS assesses two components of the swallowing mechanism; firstly, efficacy of swallow-induced inhibition of the esophageal body and secondly, "peristaltic reserve" as indicated by the augmentation of contractility immediately post-MRS. The presence of remnant peristalsis during MRS and/or attenuation of post-MRS augmentation together suggest the failure of descending inhibition due to inadequate release of endogenous nitric oxide by inhibitory post-synaptic neurons [41].

In the context of GER disease and fundoplication, abnormal MRS indicating impaired descending inhibition may predict postoperative dysphagia [41]. Furthermore, the ability to assess peristaltic reserve pre-operatively may predict whether the esophageal body contractility is sufficient to overcome the surgically induced outflow obstruction [41, 42]. Mello et al. [30] used MRS to predict postoperative IEM phenotypes during a pre-operative HRM study. Overall, post-MRS augmentation was diminished in patients with IEM and a normal MRS response was associated with resolution of IEM. MRS may also have a further role in the postoperative assessment of patients reporting postoperative dysphagia, where an

elevated intra-bolus pressure during multiple water swallows may identify the presence of EGJ outflow obstruction [43]. In the case of the patient with IEM at preoperative workup, the additional failure of peristaltic augmentation during MRS could inform surgical approach; however, this requires formal evaluation as previously discussed.

Transient LES Relaxation

The transient LES relaxation is the physiological mechanism by which excess gas is vented from the stomach (i.e., belching) it is also the main mechanism of reflux triggering both health and disease in both adults [44] and children [45]. The main factor differentiating GER disease patients from healthy controls is a higher prevalence of liquid refuxate *during* transient LES relaxation, rather than the frequency of relaxations overall [46].

The EGJ is the gatekeeper that prevents the movement of gastric contents along the positive pressure gradient between the stomach and esophagus. During transient LES relaxation the crural diaphragm is inhibited, the esophagus shortens and these factors lead to the EGJ opening and allows gastric contents to pass freely into the esophageal body [47]. The proximal spread of refluxate depends on luminal size, reflux type (gas, mixed, liquid), and the magnitude of pressure gradient which can be augmented by more positive abdominal pressures (e.g., in association with obesity [48]) or more negative thoracic pressures (e.g., in association with COPD [49]).

Transient LES relaxation episodes can now be reliably identified and quantified by E-HRM criteria [50]. An example of TLESR is shown in Fig. 20.2a. However, in most circumstances, measuring the frequency of transient LES relaxation during a short esophageal diagnostic procedure undertaken in a GER disease patient is of limited diagnostic relevance. Instead, the identification of EGJ dysfunction, based on EGJ morphology and contractility, may be more informative, as discussed below.

Esophago-Gastric Junction Morphology

Morphometric analysis utilizes E-HRM to identify the anatomical sub-components of the EGJ, namely the intrinsic lower esophageal sphincter (LES), which is tonically contracted at rest and undergoes neural relaxation during swallowing and transient LES relaxation, and the extrinsic crural diaphragm (CD), which provides passive support and undergoes neural phasic contraction during the inspiratory phase on the respiratory cycle. The anatomical alignment of the LES and CD is complex, as has been revealed by three-dimensional ultra-high-resolution circumferential pressure measurement throughout the EGJ [51, 52]. However, when measured using 1 cm spaced pressure sensors, E-HRM recording can still readily identify the different EGJ components and quantify LES pressure, CD pressure

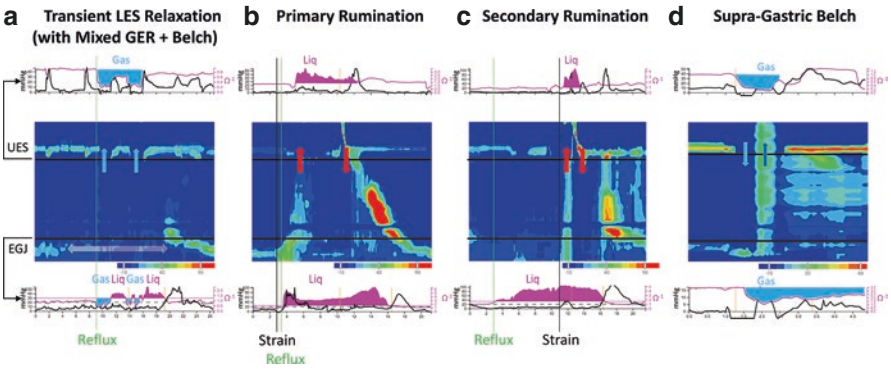

Fig. 20.2 E-HRM with Impedance to Detect and Characterize Rumination Disorders. (**a**) Transient LES relaxation of duration >10s (horizontal arrow) triggering mixed GER and belching. The reflux of gastric content is detected within the esophageal body using impedance as shown line plots above and below where shading indicates contents (blue = gas, pink = liquid). (**b**) Primary rumination episode where gastric strain drives retrograde flow of gastric juice to the pharynx which is then swallowed. (**c**) Secondary rumination where TLESR triggers retrograde flow gastric juice into the distal esophagus then, some 8 s later, gastric strain drives flow to the pharynx which is subsequently swallowed. (**d**) Supra-Gastric Belch where the UES relaxes and intrathoracic pressure gradients suck/expel air into/out of the esophageal lumen
Patient and Investigation Details: Panels A-C from a 15 year old female patients with regurgitation and throat pain and an impedance-pH rumination score of 3 (score ≥ 2 of a total of 4 is predictive of rumination [76]). Panel D from a 17-year-old female with frequent regurgitation, burping and upper abdominal pain and pH-MII rumination score of 2/4. Pressure and impedance signals were recorded using Solar GI system and solid-state catheter (MMS, The Netherlands). Plots generated using www.swallowgateway.com (Flinders University, South Australia)

augmentation, and the presence and extent of LES-CD separation which defines hiatus hernia (HH) size (see Fig. 20.1a).

In patients with GER disease, EGJ dysfunction (diminished EGJ barrier function) is indicated by a greater LES-CD separation, lower LES pressure, and weaker CD pressure augmentation. Of these morphological correlates, weak CD inspiratory augmentation is the only independent predictor of GER disease [53]. Functional failure of the CD has also been characterized in patients with esophagitis [54]. HRM criteria can detect HH and measure HH size with equivalent accuracy to endoscopy and radiology [55]. HRM allows the determination of three HH subtypes based on the degree of LES-CD separation.; type I superimposed LES and CD, type II and type III with distinct pressure signals indicating separation LES and CD <3 cm and >3 cm apart respectively [56]. Marginal to marked LES-CD separation (EGJ morphology subtypes II and III) is associated with a compromised anti-reflux mechanism as evidenced by greater esophageal acid exposure, volume reflux episodes, and symptom association [53, 57]. Thus EGJ morphology may be useful for predicting reflux severity [56].

Figure 20.1 shows an example of "Type II" EGJ morphology. Pediatric series characterizing EGJ morphology in GER disease are yet to be published.

Esophago-gastric Junction Contractility

Barrier function of the EGJ can also be assessed based on the contractility of the high-pressure zone. Past studies have shown that a reduced length and the lower pressure generated by the LES high pressure zone are associated with GER disease [58] and, conversely, anti-reflux surgery is associated with increased length and higher pressures [58, 59]. A mechanically defective LES is common in medically refractory patients undergoing diagnostic workup for anti-reflux surgery [11].

Several groups have investigated the diagnostic potential of a new HRM-based *EGJ Contractile Integral* (EGJCI) which defines contractility by measuring pressure over the length of the EGJ and over time (Fig. 20.1a). The EGJCI is measured across the LES alone in type III EGJ morphology [56]. EGJCI is lower in GER disease patients and in relation to hiatus hernia, negatively associated with acid exposure and the number of reflux episodes [57, 60, 61], is augmented by anti-reflux surgery (full fundoplication > partial fundoplication) and postoperative EGJCI is higher in patients with postoperative dysphagia [30, 62]. There is a suggestion that EGJCI may be higher in PPI non-responders [63].

The relevance of these observations to pediatric GER disease requires further investigation. However, it should be noted that shorter esophageal length is correlated with higher EGJCI with associate implications for diagnostic thresholds [3].

Pre-operative HRM to Identify Pediatric Patients at Risk Postoperative Dysphagia

Dysphagia symptoms are not uncommon in GER disease patients undergoing anti-reflux surgery. Children undergoing pre-operative workup may report bolus hold up to some food consistencies at the time of HRM study. In published adult and pediatric series "early" postoperative dysphagia, which resolves in the short term, can occur in ~20–40% of patients [8, 42, 64, 65]. The acute effects of surgery probably result in a degree of postoperative EGJ outflow obstruction which can be recorded manometrically as an elevated EGJ relaxation pressure [66].

When symptoms of dysphagia to solids are carefully assessed both pre- and post-operatively and allowing sufficient time for early symptoms to resolve, three groups of patients typically emerge; (1) those with no dysphagia, (2) those with pre-operative dysphagia which usually persists postoperatively, and (3) those who develop "new" dysphagia following the surgery. In adults, Myers et al. [67] reported proportions of 21%, 42%, and 37% for these sub-groups, respectively. Pediatric studies observed persistent or new-onset dysphagia in 12–30% of patients receiving fundoplication [8, 68], another showed an incidence of 40% amongst pediatric patients who were already pre-selected for surgery based on the appearance of normal motility [69]. However, in 4–34% of patients overall, dysphagia can become troublesome and clinically significant [8, 42, 65, 67]. These symptoms may mar an otherwise successful anti-reflux procedure and reduces patients satisfaction [42]. In large adult series, Hasak et al. 2019 [42] found that most early dysphagia occurring

with <6 weeks post-operatively resolves with conservative dietary and/or behavioral management, while dysphagia that persists is more likely to require intervention (endoscopic dilation or surgical).

Pre-operative E-HRM study can be a helpful comparator for quantifying the impact that surgery has had on the EGJ barrier. Post-surgical E-HRM evaluation would typically show elevated EGJ pressures, which is consistent with the desired effect of the surgery. However, marked distal compartmentalized pressurization during individual swallows or high intrabolus pressure during multiple water swallows could provide evidence of outflow obstruction which may explain the onset of dysphagia symptoms and indicate the need from endoscopic dilatation [43].

Ideally one would wish to be able to identify such patients early and counsel against surgery due to high postoperative risk, this has been a significant challenge. Normal HRM findings are reported by many GER disease patients receiving anti-reflux surgery [29] and symptom outcomes for patients with disordered vs. normal motility have been reported to be similar [64]. Overall, the HRM diagnosis of IEM is not *sensitive* for predicting postoperative dysphagia, neither is a normal HRM *specific* for a low risk of postoperative dysphagia. There may be a role for provocative MRS protocols for predicting late postoperative dysphagia based on evidence for poor peristaltic reserve defined when the mean MRS DCI is *less* than single-swallow DCI (ratio < 1 [41, 42]). IEM phenotypes, revealed by HRM with MRS protocols, are also thought to be useful for tailoring the operative approach.

There are pediatric and adult reports suggesting that novel intrabolus pressure measures are predictive of postoperative dysphagia. These markers appear to reflect subtle dysfunction, possibly impaired esophageal inhibition, that only become clinically relevant when the EGJ is surgically reconfigured [67–69]. A possible corollary for these findings is a report that evidence of aberrant ENS inhibition revealed by MRS testing may predict dysphagia risk [70].

Use of Manometry with Impedance to Investigate Rumination Syndrome

Rumination syndrome is considered a functional gastrointestinal disorder, rather than a motility disorder and is defined by Rome IV criteria as “Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or re-mastication and swallowing” with “regurgitation that is not preceded by retching” (see Martinez et al. [71] for clinical review of the most current information on rumination syndrome).

Recent studies have demonstrated the value of E-HRM, combined with impedance monitoring, to detect and characterize rumination episodes. The goal of investigation in this case is to observe regurgitation episodes (retrograde bolus flow from stomach to the proximal esophagus and pharynx on impedance) that are preceded by a transient rise in intra-gastric pressure due to abdominal wall contraction (gastric straining).

Studies utilizing manometry with impedance in children referred for clinical suspicion of rumination have recently been published [72–75] based on an ambulatory 24-h study using a combined pH-impedance and manometry probe [73] or stationary short post-prandial assessment using HRIM [72, 75]. An impedance-pH rumination score has been proposed to identify rumination in children presenting with refractory GER disease; a score ≥ 2 of a total four is predictive of rumination [76].

Esophageal HRM combined with impedance has identified, three main rumination patterns [72–75]; (1) primary rumination (Fig. 20.2b), when abdominal strain precedes retrograde flow, (2) secondary rumination (Fig. 20.2c), when abdominal strain follows a reflux event (usually a transient LES relaxation) and (3) supragastric belch, when air is sucked into and then expelled from the esophagus (Fig. 20.2d).

The characterization of rumination patterns may allow better targeting of interventions; for example, the use of pharmacological TLESR inhibition, by the GABA(B) agonist baclofen, can reduce rumination [77]. Of the different rumination patterns that can be identified, secondary rumination is the dominant pattern, indicating that patients may sense gastric refluxate in the distal esophagus which in turn causes an abdominal strain response that propels refluxed material into the pharynx and oral cavity (Fig. 20.2c). Overall, these findings suggest that E-HRM with impedance does have a role in confirmation of clinical suspicion of rumination syndrome and may differentiate rumination syndrome from GER disease.

Conclusion

Current consensus is that E-HRM is not a diagnostic for pediatric GER disease. However, there is evidence that E-HRM can define important features of esophageal dysmotility and EGJ barrier dysfunction that are relevant to GER disease. If included in the diagnostic workup for anti-reflux surgery, E-HRM may detect a primary motility disorder, which may alternatively explain symptoms (e.g., achalasia). The evidence available from pediatric studies is limited. While very helpful for detecting and characterizing rumination disorders, further research is needed to link E-HRM measures to GER disease severity and clinical outcomes. Pediatric studies are needed to investigate the role of E-HRM in the prediction of postoperative dysphagia risk and/or to inform operative techniques to mitigate dysphagia risk.

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Nuclear Scintigraphy and GER

21

Yvan Vandenplas and Bruno Hauser

Abstract

Gastroesophageal reflux scintigraphy (also known as a milk scan) has been mainly used to measure gastric emptying, while the technique contributes also to the diagnosis of gastroesophageal reflux (GER). Milk scan provides information on gastric emptying, GER, pulmonary aspiration, and esophageal transit. The non-invasiveness is an additional advantage. The absence of normal ranges is a weakness, but that is valid for all diagnostic techniques in children. Milk scan is an underestimated diagnostic technique. If the impedance is not available and measurement of non-acid reflux may be of interest, nuclear scintigraphy should be more frequently considered.

Keywords

Gastroesophageal reflux scintigraphy · Nuclear scintigraphy · Milk scan · Gastric emptying · Aspiration · Gastroesophageal reflux

Radionuclide gastrointestinal motility studies are non-invasive, quantitative, and physiologic diagnostic tools for evaluating patients with gastrointestinal complaints [1]. Nuclear studies have been mainly used to measure gastric emptying, but this technique is also suitable to measure postprandial gastroesophageal reflux (GER) [2]. GER scintigraphy (also known as a milk scan) is most commonly performed in infants who have symptoms of sequelae of reflux disease, or when a patient's symptoms are not responding to standard therapies. The most common indications for

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performing esophageal transit scintigraphy include achalasia, dysphagia with negative barium swallow findings. Manometry measures pressure waves in the esophagus and sphincter. However, the procedure is invasive and may not be tolerated by patients. Manometry is much more difficult to perform in children than in a nuclear transit study. Esophageal transit scintigraphy also plays a role in the assessment of treatment response.

Esophageal transit scintigraphy is performed with water or milk with ^{99m}Tc-sulfur colloid (SC) or ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA). In older children, the study can be performed with orange juice. First, there are practice swallows with water or milk only. Then, the water or milk labeled with ^{99m}Tc-SC or ^{99m}Tc-DTPA is ingested as a bolus. The patient is instructed to swallow multiple times for complete clearance of the radiotracer from the oral cavity. The infant is first administered half the volume to be ingested mixed with ^{99m}Tc-SC, followed by the remainder of milk or formula without radiotracer. Dynamic 5- to 10-s frame images are then acquired for 60 min. The images are acquired in the posterior view of the chest including the oral cavity, with the older patient erect. The infant is in a supine position. Gamma camera images of the chest are obtained at time 0, 1, and 2 h for calculation of gastric emptying and to look for aspiration. Rapid frame imaging improves the sensitivity of the reflux study. Delayed static images can then be obtained as needed to detect aspiration. The study is then viewed in static and cine modes. If reflux is present, it may be graded according to the duration of the event, as well as the extent of cephalad reflux within the esophagus. Images are acquired at a rapid framing rate of less than 1 s per frame. After recording data, the esophagus is divided into three equal regions of interest, with further region around the stomach. Time activity curves from these regions allow the qualitative and quantitative evaluation of study. Quantification may include esophageal transit time, percentage clearance at a specified time point, or percentage retained within the esophagus at a specified time point. Transit time can be defined as time (seconds) from initial swallow to 90% clearance from peak activity. Percentage transit is quantified as the number of counts at peak minus the number of counts 10 s after peak counts divided by maximal counts. Esophageal transit time less than 15 s and esophageal percentage emptying greater than 83% were established as normal in healthy adult volunteers.

Esophageal transit scintigraphy can provide unique physiologic and quantitative information regarding esophageal motility and reflux to confirm or exclude the diagnosis of esophageal motility disorders and GERD [3]. Radionuclide gastroesophageal motor studies are well suited for identifying and characterizing disorders with impaired motor function affecting the esophagus and stomach semi-quantitatively and for monitoring the efficacy of therapy [4]. The most common indications for performing esophageal transit scintigraphy include achalasia, scleroderma, dysphagia with negative barium swallow findings, and patients who do not want manometry. Esophageal transit scintigraphy also plays a role in the assessment of treatment response where repeated invasive procedures may not be desirable, particularly in patients with achalasia.

Many years before impedance was technically possible, we showed that a milk scan was very useful to detect postprandial non-acid reflux: in 65 children, 123 reflux GER episodes were recorded with pH metry and scintiscanning, but only six occurred simultaneously [5]. Significantly more reflux episodes were recorded on scintigraphy ($n = 88$; $p < 0.05$), particularly during the first half-hour period ($n = 62$), if compared with the number of pH drops greater than 1 unit, even at pH levels higher than 4 ($n = 41$; $p < 0.05$) [5].

A major shortcoming to using nuclear scintigraphy to diagnose GER-(disease) in children is the lack of normal ranges in presumed healthy children, since GER is a normal physiologic occurring event. However, it must be admitted that the absence of normal values is valid for all techniques measuring GER in children, since for ethical reasons it has become impossible to perform these investigations in asymptomatic children. In veterinary medicine, detection of postprandial GER was demonstrated in each dog investigated [6]. As a consequence, it becomes difficult to distinguish pathologic from normal [6]. GER is common in preterm infants of less than 34 weeks gestation. The incidence of positive scintigraphy and grade of reflux is not significantly different in symptomatic vs. asymptomatic babies. Though radionuclide scintigraphy is a simple, quick, and non-invasive investigation in suspected cases of GER, positive scintigraphy has no correlation with symptoms [7]. By using histopathology as standard of comparison, the sensitivity and specificity of radionuclide scintigraphy was 78.54% and 81.25%, respectively. Because of its physiologic nature, low radiation exposure and convenience, milk scan is recommended as a suitable screening test for detecting GER where available [8]. The 5-s frame acquisition technique is more sensitive than the 60-s frame acquisition technique for detecting both high- and low-level GER [9]. Antegrade pulmonary aspiration can be demonstrated as an underlying cause for persistent/recurrent lower respiratory tract infection in developmentally normal children, with age being an important clinical predictor. Combined use of salivagram and milk scan is warranted to objectively evaluate pulmonary aspiration in children. Milk scan revealed GER in 38% of children and most commonly in those above the age of 2 years [10]. The percentage yield of a positive GER position-related technique was threefold that of conventional single supine position. These results may aid a better understanding of the pathophysiology of the disease and the design of preventive and therapeutic measures [11].

Kwatra et al. attempted to establish ranges for gastric emptying according to age, feeding, and other variables in a large retrospective series of 5136 children, but of course, all these investigations were done because of the presence of symptoms [12]. Nevertheless, they could show that gastric emptying was not different in children with or without GERD [12]. Although there are statistically significant differences in gastric emptying based on age, volume, and route of feeding, the data suggest that overall normal liquid gastric emptying in infants and children $\leq$5 years of age is $\geq$80% at 3 h. One-hour emptying measurements are not reliable for detecting delayed gastric emptying [11, 12]. Gastric emptying rate of milk was not significantly different between children with GER and healthy children. A wide range of

gastric emptying rates was observed in both groups [13]. This study has suggested that the number of reflux episodes was not related to the gastric emptying rate. However, reflux could be observed in a higher frequency before gastric emptying, which also suggested that a 30-min period may be sufficient when reflux is shown early. In negative cases, a 60-min acquisition time is recommended for the diagnosis of GER [14]. However, breath test are more appropriate to measure gastric emptying [15, 16].

The reasons for this lack of widespread use are likely multifactorial, including lack of familiarity of clinicians and nuclear medicine physicians with their utility and availability, limited understanding of how to perform and interpret these studies, and lack of a standard method [16]. If impedance is not available and measurement of non-acid reflux may be of interest, nuclear scintigraphy should be more frequently considered.

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Acid-Lowering Drugs for the Treatment of Gastro-esophageal Reflux Disease

22

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Abstract

After failure of lifestyle changes, acid-lowering drugs have always represented the mainstay of the management of gastroesophageal reflux disease (GERD), despite gastric acid hypersecretion is not a constant feature in patients with reflux disease. Antacids will neutralize intragastric acid while H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) decrease acid secretion, all reducing the aggressiveness of the gastric contents refluxed into the esophagus. Alginate-containing formulations are not "true" acid-lowering drugs. Their efficacy is likely due to the barrier effect, which translates into a reduction of the proximal migration of the refluxed gastric contents. Despite some recent evidence of efficacy in infants, these formulations—like antacids—are not recommended by current guidelines. Thanks to their intrinsic mechanism of action, their duration of action and lack of tolerance, PPIs are better antisecretory drugs compared to H_2RAs. However, since CYP2C19 plays a relevant role in PPI metabolism, pharmacogenetic testing should guide PPI dosing, particularly after neonatal period. Available studies suggest that H_2RAs may be an effective short-term treatment for GERD symptoms and for healing of milder cases of esophagitis, although they are less effective than PPIs. These latter drugs control better both symptoms and mucosal lesions in children older than 1 year and adolescents, but the evidence of efficacy in infants is weak. Since GERD is a chronic, relapsing disease, both symptoms and lesions can recur in a substantial proportion of patients after

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stopping PPIs. Therefore, in selected patients, a long-term therapy should be planned. Despite being quite effective in GERD, PPIs are still far from being the ideal antisecretory drugs. As a consequence, a number of new drugs are currently being investigated to provide a significant advance on current treatments. A dual-release formulation of dexlansoprazole (the right-handed (R)-isomer of lansoprazole) has been approved in the USA for the treatment of GERD symptoms and esophagitis in adolescents, achieving a significant advance over current PPIs, and a new drug class, namely Potassium-Competitive Acid Blockers (P-CABs), has been introduced into clinical practice. These compounds, which block the K^+ exchange channel of the proton pump, result in a very fast, competitive, and long-lasting inhibition of acid secretion and have shown to be able to address the unmet clinical needs in adult GERD. Studies in the pediatric populations are, however, not yet available.

Keywords

Gastro-esophageal reflux disease · Children · Pharmacologic therapy · Antacids Alginate-containing formulations · H_2-receptor antagonists · Proton pump inhibitors · Potassium-competitive acid blockers

Introduction

Gastroesophageal reflux (GER) is the passage of stomach contents into the esophagus. It is a normal physiologic process in both adults and children. It occurs throughout the day in infants and less often in children and adolescents, typically after meals. It may be asymptomatic or cause mild, non-troubling symptoms such as regurgitation or occasional vomiting. However, when reflux of gastric contents causes troublesome symptoms and/or complications, it represents a pathological condition named gastroesophageal reflux disease (GERD) [1].

Symptoms suggestive of GER are not rare in childhood and are a major reason for parental concern, irrespective of the child's age [2]. Epidemiologic studies are complicated by unreliable reporting of symptoms in younger children (<8 years) and infants, in whom often are the parents who interpret symptoms as being troublesome or not. Therefore, the prevalence of GERD is influenced by the subjective interpretation of the child, the parents and the healthcare professionals, since not all patients with GERD develop *objective* symptoms and signs such as esophagitis. For this reason, the European Medicines Agency (EMA) advises performing pH-impedance studies before and after treatment to *objectively* quantify symptom association results [3].

It is estimated that in older children and adolescents, the overall prevalence of GERD in Europe ranges from 10% to 20% [1], with a lower proportion of patients needing some investigation or pharmacologic intervention. As a rule, a comprehensive history and clinical examination are sufficient in most infants and children to diagnose GERD, but judicious investigations are necessary in some patients [4, 5]. Although endoscopy with biopsy and histologic evaluation represents the gold

standard for detection of mucosal lesions [6, 7], the prevalence of erosive esophagitis in children is lower compared with adults [8, 9].

Over the past decade, it has been realized that there are two different phenotypes of the disease. Indeed, while some patients present esophageal mucosal lesions (i.e., erosive esophagitis), the majority (up to 80%) have a macroscopically normal mucosa at endoscopy. Although such patients are usually considered to have non-erosive reflux disease (NERD), they should be categorized—by using functional investigations—under the umbrella of "endoscopy-negative reflux disease," including three different subgroups (i.e., true NERD, reflux hypersensitivity and functional heartburn) [10].

Medical Management of GERD

Symptoms are crucial to the diagnosis of typical GERD and represent the main therapeutic target. Despite the symptom pattern does not allow to differentiate the erosive from non-erosive disease [10], patients and parents seek medical assistance because of symptoms and ask for quick symptom relief.

The aims of GERD therapy are therefore the following [6, 11]:

- Digestive Symptom relief
- Healing of esophageal lesions, if present
- Improvement of extra-esophageal symptoms and signs, if any
- Assuring normal growth and development
- Prevention of recurrences (both symptomatic and endoscopic) and of complications

Like in adults [12, 13], GERD is primarily a motor disorder and its pathogenesis is multifactorial [13, 14]. The main motility abnormalities include an impaired function of the lower esophageal sphincter (LES), an abnormal esophageal clearance, and a delayed gastric emptying in up to 40% of cases. The presence of hiatal hernia favors reflux, but this association is not mandatory. The ultimate consequence of the above motor abnormalities is the presence of acid in the wrong site (i.e., in contact with the esophageal mucosa) [12–14]. In addition, the amount of reflux increases markedly after meals both in healthy subjects and GERD patients, an event almost exclusively due to the increase of transient (inappropriate) LES relaxations by meal-induced gastric accommodation [15]. Even though the pathophysiology and symptoms, especially in older children, of pediatric GERD are similar to those in adults, children may also present with a wide range of distinct gastroesophageal and extra-esophageal symptoms and potential complications [2].

Treatment of GERD in adolescents usually starts with lifestyle changes, although their effectiveness has not been clearly shown like it was in infants and children [5, 6] as well as in adults [16]. If drug therapy is deemed necessary, the treatment can rely on acid-lowering drugs and prokinetic agents [6].

Conversely from adult patients, gastric acid secretion in children with GERD has not been extensively studied. However, some investigations found that patients with severe disease [17] or those needing surgical therapy [18] display acid hypersecretion. These findings provide a rationale for the use of acid-lowering drugs in the treatment of GERD in children. Indeed, antacids will neutralize intragastric acid while H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) decrease acid secretion, all reducing the aggressiveness of the gastric contents refluxed into the esophagus.

Antacid and Alginate Formulations

Antacids are preparations that are primarily designed to neutralize gastric acid. The proliferation of antacid formulations includes combinations and varying proportions of a number of basic materials in an attempt to produce improved neutralization characteristics with lowered untoward effects.

Pharmacology

The chemistry of each antacid is unique [19]. On the basis of their biological properties, they can be divided into systemic (i.e., sodium salts) and non-systemic (calcium, magnesium and aluminum salts) antacids (Table 22.1) [20]. Most prescribed antacids contain a mixture of aluminum and magnesium salts. The most widely known antacid combination to exploit the opposite effect of magnesium hydroxide and aluminum hydroxide on bowel habits is Maalox™, where MA stands for Magnesium, AL for Aluminum and OX for hydroxide [21]. Precise methods of preparation and presentation are important because they influence the physicochemical properties and the therapeutic effects of antacids.

Table 22.1 Classification of antacids

Antacid class	Antacid	Chemical formula
Systemic antacids	Sodium bicarbonate	$NaHCO_3$
	Sodium citrate	$Na_3C_6H_5O_7$
Non-systemic antacids	Calcium carbonate	$CaCO_3$
	Magnesium hydroxide	$Mg(OH)_2$
	Magnesium carbonate	$MgCO_3$
	Magnesium trisilicate	$Mg_2O_8Si_3$
	Aluminum hydroxide	$Al(OH)_3$
	Aluminum phosphate	$AlPO_4$
Complex antacids	Magaldrate	$Al_5H_{31}Mg_{10}O_{39}S_2 \bullet xH_2O$ $CH_{11}AlMg_3O_{12}$
	Almagate	$6Al_2(CO_3)(OH)_{16} \bullet 4(H_2O)$
	Hydrotalcite	$Al_2H_6MgO_7Si_2$
	Almasilate	$C_{35}H_{59}Al_3N_{10}O_{24}$
	Aceglutamide aluminum	

Antacid effects are due in part to the partial neutralization of gastric acid, thus raising intragastric pH (Fig. 22.1). Generally, large doses of antacids are needed to raise gastric pH significantly [22].

Antacid-induced increases in gastric pH also inhibit pepsin activity [23]. Inhibition of pepsin activity is dependent upon the rise in gastric pH and is maximally inhibited at approximately pH 4 [23] (Fig. 22.2). Aluminum hydroxide and calcium carbonate have also been reported to directly *adsorb* pepsin [24]. As a consequence, the aggressiveness of the gastric material refluxed into the esophagus is reduced [20, 25]. Thanks to their safety (being not absorbed compounds) and ease of administration, these compounds are amongst the most widely used OTC medications [26].

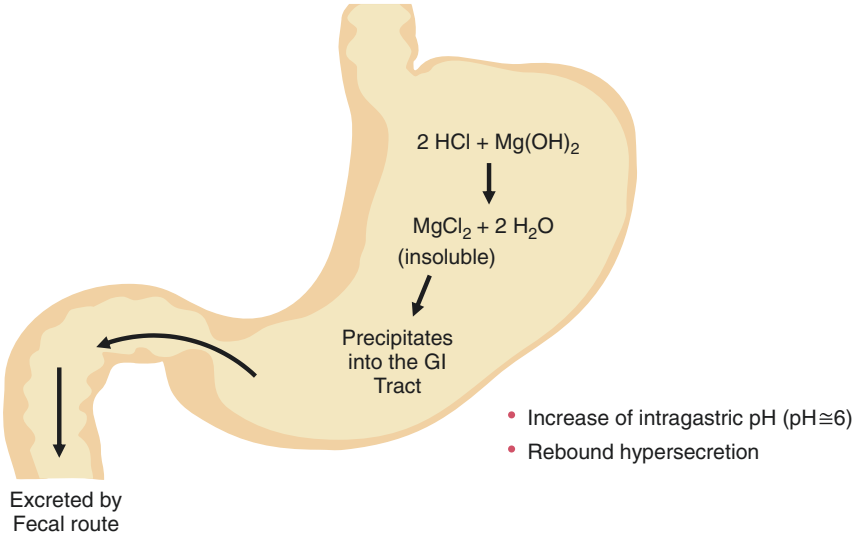


Fig. 22.1 Intragastric acid neutralization by non-systemic antacids: the case for magnesium hydroxide

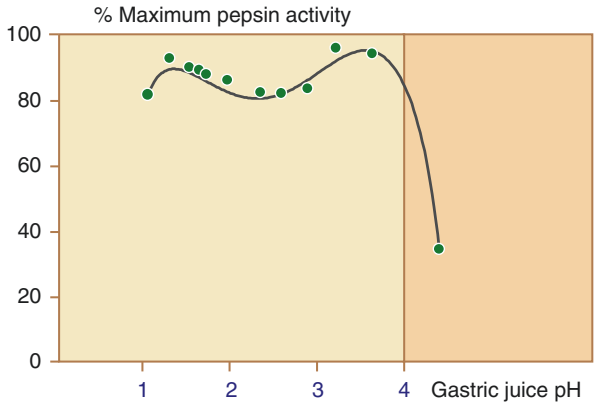


Fig. 22.2 Influence of pH on gastric pepsin activity. Any drug that will increase intragastric pH over 4 will display *indirectly* antipeptic activity (*modified* from Berstad [24])

Conversely from what is commonly thought, alginates are not "true" acid-lowering drugs. Their efficacy is likely due to the barrier effect, which translates into a reduction of the proximal migration of the refluxed gastric contents [27] and binding and inactivation of pepsin [28]. In addition, the alginate-antacid raft co-localizes to the postprandial acid pocket [29] and displaces it below the diaphragm to reduce postprandial acid reflux [29, 30]. As a matter of fact, the marketed alginate formulations contain a wide spectrum of alginate-based materials (soluble salts: sodium and potassium alginate or insoluble salts: calcium and magnesium alginate) as well as *small quantities* of antacids (such as sodium bicarbonate and/or calcium carbonate), which are not sufficient to increase intragastric pH. These formulations require three chemical reactions to take place simultaneously: transformation to alginic acid, sodium carbonate reacting with gastric acid to form carbon dioxide, calcium salts releasing free calcium ions to bind with alginic acid, providing strength to raft formation [31]. Without gas production, alginates would mix with and be emptied together with food from the stomach [32].

Clinical Efficacy

Like in adult patients with GERD, in whom antacid intake is followed by quick symptom relief [20, 33], large amounts of these medications are as effective as an H_2RA in medical treatment GERD in children [34]. However, there is insufficient evidence to conclude whether antacid therapy is effective or safe when treating GERD in preterm infants [35].

Aluminum-containing antacid administration has been followed by plasma aluminum levels previously associated with toxicity in patients with renal failure after chronic exposure to this metal [36]. As a consequence, development of osteopenia, rickets, microcytic anemia, and neurotoxicity are potential concerns of antacid therapy in children [37]. Despite being rare in children, the milk-alkali syndrome (characterized by the triad of hypercalcemia, alkalosis, and renal failure) has been associated with long-term treatment with high-dose of calcium carbonate-containing antacids [38]. Antacids should be therefore used with caution in children and prolonged use avoided, giving preference to more effective and safe drugs [5].

Alginate-containing formulations as anti-reflux medications were largely used before the advent of antisecretory drugs. As a consequence, the bulk of the available literature is quite old and not always consistent, besides being of low quality. However, in recent years, there was a renewed interest in the *mechanical* approach to this common condition. pH-impedance studies have shown that both magnesium and sodium alginate significantly decrease the number and extension of both acid and non-acid reflux episodes and associated symptoms (crying-fussiness, cough, and regurgitation) in infants [39]. An Italian study actually found that magnesium alginate plus simethicone is more efficacious on GERD symptom score than thickened formula and reassurance together with lifestyle changes [40]. In this connection, the National Institute for Health and Care Excellence (NICE) suggests the use of alginate formulations as alternative treatment to feed ticketing agents in breastfed

babies or in infants, whose symptoms persist despite conservative measures [41]. However, the more recent ESPGHAN/NASPGAN guidelines [4] do not recommend alginates for chronic treatment in infants and children with GERD.

Antisecretory Drugs

Because of the safety concern and because of their short duration of action, antacids are not recommended by any guideline and antisecretory drugs have represented the mainstay of the medical treatment of GERD [4, 6].

Regulation of Gastric Acid Secretion

Gastric acid secretion is under nervous and hormonal influence. This physiologic process is controlled by a number of redundant second messenger pathways activated as a result of the binding of gastrin, acetylcholine, histamine, and prostaglandins to the specific receptors on the basolateral surface of parietal cells (Fig. 22.3). The stimulatory effect of acetylcholine and gastrin is mediated by an increase in cytosolic calcium, whereas that of histamine is mediated by activation of adenylate cyclase and generation of cyclic AMP (cAMP). Strong potentiation between histamine and either gastrin or acetylcholine reflects post-receptor interaction between the distinct pathways as well as the ability of acetylcholine and gastrin to release histamine from mucosal enterochromaffin-like (ECL) cells. The ultimate factor in

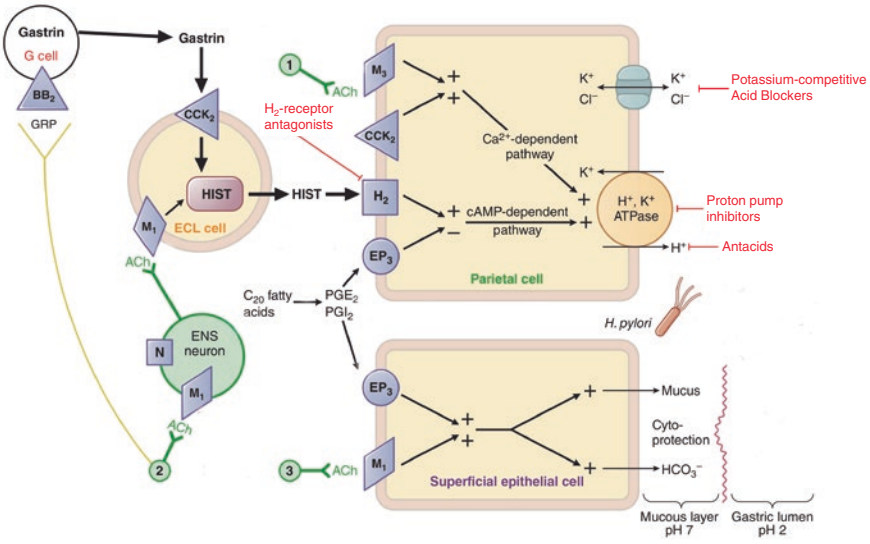


Fig. 22.3 Mediators and receptors involved in the regulation of acid secretion: site of action of acid-lowering drugs (*modified* from Scarpignato and Blandizzi [44])

acid secretion, however, is the stimulation of the proton pump (H^+, K^+-ATPase) to secrete hydrogen ions into the gastric lumen in exchange for potassium ions (Fig. 22.3) [42].

Parietal cell stimulation by histamine occurs through the histamine-2 receptors, located on the basolateral surface. As a consequence, H_2RAs are able to inhibit acid secretion in a dose-dependent fashion [43, 44]. Their introduction into the medical practice in the late 70s has been a real breakthrough in the treatment of acid-related diseases, including GERD. The recognition that H^+,K^+-ATPase was the final step of acid secretion culminated in the 80s in the development of a class of drugs, the PPIs, which are targeted at inhibiting this enzyme (Fig. 22.3) [43, 44]. They represent one of the most commonly prescribed classes of drugs in either gastroenterological and primary care settings and are considered a major advance in the treatment of GERD.

Pharmacology of H_2-Receptor Antagonists

H_2-RAs act by reducing histamine-induced gastric acid secretion and pepsin output [45, 46]. They are well absorbed from the gastrointestinal tract but, due to high first-pass metabolism, systemic bioavailability of oral doses is reduced (approximately 70% with cimetidine and 50% with ranitidine) [45, 47]. Available data from scarce and sparse studies suggest that the PK and PD of these drugs are similar in both children over the age of 1 year and adults, a result which can be understood by knowing that these drugs are primarily excreted by the kidney [47] and that renal function approaches maturity by 1 year of age [48]. As a matter of fact, H_2-RAs have longer half-lives in neonates than in older children and caution is required when using these drugs in the newborn [45].

H_2-RAs have a relatively short duration of action and, depending on the individual agent and whether the patient is in a fed or fasting state, suppress acid for approximately 4–8 h [49]. Consequently, multiple daily doses of these agents are likely to be required. Furthermore, H_2-RAs produce incomplete inhibition of postprandial gastric acid secretion. Overall, these agents inhibit acid secretion by up to 70% over a 24-h period [49, 50].

A further shortcoming is that tolerance to standard dose H_2-RAs generally develops within 2 weeks of repeated administration, resulting in a decline in acid suppression [51]. This can be explained by a gastrin-induced increase in ECL-derived histamine concentrations at the H_2-receptor on the parietal cell and up-regulation of both gastrin and H_2-receptors [51]. In contrast, PPIs control both basal and food-stimulated acid secretion and produce more complete and longer lasting acid suppression than H_2-blockers [43, 52]. Such acid inhibition virtually abolishes the damaging peptic activity of gastric juice. In addition, tolerance to PPIs has not been observed, an advantage presumably attributable to the fact that they act at the final site of acid production, thereby blocking the effects of any compensatory mechanisms promoting acid secretion [52]. The main differences between H_2-RAs and PPIs are summarized in Table 22.2, which shows that PPIs are better antisecretory

Table 22.2 Differential characteristics of H_2-receptor antagonists versus proton pump inhibitors

	H_2RAs	PPIs
Target cell	Parietal cell	Parietal cell
Target receptor	H_2-receptor	H^+/K^+-ATPase
Pharmacodynamic effects	↓GAS and ↓EEA	↓GAS and ↓EEA
Onset of action	Quick	Delayed
Duration of action	Short	Long
Tolerance development	Yes	No
Safety	Excellent	Excellent

GAS gastric acid secretion, EEA esophageal exposure to acid

compounds [43]. However, conversely from adult GERD [53], the superiority of H_2RAs over PPIs has not yet definitely demonstrated in children [54].

Despite all the above limitations, there is still a place for H_2-RAs in the era of PPIs [55]. H_2-RAs are certainly useful for symptom relief in patients with mild forms of GERD, being similarly effective to omeprazole [54]. The appreciation that even twice daily PPIs may not adequately control intragastric acidity during the night and that in a significant proportion of children with GERD a "nocturnal acid breakthrough" (NAB) does occur [56] has suggested the use of an H_2-RA to improve acid control. However, conversely from adult patients [57], there appears to be no additional benefit to supplementation with ranitidine at bedtime in children [56].

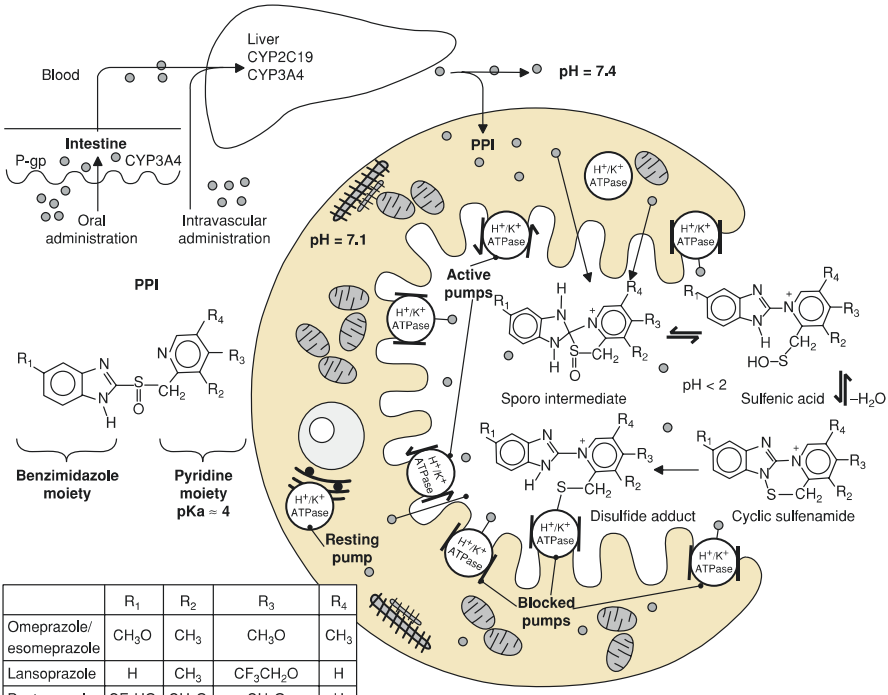
Formulations of H_2-Receptor Antagonists

H_2RAs (especially soluble or over the counter formulations) will likely become the "antacids of the third millennium" and will be particularly useful for on-demand symptom relief. In adults, OTC (low-dose) formulations are not only able to decrease gastric and esophageal acidity but actually potentiate the antacid effect in relieving meal-induced heartburn [58]. The taste of the ranitidine effervescent formulation (dissolved in water) is preferred by children and parents over the ranitidine syrup [59]. Better taste acceptance may facilitate ease of administration and compliance in pediatric patients. Unfortunately, ranitidine has been withdrawn because of concern of higher than acceptable levels of *N*-nitrosodimethylamine (NDMA), a potential carcinogen in the medication [60, 61] and, accordingly to information provided by the main manufacturer, will be not back to the market. Nizatidine, also containing NDMA impurities [61], was recalled by manufacturer in January 2020. And, since cimetidine does interact with cytochrome P450 leading to potential drug-to-drug interactions [62] as well as interference with vitamin D metabolism [63] and endocrine function [64], it is no longer recommended. Therefore, the only alternative is represented by famotidine, whose pharmacodynamics and pharmacokinetics in children older than 1 year of age appear to be similar to those seen in adults [65]. However, this H_2RA was only studied in infant GERD [66], where it may cause agitation and headache, and a liquid formulation is currently unavailable.

Pharmacology of Proton Pump Inhibitors

Currently available PPIs are all benzimidazole derivatives that need to be activated before binding to the proton pump. They are indeed acid-labile, pro-drugs. Activation of the PPI occurs within the secretory canaliculi of the parietal cell by addition of two protons to the nitrogens on either side of the sulfinyl group (Fig. 22.4). Once it is activated, the PPI can inactivate the proton pump by binding to cysteine molecules on the ATPase to form disulfide bonds [67].

Pharmacokinetics (PK) and pharmacodynamics (PD) of PPIs in children have been extensively discussed in comprehensive reviews [67–69], to which the reader is refereed. PPIs are metabolized by the hepatocyte CYP2C19 and the CYP3A4 isoenzymes, the activity of which is affected by maturation changes. These enzymatic systems show indeed a pattern of reduced activity at birth, but reach adult levels of activity in early infancy. Hepatic P450 enzyme activity levels then exceed adult enzymatic activity throughout childhood and finally revert back to adult levels sometime after puberty [68]. These data strongly suggest that administration



	R_1	R_2	R_3	R_4
Omeprazole/ esomeprazole	CH_3O	CH_3	CH_3O	CH_3
Lansoprazole	H	CH_3	CF_3CH_2O	H
Pantoprazole	CF_2HO	CH_3O	CH_3O	H
Rabeprazole	H	CH_3	$CH_3O(CH_2)_3O$	H

ATPase, adenosine triphosphatase –CYP, cytochrome P450 -P-gp P-glycoprotein –pKa, negative logarithm of the acid ionization constant

Fig. 22.4 General chemical structure and mechanism of action of PPIs (from Litalien et al. [67])

regimens should vary according to age [69]. In any event, reference should be made to individual drug monographs before prescribing.

Conversely from the other PPIs, the clearance of rabeprazole is much less dependent on CYP2C19 as it is predominantly metabolized non-enzymatically to rabeprazole thioether. Esomeprazole, the S-enantiomer of omeprazole, being—together with its metabolite (esomeprazole sulfone)—a powerful inhibitor of CYP2C19, does inhibit its own metabolism, rendering all subjects "slow metabolizers" [53].

All PPIs are rapidly metabolized in the liver and have short half-lives (about 60 min). As expected from their mechanism of action (trapping and concentration within the parietal cells), there is poor correlation between the peak plasma concentration and the degree or duration of acid suppression [68]. However, the area under the plasma concentration time curve (AUC) does correlate well with acid suppression [69].

Together with PK, additional factors may also affect the PD of PPIs. Immaturity of the parietal cell mass and a relative achlorhydria in the first 20–30 months of life [70] may hamper the ability of the active form of PPIs to accumulate effectively in the intracellular canaliculi of the parietal cells. Gastric emptying and gut transit time, which may vary with age [71], could also affect bioavailability of PPIs in the pediatric population [68]. As a consequence, safety and efficacy studies are needed to determine the most appropriate regimen for different pediatric age groups [69].

Since gastrin release after a meal is one of the most potent activators of H^+,K^+-ATPase, the PPI should be administered long enough (some 30 min) before a meal to be absorbed, but not eliminated, by the time the proton pump is activated. After the activated PPI binds to the proton pump, acid secretion is inhibited long after the PPI is eliminated from the circulation. Not all pumps are active and inhibited after the first dose, thus steady state of acid inhibition will be reached after at least 3 days [69].

Pharmacogenetics of Proton Pump Inhibitors

Several adult studies have suggested that subjects with reduced CYP2C19 metabolism have increased exposure to first-generation PPIs compared to normal metabolizers [72]. In adults, poor metabolizers have been shown to display a greater efficacy and a gastric pH less acidic compared to intermediate and normal metabolizers [73]. Taken together, these studies suggest that CYP2C19 plays a clinically relevant role in PPI efficacy. Guidelines from Clinical Pharmacogenetics Implementation Consortium (CPIC—https://cpicpgx.org) [74] are available to guide the use of CYP2C19 metabolizer status for PPI selection and dose (Table 22.3).

More recent investigations have shown increased CYP2C19 function in children compared to adults. As a consequence, the influence of CYP2C19 function on clinical outcomes in PPI users should be carefully considered also in the pediatric population. For pediatric patients, pantoprazole and lansoprazole are the two most commonly investigated PPIs with respect to CYP2C19 effects. These studies have shown that poor metabolizers have higher exposure compared to normal

Table 22.3 Pharmacokinetic consequences and CPIC therapeutic recommendations based on CYP2C19 phenotye: simplified version

CYP2C19 metabolizer	PK consequences	Therapeutic recommendations	Increased risk of
Ultrarapid	Decreased PPI plasma concentrations	Increase starting daily dose by 100%[a]	Failure
Rapid	Decreased PPI plasma concentrations	Consider increasing starting daily dose by 50–100%[a]	Failure
Normal (NMs)	Normal PPI metabolism	Initiate with standard dose but consider increasing daily dose by 50–100%[a]	Failure[b] (possible)
Intermediate (IMs)	Increased PPI plasma concentrations	Consider decreasing standard daily dose by 50% for chronic (>12 weeks) therapy	Potential toxicity[c]
Poor (PMs)	Increased PPI plasma concentrations	Consider decreasing standard daily dose by 50% for chronic (>12 weeks) therapy	Potential toxicity[c]

CPIC Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org)
[a]Daily dose may be given in divided doses
[b]Compared to IMs and PMs
[c]Increased (likely for IMs) chance of efficacy

metabolizers, with delayed clearance and longer drug half-life. Clinical studies of children taking lansoprazole have associated adverse effects and efficacy with CYP2C19 metabolizer status [75]. A recent study with omeprazole showed reduced PPI efficacy in CYP2C19 ultrarapid metabolizers versus those with reduced or normal CYP2C19 function [75]. Taken together, these data suggest that—like in adults [76]—CYP2C19 genotype can predict PPI plasma concentrations, efficacy, and toxicity in children, and support the use of CYP2C19 data to guide PPI dosing, particularly after the neonatal period [75].

In the era of precision medicine, pharmacogenetic testing has become a need to assure individualized GERD therapy [73]. In this connection, a very recent review of this approach in an Academic Children's Hospital [77] found that pharmacogenetics could be used to guide selection of current treatment options or medication dosing in almost half (48.7%) of pediatric patients tested. CYP2C19-dexlansoprazole-gastritis-esophagitis and CYP2C19-omeprazole-gastritis-esophagitis were amongst the most common gene-drug-diagnosis groups with matching diagnoses and prescriptions [77]. On the grounds of previous investigations at the same institution [78–80], a large (N = 750) study to optimize PPI therapy for different CYP2C19 metabolizer phenotypes in children with GERD is ongoing at the Nemours Center for Eosinophilic GI Diseases (Orlando, Florida, USA). Together with genetic variants, also gut microbiota composition is being studied and correlated with response to PPI therapy in order to identify the correct PPI dose for different children (https://eoekids.org/clinical-trials-and-studies/ppi-precision-medicine-study).

Formulations of Proton Pump Inhibitors

Conversely from H_2RAs, liquid formulations of PPIs are not commercially available in Europe. In the USA, pantoprazole sodium delayed-release granules for oral suspension, originally developed for adult patients with swallowing disorders [81], have later been studied in children with GERD, aged 1 month through <6 years [82].

For the other PPIs, several extemporaneous preparations [83–87] have been attempted to suit specific clinical needs (like administration via gastrostomy or via nasogastric tube), but can be used in children, who cannot swallow tablets or capsules. Suspensions are prepared with 10 mL of 8.4% sodium bicarbonate solution, but their stability is both time and temperature dependent [86]. Granules from esomeprazole magnesium delayed-release capsules can be suspended in water, but care must be taken not to chew or crash them [87]. The lansoprazole fast-disintegrating tablet [88] can be dissolved in water or Oral-Blend™ (a sweetened oral suspending vehicle) and this formulation appears to give the best results in terms of stability [85, 86] and antisecretory activity [83].

A suppository formulation of omeprazole has recently been developed that may represent a good alternative in infants [89]. Currently, all the above formulations are not licensed for use in children in any country. Their use should be therefore considered *off-label*, which is not uncommon in the pediatric populations [90, 91].

Non-Antisecretory Effects of H_2-Receptor Antagonists and Proton Pump Inhibitors

Although H_2RAs selectively block H_2-receptors located on the parietal cells, thus inhibiting gastric acid secretion, other non-antisecretory activities may become apparent [92]. They can be divided into two main groups: those connected with H_2-receptor blockade (specific effects) and those independent of this main action (non-specific effects). The specific effects are mainly class-dependent, while the non-specific ones are molecule-dependent, i.e., related to the chemical structure of the given compound [92].

The non-antisecretory effects concern central and autonomic nervous systems, cardiovascular and endocrine systems, immune systems and digestive systems [92]. The most interesting ones deal with gastrointestinal motility. Indeed, in both upper and lower gastrointestinal tract, secretion and motility are two interrelated parameters [93] that cannot be regarded or studied independently from each other [94]. Conversely from the other H_2RAs, ranitidine and nizatidine display a cholinergic-like activity [95] that translates into a prokinetic effect [96]. This additional pharmacologic activity, not shared by famotidine, can further reduce the esophageal exposure to acid in children with GERD and delayed gastric emptying [97–99].

Despite their concentration within the secretory canaliculi of the parietal cell and their pharmacologic selectivity [69, 100], PPIs also have some side effects, which are often (but not always) independent from their antisecretory activity (Table 22.4) [101].

Table 22.4 Non antisecretory activities of proton pump inhibitors

• Mucosal protective activity
• Antibacterial activity (*Helicobacter pylori* & other microorganisms)
• Inhibitory activity on GI motility
• Anti-inflammatory activity
• Antioxidant activity
• Free radical scavenging activity
• Direct and indirect antineoplastic activity

Like H_2RAs, also PPIs can affect *gastric motility* and *emptying*. The majority of studies, which have been performed with omeprazole, clearly show that this PPI is able to delay gastric emptying of both liquids and solids. The delay in gastric emptying was evident at both the onset of gastric emptying (as evidenced by prolongation of the lag phase) and during the linear emptying (as shown by the slope of the emptying curve). Compared to the omeprazole results, data obtained with lansoprazole and rabeprazole were less consistent, but nevertheless showed that both antisecretory compounds can—under given experimental conditions—delay gastric emptying, especially of solid food [102, 103]. As a consequence of drug-induced gastric motor derangement, dyspeptic symptoms may actually be worsened by PPI therapy or, alternatively, new symptoms (especially postprandial fullness) may arise during treatment. This could be more relevant in GERD patients with delayed gastric emptying [97–99] or associated functional dyspepsia (FD) [104, 105]. In this regard, a Cochrane meta-analysis [106] showed that H_2RAs are better than placebo in achieving symptom relief in patients with FD.

The mucosal protective and anti-inflammatory properties of PPIs are also relevant to GERD treatment. It now clearly established that the esophagus contains a diverse microbial population, with Gram-positive bacteria (specifically Streptococcus), dominating in health and Gram-negative bacteria prevailing in patients with GERD and Barrett's esophagus [107, 108]. Gram-negative derived lipopolysaccharide (LPS) can upregulate gene expression and increase, through activation of toll-like receptors 4 (TLR-4) and nuclear factor kappa B (NFκB) pathways, pro-inflammatory cytokine production [107]. In patients with more severe esophagitis, histologic changes characterized by T-lymphocyte predominant inflammation with papillary and basal cell hyperplasia but without loss of surface cells were reported [109]. These findings suggest reflux-induced inflammation may be cytokine mediated, with hypoxia inducible factor (HIF)-2α playing a major role, rather than the consequence of the usually acid attributed chemical injury [110]. Indeed, in response to the reflux of acid and bile, HIF-2α in esophageal epithelial cells becomes stabilized, thereby increasing the production of pro-inflammatory cytokines that attract T lymphocytes and other inflammatory cells to damage the esophagus [110]. And, of course, dysbiosis and inflammation could be related to each other.

The *esophageal mucosal protective activity* of PPIs was studied by investigating their effect on the mucosal barrier in patients with PPI-responsive esophageal eosinophilia (PPI-REE) or eosinophilic esophagitis (EoE) [111]. The integrity of the esophageal mucosa is impaired in both these patients, allowing

transepithelial transport of small molecules and allergens. Indeed, in vitro studies from esophageal biopsies found that transepithelial electrical resistance is reduced, and intercellular spaces are dilated. PPI therapy partially restores mucosal integrity in patients with PPI-REE, but not in those with EoE [111]. This normalization of dilated intercellular spaces is similar to that observed in patients with GERD [112].

The clinical relevance of PPI mucosal protective activity is difficult to ascertain. Indeed, according to the experimental studies, doses higher than the antisecretory ones are needed to exploit it. However, mucosal protection could be of value—in addition to acid suppression and to the anti-inflammatory activity (*see below*)—in healing reflux esophagitis [113] and eosinophilic esophagitis (EoE) [114].

It is not clear whether oral PPI dosing can achieve the high drug concentrations in plasma and tissue that would be needed to reproduce some of the *anti-inflammatory actions*, observed in vitro and in vivo experimental settings (for review, see [101]). Nevertheless, both antioxidant and anti-inflammatory properties of PPIs may contribute substantially to their efficacy in EoE. As a matter of fact, in vitro and in vivo studies suggest that the anti-inflammatory effects of PPI therapy rather than acid suppression *alone* may be responsible for the observed clinical and histologic improvement through inhibition of the Th2-allergic pathway. Indeed, like topical corticosteroids, PPIs down-regulated cytokine expression [115]. PPI therapy significantly down-regulated esophageal eotaxin-3/Th2-cytokine gene expression in PPI-REE, similarly to that seen in steroid-responsive EoE [115].

Clinical Efficacy of H_2-Receptor Antagonists

Both H_2RAs and PPIs are used in children at the recommended regimes (Table 22.5). Compared with adults, fewer studies have conducted in pediatric populations. The available trials are summarized in some systematic reviews [116–119], of which de

Table 22.5 Antisecretory drugs: recommended regimens for GERD treatment in pediatric patients

	Recommended pediatric regimens	Maximum dosages[a]
H_2-receptor antagonists		
Cimetidine	30–40 mg/kg/day	800 mg
Ranitidine	5–10 mg/kg/day	300 mg
Nizatidine	10–20 mg/kg/day	300 mg
Famotidine	1 mg/kg/day	40 mg
Proton pump inhibitors		
Omeprazole	1–4 mg/kg/day	40 mg
Lansoprazole	2 mg/kg/day	30 mg
Esomeprazole	10–20 mg/kg/day[b]	40 mg
Pantoprazole	1–2 mg/kg/day	

[a]Based upon adult dosages
[b]Depending on the body weight (<20 kg or > 20 kg)

Mattos et al. [119] is the most comprehensive one. None has attempted a meta-analysis due to the large heterogeneity of the included studies, many of which were of poor methodologic quality.

Studies concerning H_2RAs and extrapolation of large adult RCTs to older children and adolescents suggest that these drugs may be an effective short-term treatment for GERD symptoms and for healing of milder cases of esophagitis, although they are less effective than PPIs. It should be emphasized, however, that recommended doses of H_2RAs for children may not be optimal for *adequate* gastric acid suppression [120, 121]. And indeed, an increase of the initial dose has been advocated in case of failure to control symptoms [46], although a switch to a PPI is arguably more efficacious.

Clinical Efficacy of Proton Pump Inhibitors

The analysis of available studies with PPIs allow to conclude that these drugs are very effective in controlling GERD symptoms and esophagitis in children older than 1 year and in adolescents, but the evidence of efficacy in infants is weak [122, 123]. Erosive esophagitis (a rare condition in this patient population) is the only Food and Drug Administration (FDA)-approved indication for PPIs in infants [124]. It should be emphasized that infant studies were often "under-powered," used heterogeneous populations and may have used inadequate doses of PPIs, with some of the trials showing an effect overlapping that of placebo. There is therefore a need for well-designed, dose-ranging studies in this patient population. Meanwhile, the pervasive use of these drugs in neonates and infants [125] has led to a clinical conundrum, namely to institute a PPI treatment based on knowledge and experience or to withhold it consequent to the lack of indication in the absence of mucosal lesions [126]. Currently, in accordance with the conclusions of a specific systematic review [127], the most recent ESPGHAN-NASPGHAN guidelines [4] recommend that PPIs should not be used for the treatment of crying, distress, or visible regurgitation in otherwise healthy infants.

Combined intraluminal pH-impedance studies revealed that PPI treatment decreases only the acidity of the refluxate, leaving unaltered reflux parameters (total number of reflux episodes, percentage of time with refluxed material in the esophagus and *proximal extent of reflux*) [128]. This could explain why—like in adults [129]—PPIs, although being superior to H_2RAs, appear to be less effective in treatment of extra-esophageal manifestations of GERD [130].

GERD is a chronic, relapsing disease. There is evidence that the symptomatic manifestation of reflux disease is different in infants (younger than age 1 year) compared with children and adolescents (1–17 years). Specifically, a large proportion of infants have regurgitation (due to volume reflux) that spontaneously resolves with age, whereas GERD in childhood appears to have a manifestation similar to that of GERD in adults, with symptoms persisting for many years [1]. Despite limited, available evidence suggests that some infants, children, and adolescents with GERD are more likely than those without GERD to have symptoms later in life [131].

Like in adults [132], both symptoms and mucosal lesions can recur in a substantial proportion of patients after stopping PPIs [133]. While data suggest that the clinical presentation of reflux esophagitis is similar in pediatric and adult GERD populations, it is difficult to determine the chronicity of reflux esophagitis in the pediatric population. However, some studies indicate that GERD may be more persistent in children with comorbidities such as neurological impairment, repaired esophageal atresia, or tracheoesophageal fistula [133]. Therefore, in selected children, a long-term therapy should be planned, as it is the case for adult patients with GERD [53]. There are basically three different long-term approaches for GERD treatment with PPIs: continuous (i.e., every day), intermittent (i.e., cycles of daily PPI administration), or on-demand (i.e., symptom-driven) therapy, each selected on the basis of patients' clinical characteristics [53]. Both the half-dose or full dose PPI could be tried, this latter being more effective. However, if relapse does occur with the lower dose, the original healing dose can be used [133]. Whatever the regimen adopted, current guidelines [4] recommend the regular assessment of the ongoing need of long-term, acid suppression therapy.

Overuse and Misuse of Antisecretory Therapy

During the last three decades, prescription (often inappropriate) of antisecretory drugs (especially PPIs) has increased markedly in both adult [53] and pediatric [134–136] patients (Fig. 22.5). Their use, however, does not seem to be commensurate with the prevalence of GERD in children [136]. This is due to their good efficacy not only in GERD but also in other acid-related diseases, like peptic ulcer and *Helicobacter pylori* infection [122, 123]. However, although not being recommended in neonates and infants, PPI prescription has dramatically expanded in this patient population, despite a clear statement of guidelines [4, 6]. With rare exceptions [137], inappropriate and off-label use of PPIs has been reported in several countries [138, 139]. A European survey [140], performed in 2014, has shown that the majority of pediatricians were unaware of the 2009 ESPGHAN-NASPGHAN reflux guidelines and often prescribed PPIs despite a lack of efficacy for the symptoms being treated. However, the overall rate of children managed in full compliance with the guidelines significantly increased after training (to 46.1% compared with 1.8% before) [141]. The proportion of European pediatricians complying with guidelines overlapped that of Italian practitioners and was remarkably low (1.8% versus 2.0%) [142].

Inappropriate prescription of anti-reflux medications at the time of discharge seems to be common for extremely low birth weight infants [143] and these medications are usually continued by primary care pediatricians. The general practitioners' attitude to continuing or discontinuing PPIs depends on their level of knowledge and their perceptions of hospital physicians' competence as well as the threshold to prescribing in hospitals [144].

There are two main concerns pertaining to PPI overuse and misuse: drug expenditure, which has risen dramatically in recent years, even after the introduction of

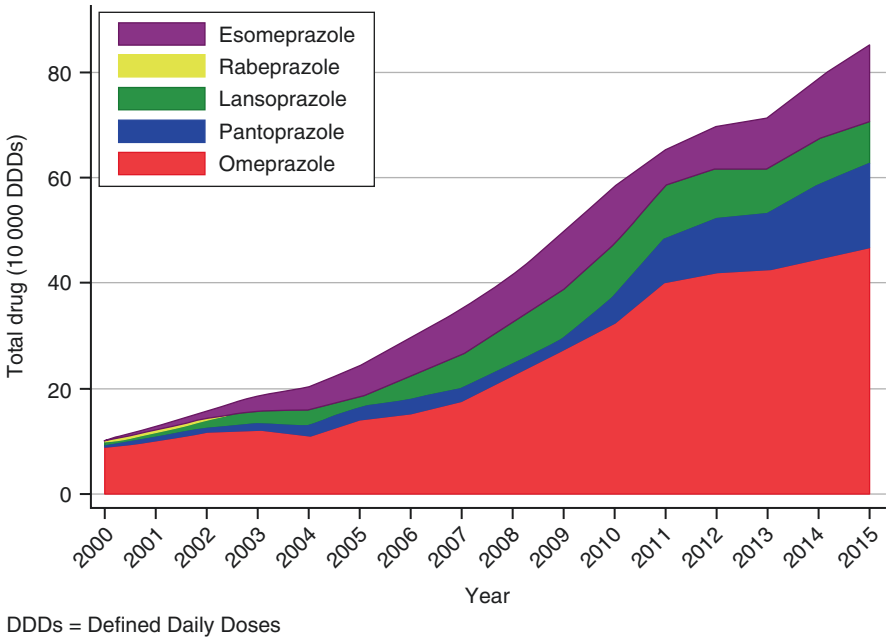


Fig. 22.5 Use of proton pump inhibitors among Danish children: total yearly amount (in DDDs) during a 16 year nationwide study (from Aznar-Lou et al. [133])

cheaper generic formulations [145], and growing safety concerns [146–148]. Despite their pharmacologic selectivity [100], also PPIs have a "dark side" [149]. Sir William Osler once famously commented that *no drug has a single effect* and these secondary actions range from mildly inconvenient to frankly dangerous [150]. PPIs are no exception.

Although PPIs represent one of the safest drug classes available and have been used worldwide for almost 30 years, the number of publications concerning safety with PPIs has increased dramatically, with many widely publicized topics appearing in high-profile journals or the media. The methodological bias of adult studies, including many confounding studies and often the lack of biological plausibility, have been extensively discussed in some thoughtful reviews [151–153]. Much of the evidence, which associates PPI treatment with serious long-term conditions, is weak with very low OR [154, 155]. It is clear, however, that many of the reported adverse effects are also relevant to pediatrics [122, 123, 147, 148, 156], especially in the long-term. PPI use potentially affects gut microbiota composition and function [157] and decreases defense against pathogens resulting in an increased risk for infections [122]. They may also interfere with absorption of minerals and vitamins as well as the digestion of proteins leading to specific deficiencies, and increased risks of developing bone fractures, allergic diseases and eosinophilic esophagitis [122, 147]. The safety of PPIs and other acid-lowering drugs in children is extensively discussed in Chap. 23 of this book [158].

In clinical practice, it is important to balance the benefits of treatment with PPIs with their *purported* risks and review the indications for the choice of drug and dose and to explain this carefully to the children and/or parents [6, 53, 122, 159, 160].

Acid Suppression Drugs: What Is New?

Despite being quite effective in GERD, PPIs are still far from being the ideal antisecretory drugs. The major limitations of this class of drugs are [52, 160, 161]:

- They are acid-labile compounds. As a consequence, they need to be given as enteric-coated formulations.
- Their onset of action is slow, usually taking 3–5 days to reach the full antisecretory effect.
- Since they are metabolized in the liver mainly by cytochrome P450 2C19 (CYP2C19), drug-metabolizing enzyme for which a genetic polymorphism does exists, there are interindividual variations in pharmacokinetics and pharmacodynamics.
- The antisecretory effect is not sustained enough to cover the nighttime period and NAB is frequent and also seen with twice daily administration.

A number of new drugs are currently being investigated to provide a significant advance on current treatments [43]. Some of them (namely potassium-competitive acid blockers (P-CABs) and CCK_2-receptor antagonists) have already reached clinical testing, while some others (like the antigastrin vaccine, H_3-receptor ligands or gastrin-releasing peptide receptor antagonists) are still under development as antisecretory treatments. Of the current approaches to reduce acid secretion, P-CABs and CCK_2-receptor antagonists hold the greatest promise, with several compounds already in clinical trials and some already approved for clinical use. It is unlikely that CCK_2 antagonists will be used alone as antisecretory compounds but, rather, their combination with PPIs will be attempted with the aim of reducing the long-term consequences of hypergastrinemia [43].

The delivery technology of *dexlansoprazole* (the right-handed (R)-isomer of lansoprazole) modified-release (MR) formulation is designed to release the drug in two separate pH-dependent phases, the first in the proximal duodenum and the second in the more distal small intestine (Fig. 22.6). This dual-release formulation uses different types of granules with pH-dependent dissolution profiles that release dexlansoprazole at different times and over a longer period of time. Dexlansoprazole MR must therefore be administered at a higher daily dose than conventional delayed-release lansoprazole.

This extends plasma concentration and pharmacodynamic effects of dexlansoprazole MR beyond those of single-release PPIs and allows for dosing at any time of the day without regard to meals [162]. Dexlansoprazole MR has been shown to

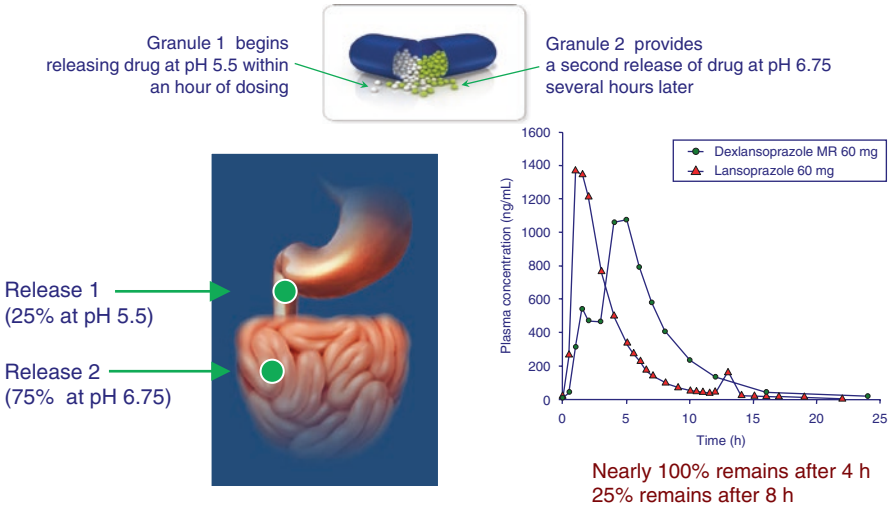


Fig. 22.6 Dual delayed-release technology, adopted in the dexlansoprazole MR formulation

be highly efficacious in healing erosive esophagitis in adult patients, maintaining healed esophageal mucosa and controlling symptoms of patients with endoscopy-negative reflux disease. Recent studies have also demonstrated that this drug is very effective in improving nocturnal heartburn, GERD-related sleep disturbances and bothersome regurgitation [163].

In June 2016, FDA approved this formulation and the SoluTab™ delayed-release orally disintegrated tablets of dexlansoprazole for patients aged 12–17 years with GERD on the basis of two multicenter trials in adolescents with erosive [164] or non-erosive [165] reflux disease. These studies showed that dexlansoprazole 60 mg once daily achieved healing of reflux esophagitis in 88% of patients at 8 weeks and—at half a dose—maintained them healed in 82% of patients at 24 weeks [164] while 30 mg of the drug once daily improved symptom (epigastric pain, acid regurgitation, and heartburn) severity in 73.8% of patients after 4-week treatment [165]. This drug is unfortunately not available in Europe.

A more innovative approach has been the development of the of H^+,K^+-ATPase reversible blockers, called *P-CABs* [166–168], which block the K^+ exchange channel of the proton pump (Fig. 22.3), resulting in a very fast, competitive, and long-lasting inhibition of acid secretion (Table 22.6) A P-CAB offers a more rapid elevation of intragastric pH than a PPI, while maintaining the same degree of antisecretory effect, the duration of which is dependent on the half-life and can be prolonged by extended release formulations (Fig. 22.7).

Vonoprazan (TAK-438) is a novel and potent orally active P-CAB, developed by Takeda and marketed in Japan since 2015 [169]. This compound is a pyrrole derivative, displaying powerful inhibition of the proton pump compared to PPIs and represent the first-in-class drug [170].

Table 22.6 Potassium-competitive acid blockers and proton pump inhibitors: main differences in the mechanism of action

P-CABs	PPIs
Act directly (after protonation) on the H^+,K^+-ATPase enzyme	Require transformation to the active form, sulphenamide
Super-concentrate in parietal cell acid space (100,000-fold higher than in plasma)	Concentrate in parietal cell acid space (1000-fold higher than in plasma)
P-CABs bind competitively to the K+ binding site of to H^+,K^+-ATPase	Sulphenamide binds covalently to H^+,K^+-ATPase
Binding to both active and inactive forms of the proton pump	Binding only to active forms of the proton pump
Reversible binding to the proton pump	Irreversible binding to the proton pump
Duration of effect related to half-life of drug in plasma	Duration of effect related to half-life of the sulphenamide-enzyme complex
Full effect from the first dose	Full effect after repeated doses
Meal-independent antisecretory activity	Meal-dependent antisecretory activity
PK not affected by genetic polymorphism	PK affected by genetic polymorphism

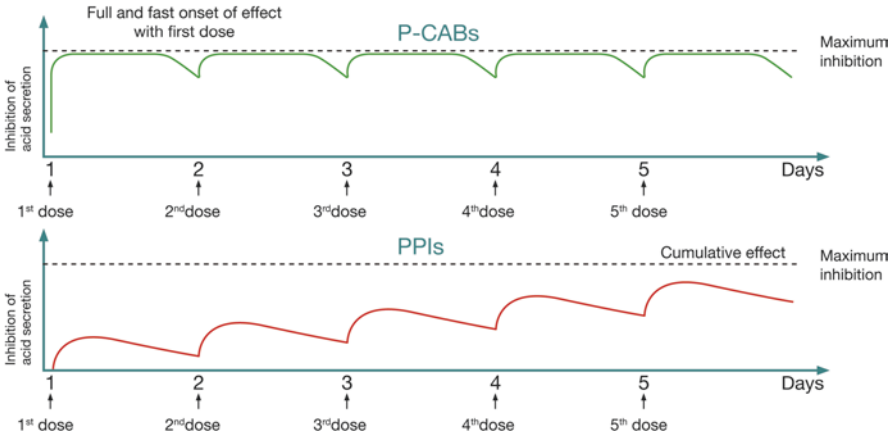


Fig. 22.7 Time course of acid inhibition by potassium channel acid blockers and proton pump inhibitors: *computer simulation*

Vonoprazan has been in clinical use for almost 6 years now and considerable clinical data are available, detailed in extensive reviews [169, 171–176]. Its peculiar pharmacological properties can be summarized as follows [172, 174]:

- Conversely from PPIs, which are acid-labile compounds, vonoprazan is stable in the acidic gastric environment.
- The drug displays good solubility both in acidic and neutral conditions.
- Vonoprazan exerts a pH-independent and direct inhibitory activity on H^+/K^+-ATPase, without need to conversion into an active form.

- Its dissociation rate from the proton pump is slow and its retention time in the gastric mucosa long (24 h or more).
- As a consequence, vonoprazan acid inhibitory activity is prolonged.

Another P-CAB, tegoprazan (formerly RQ-00000004 or CJ-12420), which is a benzimidazole derivative, has been approved in South Korea in 2018 [177] and other compounds (namely fexuprazan and linaprazan glurate) are under active development.

Several studies in adult patients with GERD have shown that this new class of drugs, not yet approved by FDA or EMA, achieves rapid, potent and prolonged acid suppression and offers the chance of addressing many of the unmet clinical needs in GERD, such as the need for fast and assured healing of severe reflux esophagitis (grade C and D according to the Los Angeles classification) and achieving rapid heartburn relief, where P-CABs are clearly superior to the currently available PPIs [178, 179]. Unfortunately, although vonoprazan-based *H. pylori* eradication regimes have already been employed in children [180–182], data on P-CAB efficacy in the treatment of pediatric GERD are not yet available, but these drugs will surely represent a useful addition to the pediatricians' armamentarium against this challenging disease.

Conclusions

The management GERD both in adults and children is still challenging, even in the third millennium [183]. The very fact that so many pharmacologic approaches (acid-lowering drugs, mucosal protective compounds, prokinetics, reflux inhibitors) have been adopted is evidence that no single drug class serves to control all the clinical manifestations of reflux disease. And indeed, there are still unmet therapeutic needs [178, 184] to address which several new compounds are under active development [183].

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Anti-Acid Drugs: Adverse Effects

23

Elvira Ingrid Levy, Sebastien Kindt, Melina Simon, and Yvan Vandenplas

Abstract

Acid-blocking drugs are more frequently prescribed by health care providers than before. This can be due to parents asking actively for these drugs, the health care system and/or confusion of health care providers about the guidelines. The effects, positive and adverse, of acid-blocking drugs have been insufficiently studied in the pediatric population. Most studies included a small number of children and considered a short follow-up, which makes it difficult to report on adverse events. Not all studies conducted report adverse events. H2-receptor antagonists have been withdrawn in the majority of the market. Alginates and proton pump inhibitors are widely available and prescribed. New drugs such as potassium-competitive acid blockers have and are being studied in children. The (severe) adverse events of acid-blocking drugs reported in pediatric studies in the short and long term highlight the need to weigh potential benefits against potential harm. Proton pump inhibitors should only be used after an appropriate diagnosis of erosive esophagitis or for a short period if objective diagnosis of acid-related GERD is not possible.

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Acid-blocking drug · Alginate · Proton pump inhibitor · H2 receptor antagonist
Potassium-competitive acid blocker · Adverse event · Infant · Child

Introduction

As mentioned earlier in this book, the definition of gastro-esophageal reflux disease (GERD) ("when GER leads to troublesome symptoms and/or complications") is especially in infants and young children open for subjective interpretation [1, 2]. Desperate parents often put pressure on health care providers to prescribe medication [3].

Acid-reducing GER(D) pharmacological treatment can be separated into two groups of medications: *antacids* and *acid-suppressive drugs*. When to use these drug options is not always in accordance or agreement with the guidelines [3, 4]. An example is the use of proton pump inhibitors (PPI) in infants and children: while the NICE ("National Institute for Health and Care Excellence" in the United Kingdom) guidelines [4] advise a diagnostic trial of 4 weeks, the NASPGHAN/ESPGHAN guidelines [3] advice a trial only in older children. These differences add to the uncertainty of health care providers to make the right treatment choices. In this chapter, we explore the safety of acid-reducing therapies [3, 4].

Antacids

Magnesium Hydroxide and Aluminum Hydroxide

These drugs are available under different brand names and are not recommended under the age of 2 years. These types of antacids contain high levels of aluminum which might be toxic for infants and young children, especially in case of an existing renal disease [5, 6]. High levels of aluminum can result in encephalopathy, anemia, and osteomalacia [5]. As a consequence, no guideline recommends this type of medication for GERD of GERD-like symptoms in infants and young children [3, 4].

Sodium and/or Magnesium Alginates

A frequently used antacid, which is composed of a brown seaweed-derived polysaccharide, makes up this drug class. It goes under the name Gaviscon Infant®, Gaviscon Nourrisson®, and Gaviscon® and does not contain aluminum [7–9]. Importantly, despite the name Gaviscon infant® and Nourrisson® suggesting the same drug but in a different language, they differ in composition. Both contain sodium alginate but Gaviscon Infant® contains also magnesium alginate [10]. The Gaviscon® and

Gaviscon Nourrisson® contain sodium bicarbonate [11]. This difference is important because of the different modes of action, including the dose and the time of administration [10, 11]. The Gaviscon Infant® should be given with meals because at the pH of the stomach the alginate gels and interacts with milk proteins and calcium ions to form softs curds, thereby thickening the stomach contents [12] and impeding reflux [10]. On the other hand, the Gaviscon Nourrisson® should not be given mixed with milk or food. The reaction between sodium bicarbonate and gastric acidic releases carbon dioxide bubbles, which become trapped in the gel, causing it to rise and float above the gastric contents, creating a physical barrier to reflux [11]. Both products have been evaluated for efficacy and safety over the years. Due to the heterogeneity of both studies [13, 14], a meta-analysis could not be performed. A Cochrane review concluded for moderate evidence for Gaviscon Infant® in infants with GERD [15]. Two papers on Gaviscon infant® showed a significant reduction in regurgitation (3.5 episodes per day) [16]) or vomiting [16, 17]. Studies evaluating Gaviscon Nourrisson® also showed a significant reduction of reflux episodes [18–20] and vomiting [20]. The NICE guideline recommends alginates for a one to 2 weeks trial for infants presenting with frequent GER symptoms [4]. However, the NASPGHAN/ESPGHAN guideline suggests not to use alginates in infants or children for prolonged periods [3].

No severe adverse events have been reported with Gaviscon Infant [13, 14, 18, 21, 22]. However, in infants adverse events such as teething syndrome, nausea, and vomiting, diarrhea as well as constipation, colic, fever, and acute nasopharyngitis are reported but not more frequent as compared to placebo [13]. With Gaviscon Nourrisson hypersensitivity and some gastrointestinal disorders, allergic manifestations like urticaria, bronchospasm, and anaphylactoid reactions have been reported [11]. Gaviscon Infant® nor Gaviscon Nourrisson® should be combined with Anti-Regurgitation formula because of the associated risk of intestinal obstruction [11, 23, 24]. The high content of sodium in both alginates needs careful consideration, especially in preterm infants, or infants suffering from renal impairment, congestive cardiac failure, and/or in case of diarrhea and vomiting with a risk of dehydration [10, 11, 22, 23]. Sodium alginates have been associated with bezoar formation [25]. Impact on nutrient absorption has not been reported for Gaviscon Infant® [26]. No study evaluated long-term consequences.

To the best of our knowledge, no papers evaluated on short- and long-term adverse effects of Gaviscon® in children.

In Summary Aluminum-free, sodium-containing alginates are associated with short-term symptom relief. No severe adverse events were reported in presumed healthy infants. However, in (young) children no studies have been conducted yet. Although safety issues have been insufficiently evaluated, the many years of experience with alginates allow to hypothesize that their short-term administration during a couple of weeks is likely to be devoid of a significant risk of severe adverse events in infants and (young) children.

Acid Suppressive Drugs

In regurgitating infants in whom non-pharmacological treatments remained without success and who present also with other reflux-related symptoms such as crying and food refusal, the NICE guideline [4] recommends a trial with an H2 receptor antagonist (H2RA) or proton pump inhibitor(s) (PPI(s)) during 4 weeks [4, 27]. The NASPGHAN/ESPGHAN guideline are in favor of PPI in combination with positional and dietary treatment as the first choice in erosive esophagitis and non-erosive acid GERD [3].

In (young) children, the NICE guideline recommends a 4 week trial of PPI or H2RA in case of heartburn, retrosternal or epigastric pain [4]. The NASPGHAN/ESPGHAN guideline however favors a trial of 4–8 weeks, because some children may suffer from persistent symptoms due to inflammation after only 2–4 weeks of treatment and because the studies were not powered to analyze symptom resolution at interim time point [3].

Meanwhile, potassium-competitive acid blockers are appearing on the market.

H2-Receptor Antagonist

Alteration of the GI microbiome ranks as the most frequent and important adverse effect observed with H2RAs [28]. This drug class has been associated with necrotizing enterocolitis in preterm infants [29]. Gut microbiota alterations during early life are associated with obesity, with a stronger association with each 30 days period of administration [30].

Up to 2020, ranitidine was the most prescribed H2RA. Reported adverse effects such as abdominal pain, diarrhea/gastroenteritis, headache, somnolence, a higher incidence of pneumonia and gastroenteritis were more frequently observed when compared to placebo (12% vs. 2%, and 47% vs. 20%, respectively) [31, 32]. In adults, drug-related pancreatitis following ranitidine intake has been reported [33]. Importantly, ranitidine sirup has been withdrawn from the market in Europe and USA in April 2020 due to the presence of nitrosamines, a carcinogenic component. Further, the sirup contains alcohol at 7.5%, or 405 mg per 5 ml syrup. As a result, a child of 10 kg receiving the recommended dose of 10 mg/kg/day would ingest the equivalent of 6 ml of wine per day. Further, ranitidine tablets which were also available for children were also withdrawn due to the high content of nitrosamines.

Cimetidine is no longer used due to its interaction with cytochrome P450 leading to multiple drug interferences [34]. It has also been associated with drug-induced pancreatitis [35].

Nizatidine was studied in one RCT (n = 210) conducted on infants and (young) children to assess the tolerability and effectiveness, including adverse events [36]. In this study, worsening of sickle cell anemia was reported [36]. Common adverse events are fever, diarrhea, pharyngitis, cough or upper respiratory tract infections, vomiting, somnolence, and eczema. However, this study was conducted during a winter period [36]. Famotidine was evaluated in three pediatric studies [37–39].

One trial conducted in an infant population (only 35 patients included), showed no severe adverse events. But in 11 of the 35 children, 16 adverse events were reported: agitation or irritability (manifested as head-rubbing), somnolence, anorexia, headache, vomiting, hiccups, and candidiasis [39]. Two other studies [37, 38] were conducted with this H2RA in more selective pediatric populations. The first study ($n = 24$ patients) was conducted on infant and (young) children in the Intensive Care Unit and no (severe) adverse events were noticed [38]. However, the second study was conducted on (young) children with an autistic spectrum disorder. One of the nine patients developed increased head-tapping behavior [37] similar to the observation in the previously mentioned study [39]. In adults, H2RA has also been associated with central nervous system toxicity (confusion, memory impairment, headache, and vertigo), cardiovascular adverse effects (cardiac arrest, hypotension, bradycardia, and different arrythmias, mainly upon rapid intravenous administration) and hematologic abnormalities [40].

In summary: all pediatric H2RA studies included a small number of patients and the longest drug intake was only 12 weeks. Studies were designed mostly for the efficacy of the drug.

Proton Pomp Inhibitors

Many side effects have been attributed to PPIs. However, the level of evidence varies largely. Almost all existing evidence is derived from observational studies, mostly performed on the adult population. A larger number of cases, statistically higher significance of association, low heterogeneity between studies, and less risk of bias are important considerations when attributing side effects to PPI in these observational studies. In their meta-analysis, Veettil et al. provide an overview of possible associations with an assessment of the credibility of the evidence [41]. Convincing evidence exists for PPI use and increased risk of all-site fracture and chronic kidney injury in the elderly. Association of PPI use with increased C difficile infection and bacterial infection in chronic liver disease patients are backed by highly suggestive evidence, while evidence for other associations remained suggestive at best. Another meta-analysis also reports a dose relationship between end-stage renal disease and fundic gland polyps [42].

There exists some evidence of side effects specifically for the pediatric population. In children use of PPI has been associated with an increased risk of gastrointestinal and respiratory infection, vitamin B12 deficiency, hypomagnesemia, bone fractures, and rebound hyperacidity of cessation [43].

Most side effects of PPI are thought to derive from their impact on the gut flora. Similar to H2RA, PPIs modify the microbiome of mouth, gut, and lungs [44]. In the gut, after 4 week of PPI therapy, modification of the microbiome was observed in infants [45, 46] and (only study) after 12 weeks in (young) children [46]. This is probably due to decreasing gastric acid, consequently resulting in gastrointestinal dysbiosis, inducing small bowel bacterial overgrowth [46–49]. Small bowel bacterial overgrowth is associated with symptoms such as bloating, abdominal pain,

diarrhea, nutrient malabsorption, and weight loss/failure to thrive [32, 46, 48, 50]. These symptoms are similar to (some) of the GERD or GERD-like symptoms in infants. Also important to know is that, in infants and (young) children, PPIs are associated with adverse effects such as infectious gastroenteritis including (*Clostridioides* difficile infection), lower respiratory tract infections, asthma, an increased risk for bone fractures, micronutrient deficiencies, and obesity [40]. The carriage of *Clostridioides* difficile is high among neonates and infants (37% and 30%) due to contact with environments [51, 52]. This bacterium has a chance to grow more and faster due to the gut dysbiosis caused by PPIs. PPI was more than H2RA associated with *Clostridioides* difficile infection in infants (OR, 5.24; 95% CI, 1.13–24.4) and (young) children (OR, 9.33; 95% CI, 3.25–26.8) [53]. But it rarely causes symptoms before 2 years of age. This is due to a lack of cellular machinery to bind and process the toxins of the *Clostridioides* difficile [43].

Concerning lung infections, studies did show a significant association of pneumonia or lower respiratory tract infection with PPI use in infants [32, 54] and (young) children [32]. The study conducted on infants even showed a significant sixfold increase in lower respiratory tract infection, already after 4 weeks of intake [32]. A hypothesis to explain this adverse event is the existence of a lung-gut axis, which allows intestinal bacteria to enter the lungs due to micro-aspirations. Another explanation is that due to the dysbiosis in the gut, there is an alteration of the immune system, making children more susceptible to infections [55–57]. However, another study did not show an increased prevalence of infections [58]. Concerning developing asthma, two studies in infants and (young) children [59, 60] have shown an association with PPI use, but not for allergy [60, 61]. A retrospective study in infants and (young) children showed a 57% increased risk of developing asthma (HR = 1.57, 95% CI 1.49–1.66) [59]. The risk of developing asthma was higher among infants (HR = 1.83) compared to children (HR = 1.49), and the presence of atopic disease (HR = 1.60 vs 1.22, atopic versus non-atopic) [59].

In adults, micronutrient deficiencies for iron, vitamin B12, calcium, zinc, vitamin C, magnesium, beta-carotene, and fat levels were described in relation to PPI use [44]. In (young) children, 6 months of use of PPI could not be associated with iron deficiency [62]. A retrospective study has suggested that PPIs (single or combined with H2RAs) [63, 64] in infants and (young) children [64, 65] were associated with an increased fracture hazard during childhood [63–65]. A meta-analysis of six studies reporting the outcomes of more than 900,000 children and young adults, confirmed a significant pooled relative risk for fracture in children of 1.17 (1.1–1.25) [66]. The pathophysiological mechanism underlying the increased fracture risk remains uncertain [67]. Decreased gastrointestinal absorption of calcium seems insufficient an explanation.

In (young) children with pancreas deficiencies, like cystic fibrosis, PPI and pancreas enzyme supplementation decrease fecal fat from 13 g/day to 5.5 g/day [68]. The lipolytic enzyme activity increases when the pH is higher and may improve fat absorption. Also, conjugated and unconjugated bile becomes more soluble in an alkaline environment. Other micronutrient deficiencies have not been researched in the pediatric population.

Childhood obesity is associated with prolonged use of PPIs (hazard ratio 1.02; 95% CI 1.01–1.03) [30]. Every 30-day period of intake increases this risk, at least up to the age of 8 years [30].

Based on multiple reports and further substantiated by systematic reviews and meta-analyses in the adult population, it is accepted that prolonged PPI intake is associated with an increased risk of hypomagnesemia [69], requiring PPI cessation. Potential mechanisms are on the one hand the reduced absorption of magnesium by transient receptor potential melastatin cation channels TRPM6 and TRPM 7 and on the other hand the increased pH of the gastrointestinal tract preventing magnesium uptake [70].

Similarly, multiple observational studies reproduced the causal relationship between PPI with acute interstitial nephritis and acute kidney injury, suggesting at least a weak relationship [42]. An association of PPI use and chronic kidney injury has been demonstrated (adjusted HR 1.18) [67]. It is not entirely certain whether chronic kidney injury results from hypomagnesemia, progression of acute interstitial nephritis or from another pathophysiological pathway of kidney damage and endothelial dysfunction [71]. Data in children confirming this association are lacking.

Potassium-Competitive Acid Blockers

New drugs such as Vonoprazan, Revaprazan, Tegoprazan, and Fexuprazan are potassium-competitive acid blockers, which may overcome some of the PPI drawbacks and limitations such as 24–72 h needed before drug activity, instability in acidic conditions resulting in the need for enteric coating, influenced by cytochrome P450 polymorphisms and unsatisfactory eliminate of heartburn at night [72, 73]. However, owing to their recent introduction, data on the efficacy of potassium-competitive acid blockers for GERD in children are not yet available, nor are reports about adverse events. Only Vonoprazan has been recently researched in the pediatric population. Two Japanese studies [74, 75] in older children used Vonoprazan as part of the triple therapy for *Helicobacter pylori* eradication. The first study reported that 21% of subjects developed some adverse events, of whom seven required hospital treatment for rash and vomiting [74]. However, these adverse events can as well be caused by antibiotics as by acid-blocking medication. In the other study, no severe adverse events were reported [75], but 16/151 developed diarrhea and 2/151 abdominal pain. An altered microbiota composition was reported which normalized 3 months after stopping the drug [75].

In summary, acid-blocking drugs modify the microbiome and may induce adverse effects. Many studies are not randomized, not blinded trials, and only evaluate short-term treatment. Therefore, these drugs should only be used in established indications.

Conclusion

Alginates, PPIs, and potassium-competitive acid blockers are the acid-reducing drugs remaining on the market for the pediatric population, since most of the H2RAs have been withdrawn. Many and frequent adverse events have been reported, although no study had safety aspects as the primary endpoint. More evidence exist from adult literature. Disturbance of the microbiome is probably the most important adverse event, because dysbiosis at a young age is associated with short and long-term adverse effects. However, the increased risk of bone fracture and renal impairment needs consideration when prescribing PPI long-term for children.

Taking this into consideration, together with the fact that guidelines are not always advising the same treatment strategies and the fact that modern parents often demand quite actively for medication, it is difficult for health care providers to make correct management decisions. In our opinion, acid-blocking drugs should not be taken for granted, potential benefits should always be weighed against potential adverse effects.

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GER and Prokinetics

24

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Abstract

Prokinetic drugs have been widely employed in pediatric patients in order to reduce the symptoms of GERD. These agents seem to enhance lower esophageal sphincter (LES) tone, to improve esophageal clearance and gastric motility thus increasing the emptying of gastric contents.

Cisapride was probably the best-studied prokinetic agent in infants and children; however, it was taken off the market in the 2000s by the European and American authorities owing to its cardiac adverse effects. Other agents such as metoclopramide and domperidone have been evaluated, but a high incidence of side effects including drowsiness, restlessness, and extrapyramidal reactions has been reported. Bethanechol, a direct-acting cholinergic agonist, has been evaluated in a few studies and also has uncertain efficacy and a high incidence of adverse effects in children with GERD. Other prokinetic molecules, including mosapride, itopride, and prucalopride, have not been studied or have been insufficiently tested in children. Baclofen, used to treat patients with neurological impairment, is a γ-aminobutyric acid receptor agonist that was shown to be effective in reducing the number of transient lower esophageal sphincter relaxations (TLSERs) and acid GER as well as to accelerate gastric emptying. However, data on baclofen in pediatric GERD are very limited and the high incidence of adverse events does not support its use. Other agents acting on TLSERs such as arbaclofen and lesogaberan have been evaluated in adult patients, but studies in children are lacking.

Overall, although the prokinetic concept is attractive, no effective and safe drug is currently available. Furthermore, all agents may pose a risk of adverse effects that outweigh the benefits achieved with their use.

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Pharmacological therapy of GERD has primarily focused on the suppression of acid. However, it has been shown also that non-acid reflux may cause symptoms, such as regurgitation, cough, and heartburn [1].

Other therapeutic agents have been studied, in particular focusing on gastrointestinal motility and on transient lower esophageal sphincter relaxations (TLESRs). Considered to be the predominant mechanism of reflux in adults and children, TLESRs are defined as periods of simultaneous relaxation of the lower esophageal sphincter and crural diaphragm that are not induced by swallowing. Inappropriate TLESRs are elicited by stimulation of gastric mechanoreceptors of the subcardial region, mainly in the postprandial period [2].

Prokinetic agents have been widely employed in pediatric patients. These compounds have potential benefits for improving symptoms of GERD by enhancing lower esophageal sphincter (LES) tone, increasing esophageal motility, and gastric emptying. From the pathophysiological point of view, the use of prokinetics is the most rational therapeutic approach to treating GERD symptoms. These compounds act on different receptors, including 5-hydroxytryptamine 4 (5-HT4) receptor agonists, dopamine2 (D2) receptor antagonists, and motilin and ghrelin receptor agonists [3]. However, the use of these agents is associated with undesirable side effects and has not been recommended by current guidelines.

Metoclopramide

Metoclopramide blocks dopamine and serotonin receptors and has sympathomimetic activity increasing acetylcholine release from postganglionic nerve terminals. This agent acts by enhancing LES tone and improving gastric emptying [4, 5]. Due to its prokinetic properties, metoclopramide was widely used in the past as a treatment of GERD in infants and children, despite the lack of rigorous evidence approving its prescription [6].

A systematic review and meta-analysis of metoclopramide use in infants concluded that there may be some benefits when compared to placebo [7]. However, the usage of metoclopramide might cause adverse effects, particularly, irritability, dystonic reactions, lethargy, oculogyric crisis, and, eventually, apnea [8–13]. A further review evaluating 12 studies, concluded that the current scientific evidence is insufficient to recommend the employment of metoclopramide in the treatment of GERD [6]. No other recent trials using metoclopramide for GERD treatment in children are available.

Bromopride

There are no controlled trials with this agent to support its use or prove its benefits, and bromopride is not mentioned in any pediatric guideline for GERD. As the neurological side effects of this drug are similar to those observed with the use of metoclopramide, it must not be recommended for the treatment of GERD [14].

Bethanechol

Bethanechol is a direct cholinergic agonist that has been shown to increase the lower esophageal sphincter tone. This agent has been evaluated in a few studies and also has uncertain efficacy and a high incidence of adverse effects in children with GERD [15–17].

Cisapride

Cisapride is the most largely investigated prokinetic agent and was widely used in the past. It is able to enhance the release of acetylcholine from the mesenteric plexus [18]. Nevertheless, this compound seems to act as a III class antiarrhythmic agent [18, 19]. The clinical efficacy of cisapride in reducing GER in preterm infants was demonstrated to decrease the reflux indexes and the number of GER episodes lasting more than 5 min, but not the total number of reflux episodes/24 h and the duration of the longest episode [20].

As the drug is metabolized via the cytochrome P 450 (CYP 450) system, which is not fully developed in preterm infants, the simultaneous use of other drugs inhibiting the CYP 450, such as azole antifungals and macrolides, may further reduce cisapride clearance resulting in an increased risk of toxicity [18, 20]. The relationship between the administration of cisapride in preterm infants and the prolongation of QTc interval was widely investigated. A prolongation of QTc interval in infants and children receiving cisapride was previously reported by other authors [21]. Abnormalities of repolarization were demonstrated in patients treated with cisapride, especially in infants with gestational age lower than 32 weeks and with intrauterine growth retardation [18, 22]. Thus, due to the possible cardiac toxicity of cisapride and the increased risk of potentially lethal cardiac arrhythmias or sudden death, cisapride was gradually withdrawn from the market, and it is no longer an approved therapy for GERD [23].

Furthermore, a Cochrane systematic review on cisapride carried out after its withdrawal concluded that there was no solid evidence that cisapride reduces GERD symptoms, also suggesting potential publication bias toward studies showing a positive effect of cisapride [24].

Domperidone

Since the withdrawal of cisapride, domperidone has become increasingly used. Domperidone is a peripheral dopamine dopamine-2 receptor antagonist, commonly used to treat regurgitation and vomiting. It is able to reduce postprandial reflux time and to enhance gastric motility and emptying [25]. Clinical trials assessing domperidone use in infants and children with GERD are limited and showed very little efficacy in the reduction of symptoms in both GER and GERD with poor evidence for its effectiveness [26–30]. The pediatric population is particularly susceptible to adverse effects, due to an immaturity of the nervous system and blood-brain barrier. Domperidone might occasionally provoke neurologic side effects, such as extrapyramidal symptoms, oculogyric crises, and hyperprolactinemia [31, 32]. One of the most common side effects is irritability and colic in infants, which may worsen the clinical symptoms and further confuse the pediatrician. Additionally, domperidone, such as cisapride, is metabolized via CYP 450; the immaturity of this system, or the concurrent administration of compounds that may inhibit its functionality, may lead to higher serum concentrations, consequently enhancing its toxicity. Recent studies have shown possible cardiac adverse effects of this drug including prolongation of QTc interval (>460 ms) and ventricular arrhythmia, reported to be comparable to those of cisapride [33–38]. High doses of domperidone are associated with an increased risk of sudden cardiac death [39]. Therefore, it is not possible to recommend the routine prescription of domperidone for the management of GER and GERD in infants and children.

Drugs Acting on Lower Esophageal Sphincter

Transient lower esophageal sphincter relaxations (TLESRs) are the predominant pathophysiological mechanisms underlying reflux events and are mediated by a vasovagal reflex stimulated by gastric distention [40–44]. Drugs that interact with these receptors may help to reduce GER through a peripheral action but unfortunately also may trigger central side effects. Baclofen is a γ-aminobutyric acid (GABA)-B receptor agonist that is often used to reduce spasticity in patients with neurological impairment. Baclofen was shown to accelerate gastric emptying and to reduce the number of TLSERs and acid GER [45]. A small trial in eight neurologically impaired children with GERD treated with baclofen for 1 week showed a reduction in the number of acid reflux episodes and in the frequency of emesis (in six children). Nevertheless, there was no reduction in esophageal acid exposure (reflux index) and there was an increase in esophageal clearance time (in four out of eight patients) [46]. There is only one randomized, placebo-controlled trial evaluating the efficacy of baclofen in children with refractory GERD. In this study, 30 children affected by resistant GERD were evaluated after a single dose of 0.5 mg/kg baclofen or placebo. Measurement of esophageal motility and pH during the 2 h test period showed a significant reduction of the incidence of TLESRs and a significant acceleration of gastric emptying [47]. No important adverse effect occurred during the first 48 h post treatment. A retrospective study of medical charts including 53

children with a mean age of 6.1 years with persistent GER symptoms treated with baclofen was carried out. Treatment with 0.5 mg/kg/day of baclofen in three divided doses showed a significant reduction in symptoms in 35 (66%) patients at their first follow-up evaluation and in 22 patients after 12 months, respectively. In the remaining 18 patients, however, baclofen was stopped because of either no response ($n = 15$) or adverse events ($n = 3$). A total of 27 patients continued treatment and were assessed for long-term response. Of those, 22 (81%) had a sustained response to baclofen at 12 months, whereas 5 (19%) lost response [48]. Presently, data on baclofen in pediatric GERD are very limited and the high incidence of adverse events precludes its routine use. Current guidelines from NASPGHAN and ESPGHAN suggest, based on expert opinion, that baclofen can be considered prior to surgery in children in whom other pharmacological treatments have failed [49].

Other agents such as arbaclofen placarbil and lesogaberan have been developed to overcome these limitations and have only been studied in adults. Studies with arbaclofen have failed to demonstrate significant efficacy when compared to placebo in reducing symptoms of GERD [50]. A randomized, placebo-controlled study evaluated the effectiveness of lesogaberan for GERD in 25 adult patients in the efficacy analysis and 27 in the safety analysis. The effect of lesogaberan on the mean number of reflux episodes was dose-dependent, and all doses significantly reduced the mean number of reflux episodes when compared to placebo [51]. These agents have not been studied in children.

Other prokinetic molecules such as mosapride, itopride, and prucalopride have not been evaluated for the treatment of GERD in infants in children.

The causes of refractory GERD are complex, and it has become apparent that acid suppression is not effective for all patients. Prokinetic medications have a potential role in the treatment of GERD in infants and children and may provide additional benefits in special groups. However, as the adverse effects of currently available prokinetic agents exceed the potential therapeutic benefits for the treatment of GERD, these compounds are not recommended by pediatric practice guidelines [49].

There is a need for continued research into the beneficial role of prokinetics and the further development of new pharmacological agents to provide viable options with therapeutic effectiveness and an acceptable safety profile.

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Adverse Effects of GER Medication Except Anti-Acid Drugs

25

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Abstract

The use of medication in gastro-esophageal reflux disease (GERD) in young children and infants is most of the time limited to anti-acid drugs. However sometimes prokinetics, erythromycin, baclofen, or bethanechol are prescribed. The literature about the safety of these drugs in infants and children is limited but it is important to keep in mind that most of the drugs can have serious adverse effects. There is a broad range of reported adverse effects from diarrhea, vomiting, and drowsiness to extrapyramidal symptoms and QT prolongation.

Especially neurologic and cardiac adverse events can be severe and they are not rare. Before starting drugs to treat GERD, it is important to weigh the benefits against the potential harm.

Keywords

Safety · Adverse events · Baclofen · Bethanechol · Prokinetic · Metoclopramide Domperidone · Cisapride · Infants · Children · GER

Introduction

Gastro-esophageal reflux disease (GERD) GER is worldwide diagnosed in infants and children with increasing frequency. Consequently, the number of infants exposed to treatment is increasing. When managing GERD with pharmacological treatment, pros and cons should always be considered. The most often used medications in GERD are anti-acid drugs. However, in some children prokinetics,

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erythromycin, baclofen, and bethanechol are prescribed as well. Literature about these drugs in infants and children is limited.

Before prescribing drugs it is always important to keep in mind the risk of adverse events of the treatment. In this chapter, we will discuss the safety and adverse effects of the drugs used in GERD other than acid-reducing medications.

Prokinetics

Metoclopramide

Metoclopramide is a dopamine antagonist as well as a mixed 5-HT3 antagonist and 5-HT4 agonist, with a combined antiemetic and prokinetic effect [1]. In 2013, the European Medicines Agency released a statement that the risk of neurological adverse events for metoclopramide outweighed the benefit when taken for a prolonged amount of time at a high dose [2]. It was advised not to use metoclopramide in children under 1 year and no longer than 5 days at a maximum dose of 0.5 mg/kg/day [2]. A similar warning had already been made by the Food and Drug Administration in 2009 [3]. Extrapyramidal symptoms (9%, 95% confidence interval [CI] 5–17), diarrhea (6%, 95% CI 4–9), and sedation (multiple-dose studies: 6%, 95% CI 3–12) are the most common side effects in the prospective studies included in a meta-analysis in children and infants but also irritability, gynaecomastie and gallacthorrhea were seen [4]. In the retrospective studies and case reports in this meta-analysis, eight cases of life-threatening adverse effects were reported due to dysrhythmia, respiratory distress/arrest, neuroleptic malignant syndrome and tardive dyskinesia [4]. Also in a study in infants hospitalized in the NICU laboratory abnormalities, especially hyperkalemia (11/1000 infants) en hypocalcemia (4.4/1000 infants), were frequent adverse events however it as only compared with infants using erythromycin and not with placebo or nothing [5]. Because of the relatively high risk of adverse events, especially extrapyramidal symptoms, and the overall risk of serious adverse events the benefits do not outweigh the risk [6]. Metoclopramide is not advised for the treatment of reflux in infants in the ESPHGAN and NASPGHAN guidelines [7].

Domperidone

Domperidone is, as metoclopramide, a dopamine antagonist. However, unlike metoclopramide, it has only minimal penetration through the blood–brain barrier and therefore it has less neurological effects such as extra pyramidal syndrome [8]. Domperidone was never marketed in the USA. In Europe, the Agency of Medicines and Health Products has withdrawn the domperidone suspension for children, recommending not to use domperidone in children <12 year of <35 kg and a warning for the use in adults [9]. The most concerning adverse effect of domperidone is prolongation of the QTc interval [10]. In studies in adults, there is evidence for an

increased risk of ventricular arrhythmias and sudden death with the oral use of domperidone [11, 12]. In infants and children, there are reports confirming QTc prolongation, although mostly asymptomatic [13–17]. A meta-analysis found that 4.1% of the 148 infants studied showed a QTv prolongation of more then 450 ms, none of the infants showed an arrhythmia [18].

Except for the cardiac adverse events, there are also a few reports of extrapyramidal side effects of domperidone in older children, suggesting that in some patients there is blood-brain barrier crossing [19, 20]. Also, less severe adverse effects such as dry mouth, headache, stomach cramps, and many more are reported by adult users but not confirmed in randomized controlled trials [21]. There is one case of an infant with gynecomastia and in adults galactorrhea is described after prolonged use of domperidone [22, 23].

Guidelines by NASPGHAN and ESPGHAN do not recommend the use of domperidone for GERD [7]. The evidence regarding the efficacy of domperidone for reflux symptoms is very low. Regarding the safety warnings because of the cardiac adverse effects, domperidone should not be used as a first-line treatment for GERD in infants.

Cisapride

Cisapride is able to enhance the release of acetylcholine from the mesenteric plexus, therefore decreasing GER. Cisapride seems to be an important antagonist of the rapid component of the delayed rectifier current of potassium in cardiac cells, thus acting as a III class antiarrhythmic drug which explains the side effects [24]. Cisapride was withdrawn from the market in 2002 in most countries after reports of prolongation of the QTc interval with a risk for sudden death [25]. Also in children there were cases reported of serious ventricular arrhythmias and sudden death under the use of cisapride [26]. However in a placebo-controlled trial in a small group of only 49 children with GERD, there was no pathological QTc prolongation, but a minimal change of 2 ms in QTc duration was observed [27]. A Cochrane review on the efficacy of cisapride found four trials reporting on adverse events. They reported no significant difference in adverse effects when comparing cisapride with placebo, however the odds ratio was 1.86 for adverse events in the patients using cisapride vs no treatment [28]. Data from the manufacturer in adults showed headache in 19% vs 17% in the placebo group, diarrhea in 14% vs 10% in the placebo group and abdominal pain in 10% vs 7% as the most prevalent adverse effects [29].

Erythromycin

Erythromycin is a macrolide antibiotic used for the treatment of a number of bacterial infections. This includes respiratory tract infections, skin infections, chlamydia infections, pelvic inflammatory disease, and syphilis [10]. Besides, erythromycin is also a motilin receptor agonist that contributes to gastric emptying and induces

phase III activity of the interdigestive migratory motor complex [10]. Phase III, which is the most characteristic phase of the migrating motor complex, is when the smooth muscle of the gastrointestinal tract rapidly contracts. In phase III, the pylorus remains open, allowing food to move from the stomach into the small intestine [30].

A large retrospective cohort study including more than 14,000 infants showed an increased risk of developing pyloric stenosis was noticed in infants who received erythromycin before the age of 2 weeks (relative risk = 10.51 95% CI 4.48, 24.66) [31].

According to another large retrospective analysis in 348 NICUs, the outcome of the infants exposed to ≥1 dose of erythromycin or metoclopramide, showed that 0.9% (14/1587) of the infants receiving erythromycin developed pyloric stenosis and 0.4% (77/19,200) of these receiving metoclopramide [5]. The incidence of pyloric stenosis in the overall population is also around 0.2–0.4% [9]. Also, electrolyte disorders like hyperkalemia (8.6/1000 infants) and hypocalcemia (5.4/1000 infants) were seen as adverse effects in infants hospitalized in the NICU; however, in this cohort study there was no placebo or control arm and there was only a comparison with infants using metoclopramide [5].

There are also a few case reports of severe arrhythmias associated with the use of erythromycin in neonates but only when administered intravenously [32]. In adults the risk of QTc prolongation and torsade des pointes is serious especially when used in combination with CYP3A4 inihibitory drugs [33]. The most frequent adverse events in adult patients using erythromycin were abdominal pain OR 3.16 (95% CI 1.14–8.75), nausea with an OR 1.58 (95% CI 1.23–2.04), diarrhea OR 1.36 (95% CI 0.94–1.98) [34].

Regarding the concern of developing resistance to the antibiotic by the microbiota, unnecessary use of antibiotics should be avoided because of potential later metabolic effects, thought to be due to perturbation of the host's microbiome [35]. Theoretical risks of prolonged antibiotic use, such as emergence of antibiotic resistance and abnormal intestinal microbiota, have not been fully evaluated [35]. Overall, neither low-dose regimes nor prophylactic trials have shown to be useful [36].

In summary, there is no evidence that erythromycin has a beneficial effect on reflux in infants or children. Therefore, the use of erythromycin in infants with GERD is not recommended as a first-line approach.

Bethanechol

Bethanechol stimulates muscarinic acetylcholine receptors peripherally at the neuromuscular junction of smooth muscle [10]. The effect of bethanechol is mainly due to increase of the lower esophageal sphincter pressure [10]. Normally bethanechol does not pass the blood–brain barrier. However, as with other peripherally acting medication such as domperidone, there are reports of neurologic side effects in children [37]. The serious side effects are due to the stimulation of muscarine

receptors in all organs. There is a risk for cardiac arrhythmias and sudden death, bronchospasm, diarrhea, extensive sweating and other symptoms. In adults the therapeutic range seems to be small and side effects are frequent [38].

Because of the potential high risk of adverse effects, the NASPGHAN and ESPGHAN guideline does not recommend bethanechol for the treatment GERD in infants [7].

Baclofen

Baclofen is a GABA agonist working as a centrally acting muscle relaxant [10]. A meta-analysis of randomized controlled trials about the use of baclofen in GERD showed an elevated risk for adverse events when comparing baclofen with placebo OR 1.62; 95% CI: 1.03–2.54; $P = 0.04$ [39]. Adverse effects reported are dyspeptic symptoms, drowsiness, dizziness, fatigue, and lowered threshold for seizures, headache, breathlessness and nasal pain [39, 40]. Because of the frequency of side effects, baclofen is not recommended for routine use but can be tried prior to surgery when other therapies have failed [7].

Conclusion

Prokinetic agents and bethanechol have a risk of serious adverse events and death, especially neurologic and cardiac adverse events are not rare. Therefore, prokinetics and bethanechol are not safe to use in infants and children. Erythromycin possibly increases the risk of pyloric stenosis however mostly in the first 2 weeks of life, also it is always important to keep in mind the antibiotic resistance when prescribing erythromycin. There has been no benefit of erythromycin in the treatment of GERD so its use is not advised as routine treatment. Baclofen has frequent side effects however very rarely serious adverse effects. It can be tried in children and infants with therapy-resistant GERD.

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GER and Hypnotherapy

26

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Abstract

During hypnosis, gastric functions, like motility and acid secretion, can be modulated. However, no randomized controlled studies have assessed the efficacy of hypnotherapy in pediatric patients with gastro-esophageal reflux (GER). Given the positive effects found in studies with patients with functional heartburn, non-cardiac chest pain, or duodenal ulcers, it seems reasonable to conduct hypnosis trials in patients with GER in the near future.

Keywords

Hypnotherapy · Hypnosis · Relaxation · Gastric functioning · Gastro-esophageal reflux

Introduction

Hypnotherapy (HT) has been investigated for more than 40 years as a treatment for gastrointestinal disorders. In the last two decades, the popularity of hypnotherapy has increased significantly among (pediatric) gastroenterologists. This has been caused by the numerous positive hypnotherapy trials in both adult and pediatric patients with irritable bowel syndrome (IBS), showing its effectiveness with an estimated number needed to treat between two and three (reviewed in [1]). Not only IBS patients may benefit from HT; its efficacy has also been shown in adult patients with functional dyspepsia and patients with non-cardiac chest pain [2, 3].

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Therefore, it seems reasonable to devote a chapter to hypnotherapy in this book. However, to date, no randomized controlled studies have assessed the efficacy of HT in patients with gastro-esophageal reflux (GER), let alone in pediatric patients with GER. A few preclinical studies have investigated whether hypnosis can influence gastric functions. Several clinical trials have shown the efficacy of HT in patients with signs and symptoms that can also be present in patients with GERD, like heartburn and the presence of ulcers. This chapter will discuss these studies as well as give possible directions for future research.

What Is Hypnosis?

Hypnosis first emerged as a treatment for medical conditions in the late 1700s, but it was not until more than 150 years later that the first clinical studies on hypnosis were performed. The British Medical Society recognized hypnosis as a legitimate medical tool in 1955 and was followed by the American Medical Association in 1958. Since then, many clinical studies have been performed demonstrating the effectiveness of hypnotherapy. Nonetheless, its use is still not widespread within conventional medicine, mainly because hypnosis has a negative perception among medical practitioners as well as many patients. Perpetuating misconceptions about hypnosis, due to popular stage hypnotherapists, may play a major role in this negative perception [4].

During hypnotherapy, a patient is introduced into a hypnotic trance and guided by a therapist to respond to suggestions for changes in subjective experience, alterations in perception, emotion, thought, or bodily functions. The hypnotic trance is defined as a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion [5]. The trance usually has several elements such as a feeling of ease or relaxation, absorbed attention, an absence of judging, and disorientation toward time and location.

Children are, in general, more hypnotizable than adults, especially before puberty, suggesting that hypnosis is more effective for them [6]. Hypnotherapy is usually applied to children 7 years and older, although simple hypnotic exercises, like storytelling with embedded hypnotic suggestions, can be done with children from 3 years onward. Children are often enthusiastic about hypnotic exercises, and side effects are infrequent, making HT a valuable therapeutic tool. An advantage of HT is that children can keep practicing self-hypnosis in the years after treatment by inducing the hypnotic trance themselves while repeating positive suggestions, for example, to improve sleep or self-confidence. Hypnotherapy has no absolute contraindications, although its use is not recommended for people with psychosis. For some time, depression was also considered a contraindication, but there is now ample evidence for the positive effects of hypnosis in children with GI disorders on their (feelings of) depression or anxiety [7, 8].

Hypnosis and Gastric Functioning

There is overwhelming experimental and clinical evidence that stress influences gastric functioning (summarized in [9]). Acute stress, stressful life events, and chronic psychological stress can affect the stomach's different functions, leading to an increase in gastric secretion, slowing of gastric emptying, and a decreased accommodation to food. This may result in functional gastric disorders like functional dyspepsia and gastro-esophageal reflux disease.

Hypnosis is a well-known relaxation technique, and it is not surprising that studies have been performed to investigate whether hypnosis can be used to improve gastric functioning. Klein and Spiegel demonstrated in highly hypnotizable subjects that hypnosis could both augment and inhibit gastric acid secretions, depending on the type of hypnotic suggestions [10]. In another study, stomach-oriented hypnosis appeared to be highly effective in shortening gastric emptying in dyspeptic patients. Gastric emptying time shortened from an average of 274 min to 150 min after only one hypnosis session of 90 min in which patients received suggestions of relaxation and improved gastric function [11]. These studies, however, lacked appropriate control conditions, and it was, therefore, unknown if these hypnotic effects on gastric functions were hypnosis-specific or simply unspecific effects of relaxation. In 2013, Enck et al. demonstrated in 60 healthy volunteers that imagining appetizing food with and without the induction of a hypnotic trance exhibited similar changes in electrogastric recording, suggesting that relaxation is the most important mechanism by which hypnotherapy can modulate gastric functions [12].

Hypnotherapy and Gastric Symptoms

Despite the demonstrated positive effects of hypnosis on gastric functioning, thereby showing its therapeutic potential, to date, no RCTs have been conducted on the effect of hypnotherapy in patients with GER. However, several hypnotherapy studies have been performed on patients with other upper GI diseases. In 1988, a controlled trial studied the additional effect of hypnotherapy in 30 patients with rapidly relapsing duodenal ulceration whose ulcers had been successfully treated with medication. The patients receiving a course of HT were significantly less likely to suffer ulcer relapse within 1 year than controls (53% vs. 100% relapse rate), suggesting that hypnotherapy may be a useful therapeutic adjunct in patients with duodenal ulcers [13]. In a second study by the same research group, 126 patients with functional dyspepsia were randomized to hypnotherapy, supportive therapy + placebo medication, or medical treatment for 16 weeks. The hypnotherapy group showed a significantly greater reduction in epigastric pain scores than both other groups at the end of treatment and at follow-up 40 weeks later. Also, appetite and early satiety improved significantly in the HT group compared to both control groups [3].

Two studies have looked at the effect of HT in patients with retrosternal pain. The first was a placebo-controlled trial in 28 patients with non-cardiac chest pain, which showed that gut-directed hypnotherapy according to the Manchester protocol resulted in significant pain reduction, decreased medication use, and improvement in well-being compared to the placebo group [4]. The second, a small pilot study, looked at the feasibility and acceptability of esophageal-directed hypnotherapy in nine patients with functional heartburn. Regardless of hypnotizability, there were consistent and significant changes in heartburn symptoms, visceral anxiety, and quality of life as well as a trend for improvement in catastrophizing [14].

Future Directions

In conclusion, several preclinical and clinical studies suggest a role for hypnotherapy in the treatment of patients with symptoms of GER. Despite limitations of low sample size in these studies and the inability to double-blind a trial of hypnosis, it seems reasonable to explore the role of hypnotherapy in patients with symptoms of GER, especially in those patients who are either non-responsive to medications or who would prefer a lifestyle intervention instead of medication.

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Alternative Medicine and Lifestyle Changes in GERD

27

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Abstract

Alternative medicine interventions to decrease gastro-esophageal reflux has been poorly studied. Therefore, no recommendations can be made. There is some evidence for an impact of lifestyle and over-weight, especially dietary habits, in children. The impact of positional treatment and dietary changes are not considered to be part of "alternative medicine" in infants since they have been well studied, making these interventions part of the recommended first-line approach. More research on the impact of alternative medicine interventions in adolescents is needed.

Keywords

Acupuncture · Dietary supplements · Gastro-esophageal reflux · Herbs · Massage Mind–body · Weight loss

Introduction

Gastrointestinal conditions such as gastro-esophageal reflux (disease) (GER(D)), are prevalent in the population and account for significant morbidity and health care costs [1]. Patients with gastrointestinal conditions use integrative medicine. There is growing evidence that integrative medicine approaches can improve symptoms and affect physiology and disease course [1]. Alcohol and tobacco use and/or exposure are lifestyle factors with a clear impact on GER. Eating habits (large volumes, rapid

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eating, insufficient chewing) and overweight as well as undernutrition are other relevant lifestyle factors [2]. Consumption of fewer meals with a large meal in the evening is associated with increased GERD symptoms [3].

The composition of the gastrointestinal (GI) microbiota has an impact on GI motility. Probiotics but also prebiotics do have an impact on GI motility and thus on GER. This aspect was discussed in Chap. 15.

Although massage therapy, complementary therapy (hypnotherapy, homeopathy, acupuncture, herbal medicine), are quite popular in some regions of the world and in some environments, hardly any study has been performed.

Weight Loss in Obesity

In children, obesity has been associated with a small increase in risk of GERD symptoms compared to non-obese children [4, 5]. About 40% of obese children and adolescents experience GERD symptoms [6]. Gastric emptying time was directly related to the narrow waist circumference of obese children with GERD and was significantly delayed in obese children with increased reflux events [6]. Both symptomatic and asymptomatic obese patients had a worse quality of life compared with non-obese healthy patients [6]. Children with GERD are characterized by a higher caloric intake and larger amounts of fat intake compared to a control group [7]. Low dietary fiber consumption is an additional factor associated with GERD in children with excessive weight and obesity [7]. Compared to non-erosive GERD, a higher intake of energy, protein, and total fat and lower polyunsaturated fats were revealed in patients with GERD with erosive esophagitis [7]. Data from Iran suggest that central obesity as determined by waist circumference and citrus fruit intake were independent factors associated with GERD [8]. Therefore, lifestyle modification might have a positive effect on the treatment of GERD in an urban population [6]. A review of lifestyle changes in adults with GERD concluded that only weight loss improved pH-metry profiles and symptoms [9].

In adults, studies of the effects of diet on heartburn and reflux symptoms have often yielded contradictory results, perhaps because different foods or nutrients exacerbate symptoms in different individuals [3, 10]. Foods that have been associated with increased GERD-related symptoms include: fat, fried, spicy foods, citrus, tomato-based products, and alliums (e.g., onion, garlic). Chocolate, peppermint, coffee, carbonated beverages, and alcohol can all decrease lower esophageal sphincter tone and may play a role. The incidence of GER was shown to increase in infants treated with caffeine because of apneas [11]. Elevating the head of the bed can help decrease symptoms [10]. The positioning of the infant has an impact on GER (Chap. 15).

Massage Therapy

The study by Neu et al. included 36 infants with GERD diagnosed with the I-GERQ-R questionnaire which were randomized to massage therapy or sham therapy including rocking and holding [12]. This study was limited by the selection of

the patients (by an online advertisement, thus selecting a population of parents "open" for this kind of intervention), its small size and short length of intervention (6 weeks), without follow-up after the intervention [12]. Both groups experienced an improvement in GERD symptoms, measured by I-GERQ-R scores. Nursing Child Assessment of Feeding Scale (NCAFS) scores were significantly lower than national norms. Small to moderately sized effects showed improvement in the massage group relative to the non-massage group for Sensitivity to Cues, Social-Emotional Growth Fostering, Cognitive Growth Fostering, and Clarity of Cues (Cohen d) and ranged from 0.24 to 0.56 [12]. Pretreatment salivary cortisol levels decreased significantly over time in the massage group while increasing in the non-massage group [13]. However, massage therapy administered by a professional therapist did not affect symptoms of GERD differently than a sham treatment, but it did decrease infant stress as measured by cortisol [13].

Acupuncture

There are no pediatric studies on this topic. Two studies from China suggest that acupuncture (4 points stimulated daily for 6 weeks with a 2–3 day break between each week of stimulation) significantly reduces acid and non-acid reflux and decreases GERD symptoms [14, 15]. The addition of acupuncture (10 sessions over 4 weeks) in individuals with ongoing GERD symptoms despite once daily proton pump inhibitor (PPI) therapy, was more effective than doubling the PPI dose [10]. Acupuncture was reported to be effective for have functional dyspepsia ii GERD patients, possibly through a centrally mediated mechanism [16].

Mind–Body Therapies

There are no pediatric studies on mind–body therapies. Anxiety and depression are known to increase reports of GERD symptoms, and patients who respond less well to PPI therapy are more likely to suffer from psychological distress [14]. Hypnotherapy, biofeedback, and muscle relaxation techniques improve GERD symptoms [14]. However, these studies have a small sample size [14]. After 4 weeks, diaphragmatic breathing exercises and relaxing music for patients with non-erosive GERD for 30 min daily decreased significantly esophageal acid exposure by esophageal manometry and improvements in quality of life [17]. There were no changes in the control group [12]. In the group still practicing at 9 months, PPI use was decreased [17].

Herbs and Dietary Supplements

Melatonin is synthesized in the GI tract and is an important gut motility signal. Two studies in adults suggest that melatonin may be equally or even more effective than omeprazole 20 mg in reducing GERD-related symptoms [10]. One study examined

3 mg of melatonin daily, and the other examined 6 mg of melatonin in combination with several vitamins and amino acids. The only side effect noted in the latter study was somnolence [10].

STW 5 (Iberogast) is a commercial formula that includes alcoholic extracts of nine botanicals: Iberis amara, Matricaria chamomilla, Carum carvi, Mentha piperita, Glycyrrhiza glabra, Melissa officinalis, Chelidonium majus, Silybum marianum, and Angelica archangelica [10]. In three studies of functional dyspepsia that included patients with GERD symptoms, those receiving STW 5 were more likely to have an improvement in symptoms than those receiving a placebo [10]. STW 5 was most effective for epigastric pain, retrosternal pain, and acid regurgitation [10]. STW-5 was shown to reduce abdominal pain in children with irritable bowel syndrome [18, 19]. The product has been sold in Germany for 40 years and has a good safety profile.

The powder extract of rikkunshito is a mixture of Atractylodis Lanceae Rhizoma, Ginseng Radix, Pinelliae Tuber, Hoelen, Zizyphi Fructus, Aurantii Nobilis Percarpium, Glycyrrhizae Radix, and Zingiberis Rhizoma [20]. Rikkunshito (TJ-43; Tsumura Co, Tokyo, Japan) was given in three divided doses before meals. Rikkunshito effectively reduced acid reflux, but not esophageal clearance, in patients with GERD [20].

Raft-forming agents include alginate, pectin, and carbenoxolone (a synthetic derivative of glycyrrhizin) and are discussed elsewhere in this book (Chap. 15). When these compounds come in contact with gastric acid, they form polymers and float to the surface of the stomach contents, providing a barrier that protects the esophagus from acid reflux. These agents lack major side effects and are useful in treating mild-to-moderate GERD.

Some adult patients take deglycyrhiziniated licorice, chamomile, slippery elm, marshmallow root, D-limonene, and/or betaine. These products are part of the herbal and naturopathic medicine traditions for GERD treatment, however, there are no rigorous studies evaluating their efficacy. It is important to note that herbs from the mint family (e.g., peppermint, spearmint) can reduce lower esophageal sphincter pressure and may exacerbate reflux [3, 10]. However, peppermint was reported to reduce abdominal pain in children with irritable bowel syndrome [19].

Summary

Dietary modification and weight loss in case of obesity can be of some benefit. There is some evidence for raft-forming agents and elevating the head of the bed for reducing GERD-related symptoms. It is uncertain whether the use of massage therapy reduces crying/distress or other signs and symptoms of GERD in infants based on the I-GERQ-R questionnaire. While there is a lack of evidence supporting nonpharmacologic interventions, some interventions (such as tobacco avoidance) are low to no cost and risk and may merit a trial before considering more costly or risky therapies. Acupuncture and Iberogast were shown to have some effects in adults. In adults, there is reasonable evidence to consider mind–body approaches (especially

if stress may be playing a role) and melatonin; however, no data are available in children. Massage therapy, complementary therapy (hypnotherapy, homeopathy, acupuncture, and herbal medicine) have not been adequately studied and therefore cannot be recommended.

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GERD and Endoscopic Therapeutic Approach

28

Shishu Sharma and Mike Thomson

Abstract

Gastro-esophageal reflux disease (GERD) is symptomatic reflux associated with sequelae. The aims of the treatment of GERD are to achieve relief of symptoms and prevent complications. The most frequently used medication to treat GERD are proton pump inhibitors (PPIs); however, recently, there has been an increase in the number of studies highlighting the adverse effects related to long-term use of PPIs. An anti-reflux procedure may be indicated in patients who fail to achieve control with medical therapy or become long-term dependent on anti-reflux treatments or when medications are not desirable. In recent years, laparoscopic fundoplication has become popular and, in general, has replaced the open Nissen fundoplication. Various endoscopic anti-reflux therapeutic techniques have been discussed in this chapter, primarily focusing on the delivery of radiofrequency energy (Stretta® system).

Keywords

Gastro-esophageal reflux disease · Pediatric · Stretta® · Endoscopy

Introduction

Gastro-esophageal reflux disease (GERD) is symptomatic reflux associated with sequelae. These include faltering growth, recurrent aspiration pneumonia, acute life-threatening events, chronic otitis media, chronic sinusitis, hematemesis,

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anemia, reflux esophagitis, esophageal stricture, and Barrett's esophagus [1–3]. The aims of the treatment of GERD are to achieve relief of symptoms and prevent complications.

A follow-up of 126 children with GERD in infancy showed that 55% were symptom-free by 10 months and 81% by 18 months of age [4]. However, those with frequent symptoms (>90 days) in the first 2 years of life are more likely to have symptoms by 9 years of age [1].

There is limited pediatric data regarding GERD disease burden having a socio-economic impact. Most of the data is extrapolated from the adult population. As per a US study, GERD was the most common diagnosis for patients presenting with gastrointestinal complaints in 2012, accounting for nine million outpatient visits [5]. Another study suggested that the treatment cost of GERD in 2004 was around $12 billion, with proton pump inhibitors (PPI) accounting for 2/3 of the treatment cost [6]. We also know that the use of PPIs for the treatment of GERD is ever-increasing [7]. However, recently, there has been an increase in the number of studies highlighting the adverse effects related to the long term use of PPIs: Vitamin B12 deficiency [8]; bone fractures [9]; low magnesium [10, 11]; enteric infection [12]; pneumonia [13–16] and increased cardiovascular risk [17].

Patients who fail to achieve control with medical therapy may have persistent, severe esophagitis or become long-term dependent on anti-reflux treatments [18], or in some situations medications are not desirable due to significant side effects. In such cases, an anti-reflux procedure may be indicated.

The principle of surgery in GERD is to form some kind of reconstruction of the anti-reflux barrier, although exactly how efficacy is achieved is not fully understood. Open Nissen's fundoplication has been the treatment of choice to date, but it is an invasive surgical procedure associated with frequent postoperative complications (up to 26–59%) including dysphagia, gas bloating, retching, vomiting, dumping syndrome, para-esophageal hernia, and recurrence of reflux (nearly 20%) particularly in neurologically impaired children [19–21]. In recent years, laparoscopic fundoplication has become popular [22] and, in general, has replaced the open Nissen's procedure, although superior efficacy and safety have yet to be demonstrated [23]. With the laparoscopic procedure, cosmesis is clearly superior, and in adult studies, complications appear less common, with good success rates. It could be argued, therefore, that there remains little or no place for open anti-reflux procedures in pediatrics.

Various endoscopic techniques have been devised and used for the treatment of pediatric GERD. These are described below.

Endoscopic Suturing Devices

Endoluminal gastroplication makes use of an EndoCinch® sewing machine attached to the endoscope (gastroscope) placing three pairs of stitches below the gastro-esophageal junction (GEJ) to create three internal plications of the stomach [24–26].

Plications may be applied either circumferentially or longitudinally dependent on operator preference. The authors have a preference for placing two plications circumferentially 1.5 cm below the GEJ and one 0.5 cm below the GEJ, which we believe may be anatomically superior to other formations (Figs. 28.1, 28.2, 28.3, and 28.4).

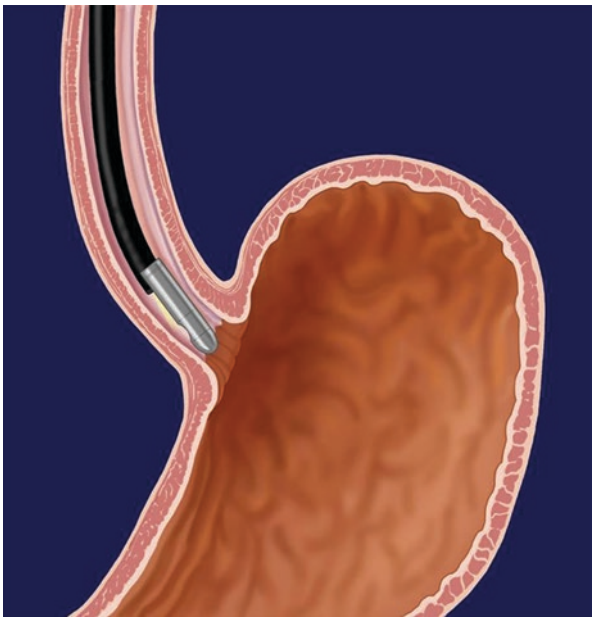

Fig. 28.1 EndoCinch—Front mounted on the endoscope. Reproduced from Digestive and Liver Disease Endoscopic treatment of gastro-esophageal reflux disease (GERD): a systematic review, with kind permission from Elsevier and Copyright Clearance Center. Licence number 5203660918539

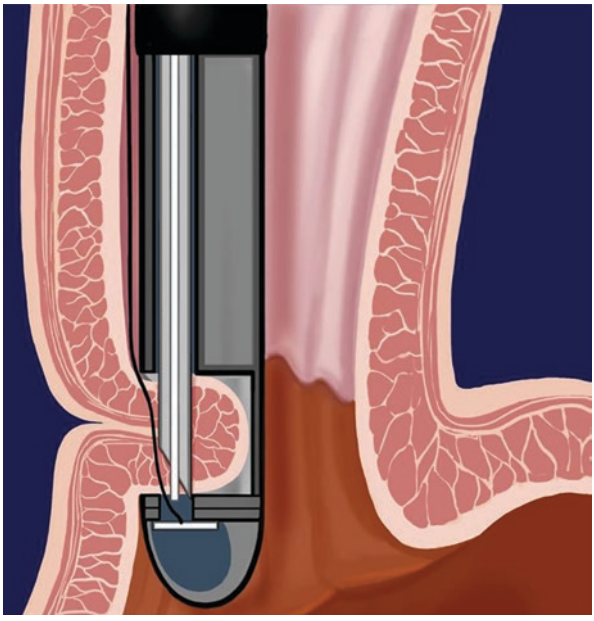

Fig. 28.2 Full-thickness tissue capture followed by needle and push wire placement of stitch. Reproduced from Digestive and Liver Disease Endoscopic treatment of gastro-esophageal reflux disease (GERD): a systematic review, with kind permission from Elsevier and Copyright Clearance Center. Licence number 5203660918539

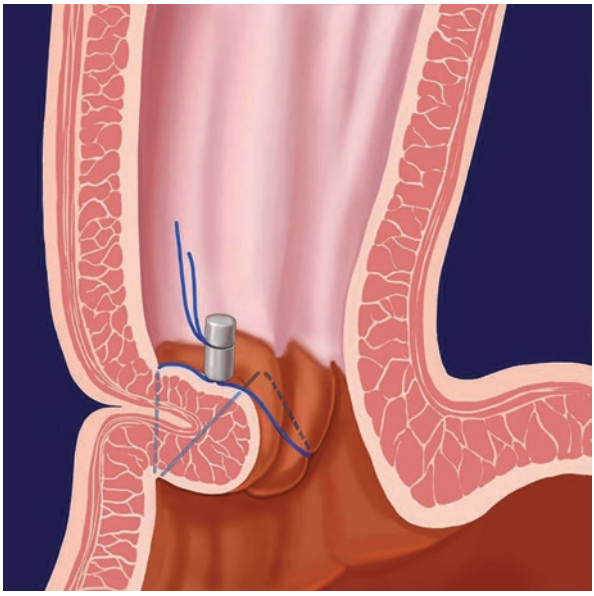

Fig. 28.3 Zig-zag stitch pattern of EndoCinch sewing machine. Reproduced from Digestive and Liver Disease Endoscopic treatment of gastro-esophageal reflux disease (GERD): a systematic review, with kind permission from Elsevier and Copyright Clearance Center. Licence number 5203660918539

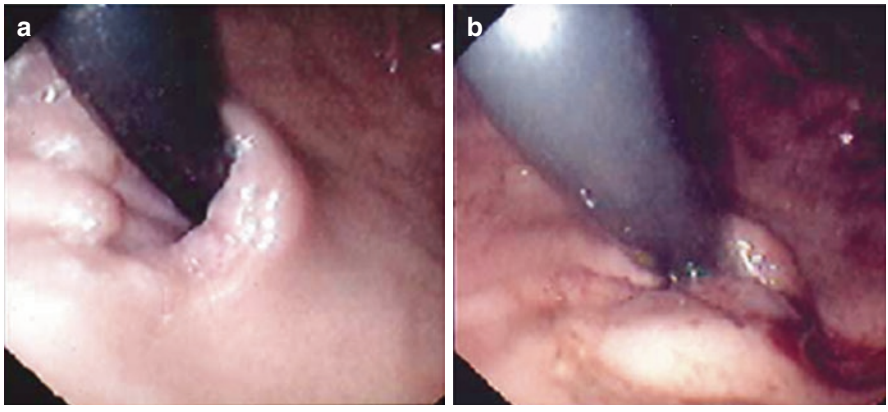

Fig. 28.4 (**a**) Pre EndoCinch fundal view of a patient with severe reflux disease and hiatus hernia. (**b**) Fundal view after EndoCinch stitch placement of the same patient

Endoluminal gastroplication is now routinely carried out as a day-case procedure in adults [27]. Preliminary studies have shown it to be quick, non-invasive, effective, and safe. Results are comparable to the laparoscopic fundoplication in adults, which has been studied as a preferable alternative choice to an open Nissen fundoplication [28].

The authors have used EndoCinch® in the treatment of 17 children (eight males, median age 12.9 years, range 6.1–17.7, median weight 45 kg, range 16.5–75) with

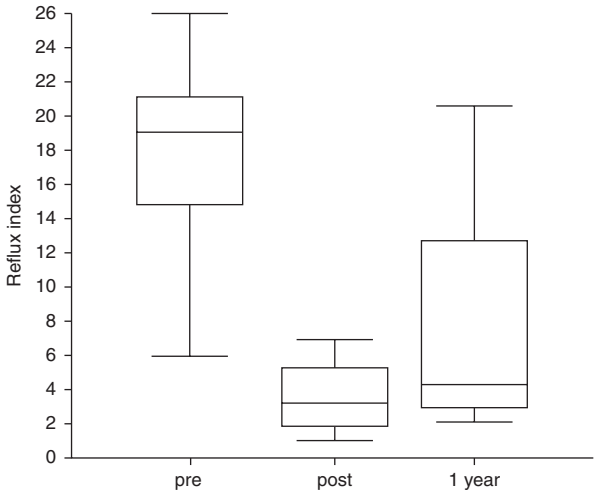

Fig. 28.5 Reduction in reflux index, 6 months and 12 months post EndoCinch procedure

GERD refractory to or dependent on (>12 months) proton pump inhibitors [29, 30]. All patients showed post-treatment improvement in symptom severity, frequency, and validated reflux-related quality of life scores ($p < 0.0001$) (Fig. 28.5).

At 36 months of median follow-up, 11 out of 17 patients were asymptomatic and no longer taking any anti-reflux medications.

At 12 months follow-up, all pH parameters improved and had returned to normal in eight of nine patients who underwent pH studies (reflux index fell from 16.6% [0.9–67%] to 2.5% [0.7–15.7%], $p < 0.0001$) (see Fig. 28.5).

The duration of action is open to ongoing assessment and debate and has not been particularly impressive in adult studies. The reasons for superior efficacy and duration in children may be conjectured and due to some or all of the following: three pairs versus two pairs of sutures; greater time and care taken by the operator allowed by general anesthetic with the added advantage of the absence of movement or retching during the procedure; and lastly the relatively deeper suture depth in the thinner pediatric esophagus compared to the thicker adult one.

Data are available indicating medium-term success in terms of reflux-related quality-of-life scoring at 1-year post EndoCinch® and in terms of avoidance of PPI in the majority of patients [31, 32].

Despite the loss of sutures in observational follow-up studies, some efficacy has been maintained, and the human and porcine endo-ultrasound studies of Liu et al. [33], along with cadaveric analysis of the porcine model post EndoCinch®, may throw some light on this observation. They suggest that the tissue remodeling is in response to the foreign body, which is the suture, resulting in significant hypertrophy of the circular muscle layer of the esophagus may be the reason. Nevertheless, EndoCinch® has not maintained its initial enthusiastic uptake [34] and has been recently superseded by the next generation of full-thickness gastroplication transoral endoscopic techniques.

Full Thickness Plicator®

The next technique to appear was the Full-Thickness Plicator® (Ndo-Surgical) [35]. This is placed under direct vision with a neonatal size endoscope passed through a specially designed endoscopic delivery system with an outer diameter of more than 20 mm. The retroflexion of both allows observation firstly of the opening of the jaws of the device, followed by the insertion of the corkscrew into the fundal tissue, allowing capture of the fundus and withdrawal into the jaws which are then closed. A pre-tied full-thickness plication is then applied by the mechanism of shutting the jaws and a serosa-to-serosa plication is made. A multi-center adult study has shown acceptable efficacy and a reduction of PPI requirement in a small adult cohort, but further study is necessary before this can be applied to children—the device is size and age constrained due to its large outer diameter.

EsophyX®

This device is an alternative to the plicator technology along a similar theme, although not identical. The novel Transoral Incisionless Fundoplication (TIF) procedure using EsophyX® (Texas Laparoscopic Consultants) mimics anti-reflux surgery in constructing an anterior partial fundoplication with tailored delivery of multiple fasteners during a single device insertion (Figs. 28.6 and 28.7). The TIF procedure was designed to restore the anti-reflux competency of the GEJ by reducing small hiatal hernias, increasing lower esophageal sphincter (LES) resting pressure, narrowing the cardia, and recreation of the acute angle of His [36].

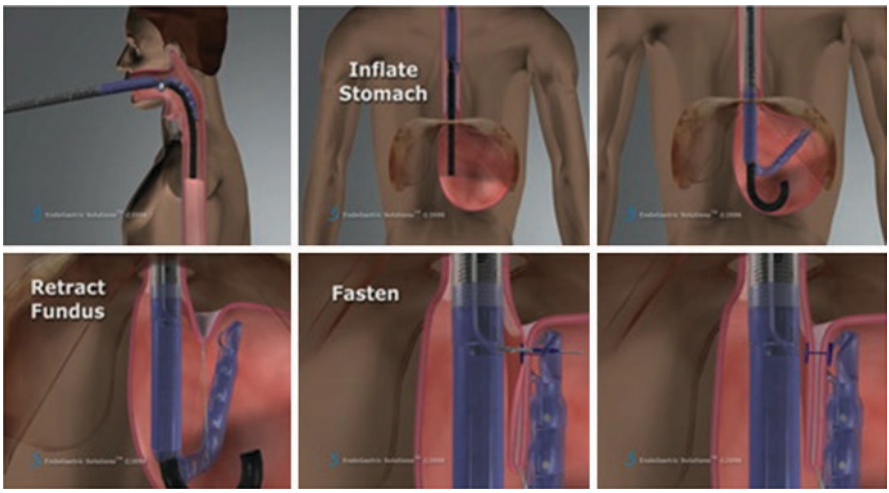

Fig. 28.6 Esophyx device—Mechanism of action

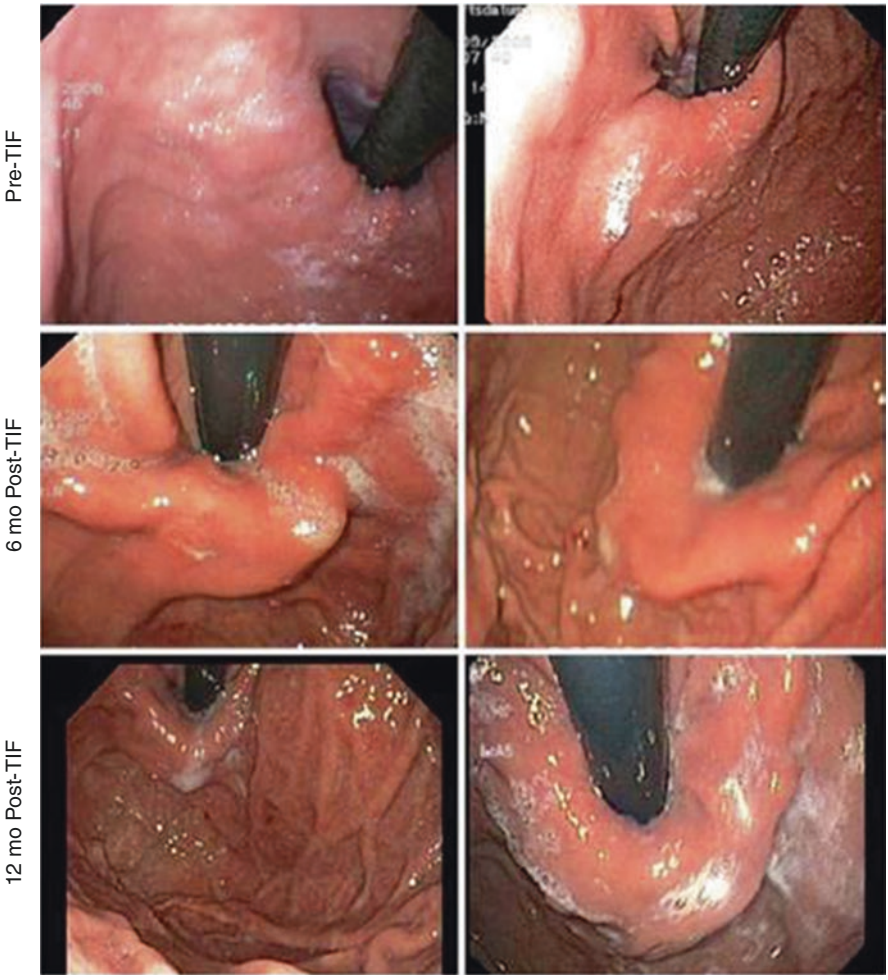

Fig. 28.7 Endoscopic images of gastro-esophageal valves from two subjects before and at six and 12 months following TIF.—Reproduced from Cadiere GB, Buset M, Muls V, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. World J Surg 2008, 32, 1676–1688, with kind permission from Springer Nature. Licence number 5203610461306

Clinical results with TIF at 1, 2, and 3 years support its efficacy in eliminating heartburn and regurgitation, reducing the daily use of PPIs, normalizing esophageal acid exposure, and reducing the proximal extent of refluxate [37]. Based on 1-year results, in September 2007 the FDA cleared EsophyX® for the treatment of GERD and small (<2 cm) hiatal hernia. The TIF procedure has been demonstrated to be safe in adults [38, 39]. Post-TIF adverse events are mild and transient and include musculoskeletal and epigastric pain, nausea, and dysphagia for up to one week

secondary to a sore throat. Only three esophageal perforations have been reported to date for 3000 cases performed worldwide. None of the subjects experienced chronic dysphagia, gas bloating, or diarrhea at long-term follow-up.

A feasibility pilot cohort in children as a service evaluation project was started in December 2008 after obtaining appropriate training in the use of the EsophyX® device in its second iteration—the so-called TIF2 procedure. This occurred with 12 children (eight male) with a median age of 12.25 years (range 8–18) years and a weight of 38.2 kg (range 26–91). The median duration of GERD symptoms was 45 months (range 24–70) and all were on GERD medication for more than 6 months. The median pre-TIF2 reflux index off treatment was 11.4% (range 6–48%). Hiatus hernia was present in 17% (2/12). Median operative time was 42 min (range 25–94). Adverse events were experienced by three children and consisted of mild or moderate pharyngeal irritation and epigastric pain. Two of the three also had retrosternal chest pain and were subsequently found to have pneumomediastinum on the CT chest but no leak on barium swallow. One of these two patients had pyrexia accompanying chest pain and was treated for possible mediastinitis and discharged home after 5 days of intravenous antibiotics. Subsequently, CO_2 insufflation was employed and more rapid absorption resulted in no further peri-procedure mediastinal gas leak.

At the 6-month follow-up, 10 patients had discontinued PPIs, 80% were asymptomatic and 70% had normalized or clinically significantly reduced reflux index (10% time pH <4).

Furthermore, the speed of the procedure, the days of hospitalization, the relative cost-efficacy, and cost–benefit are identified in Figs. 28.8, 28.9, and 28.10.

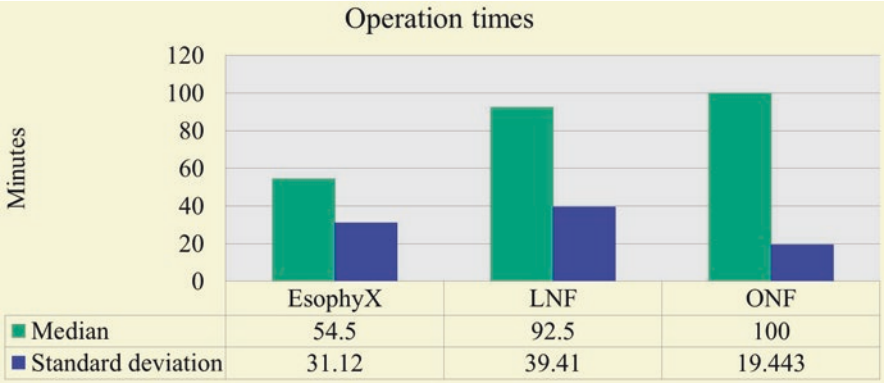

Fig. 28.8 Comparison of operating times for EsophyX, laparoscopic fundoplication, and open fundoplication

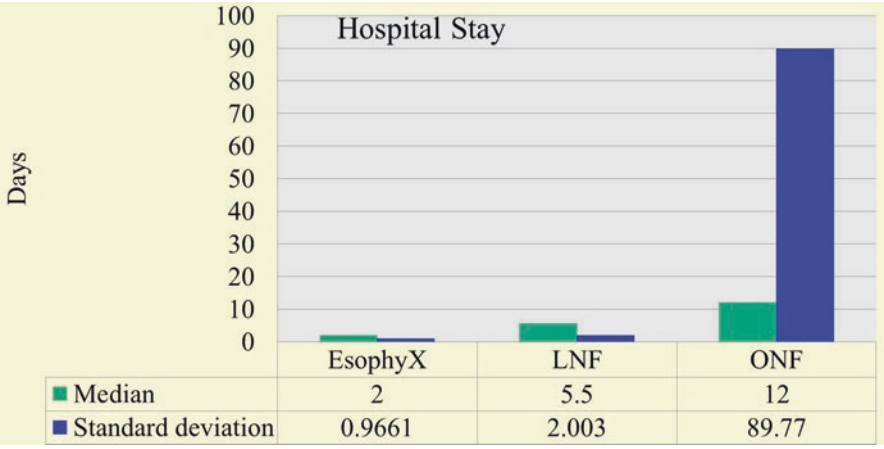

Fig. 28.9 Comparison of hospital stay (days) post-EsophyX, laparoscopic fundoplication, and open fundoplication

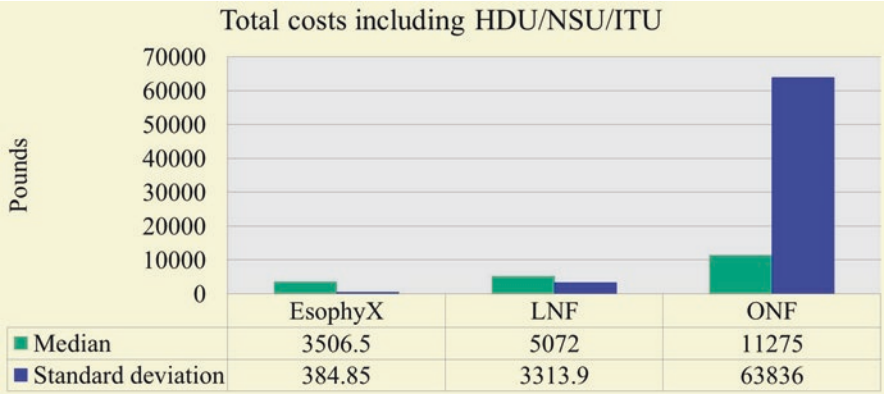

Fig. 28.10 Comparison of total cost (GBP) for EsophyX, laparoscopic fundoplication, and open fundoplication

Delivery of Radiofrequency Energy (Stretta® System)

The Stretta® procedure is an innovative alternative for simple, precise and safe delivery of radiofrequency energy to the LES muscle and gastric cardia [40–43]. This treatment has been shown to remodel tissue and improve the barrier function and motility of the LES, reducing the frequency and severity of reflux events [44]. The Stretta® system has two parts—a catheter and a control module. The Stretta®

Fig. 28.11 (**a**) Stretta catheter. Courtesy Restech. (**b**) Stretta radiofrequency generator. Courtesy Restech

catheter (Fig. 28.11a) is a flexible, hand-held, single patient-use device that delivers radiofrequency (RF) energy generated by the control module (Fig. 28.11b).

The procedure involves introducing a flexible tip guidewire along a gastroscope into the stomach, followed by passage of an inflatable balloon with surface electrode sheaths, over the guidewire. This balloon is then inflated to the diameter of the esophagus leading to the insertion of electrodes into the muscularis layer of LES and gastric cardia. The electrodes then deliver several cycles of radiofrequency energy to the muscular layers of the esophagus and GEJ (Fig. 28.12). As these lesions heal, tissue remodeling occurs (Fig. 28.13), this in turn leads to a reduction of reflux episodes and symptomatic improvement (Fig. 28.14a, b—demonstrating post-operative intraluminal view of the lower esophagus and gastric cardia respectively).

The Stretta® control module delivers this radiofrequency while, at the same time, providing feedback to the physician regarding treatment temperatures, tissue impedance values, elapsed time, catheter position measurement, and irrigation rate. This treatment has been used in adults since 1999. The Stretta® procedure is now widely documented by experimental studies and clinical trials, to be easily feasible and with a reasonable cost. Radio frequency (RF) energy delivery to the LES is considered safe and effective in adults [45]; it produces durable and significant improvement in GERD symptoms and quality of life, as well as reduces the use of anti-reflux medications, with very low morbidity. For those patients that might show only transient efficacy, Stretta® would act as an effective temporary "bridge" therapy between

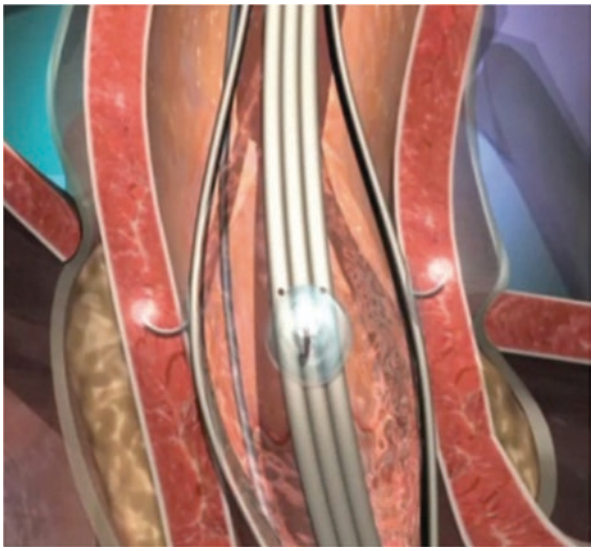

Fig. 28.12 Inflated Stretta balloon with radiofrequency delivered through needles in muscularis layer of GEJ. Courtesy Restech

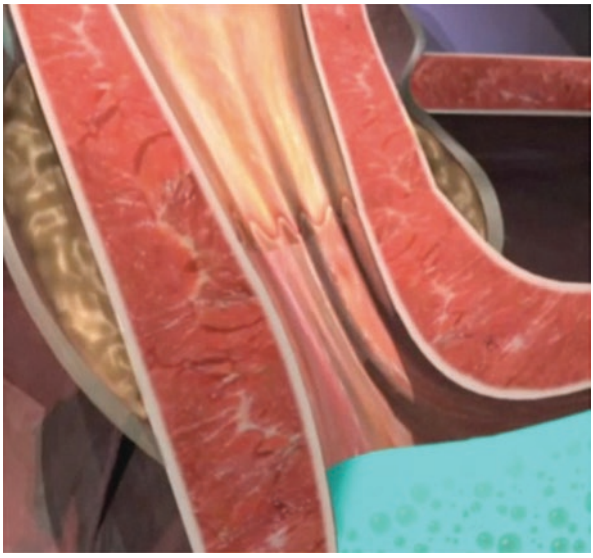

Fig. 28.13 Tissue remodeling after Stretta procedure resulting in thickened muscularis layer of GEJ. Courtesy Restech

medical and surgical treatment. Importantly, Stretta® does not preclude the opportunity to undergo surgery in the future, so all treatment options remain open for the patient.

Contraindications include: patients without a diagnosis of GERD; hiatal hernia >3 cm; very low LES pressure (LESP <5 mmHg); no response or change of symptoms with PPI use; achalasia or incomplete LES relaxation in response to swallow; and any type of permanent foreign body implant in or near the GEJ.

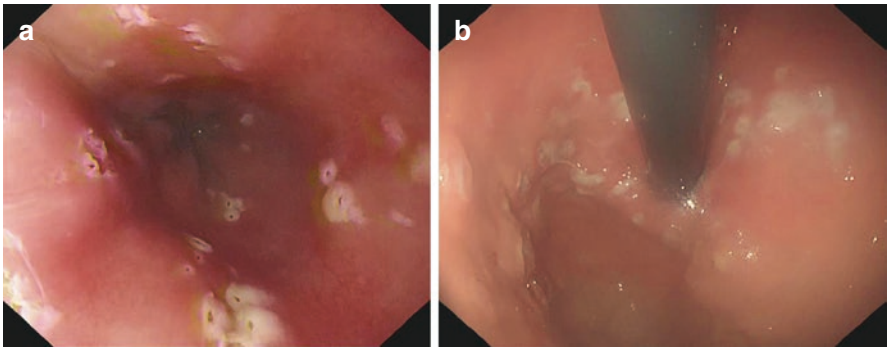

Fig. 28.14 (**a**) Post Stretta esophageal view. (**b**) Post Stretta fundal view

Complications are rare but among those reported are ulcerative esophagitis, esophageal perforation, gastroparesis, and a case of aspiration following the procedure. Short-term (1 year) success was reported in an open-label trial. In a prospective study (non-randomized controlled trial) of 75 patients (age 49 ± 14 years, 44% male, 56% female) undergoing laparoscopic fundoplication and 65 patients (age 46 ± 12 years, 42%, 58% female) using the Stretta® procedure—at 6 months 58% of Stretta® patients were off PPIs and an additional 31% had reduced their dose significantly. In comparison, 97% of laparoscopic fundoplication patients were off PPIs. With a long-term follow-up of the patients receiving the Stretta® treatment, beyond 2 years, 56% had discontinued use of all anti-secretory drugs.

This treatment has been reported in an uncontrolled study of eight children with a variable follow-up period of 5–15 months [46]. It was reported that six of eight children improved, and the cohort included three neurologically impaired children who also had concomitant PEG placement. One patient from this group had a post-procedure aspiration which was successfully treated. Of the two failures, one remained dependent on PPI and the other had a successful Nissen fundoplication.

Pediatric gastroenterologists may be guarded in using this form of treatment as clearly, using thermal energy treatment in a 70-year-old is different from using it in a child who may have unknown consequences in the long term. With the more recent and probably safer iterations of this technique, there are a number of studies occurring in pediatrics (including one conducted by the authors) and these may provide positive results in due course.

Gastro-esophageal Biopolymer Injection

In the Enteryx® (Boston Scientific) procedure, a liquid polymer is injected into the lower esophageal sphincter with a needle catheter via an endoscope. After the injection, the polymer solidifies into a sponge-like permanent implant. This improves the GEJ, by supporting and improving its elasticity and therefore reducing the degree of gastro-esophageal reflux (Fig. 28.15).

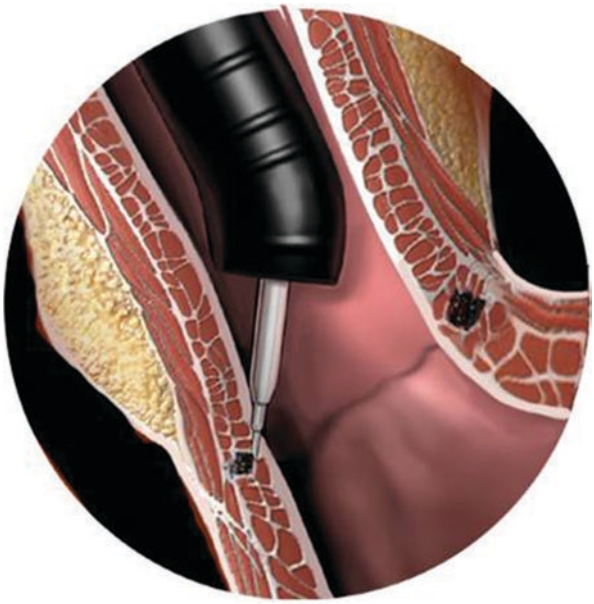

Fig. 28.15 Enteryx Procedure—Injection of the liquid polymer at an ante-grade angle in the muscles of GEJ at or below the squamocolumnar junction. Johnson, D.A. Enteryx implant for gastroesophageal reflux disease. Curr Treat Options Gastro 8, 51–57 (2005). https://doi.org/10.1007/s11938-005-0051-7 'With kind permission from Springer Nature. Licence number 5225300212986'

In an international open-label clinical trial on 144 patients, Cohen showed a greater than 50% reduction in PPI in 84% at the end of 1 year and 72% by 2 years, with elimination in 67% of patients [47]. In a prospective, randomized trial, endoluminal gastroplasty (EndoCinch®) was compared with Enteryx® in 51 consecutive patients dependent on PPI therapy. At 6 months, PPI therapy could be stopped or dosage was reduced by more than 50% in 20 of 26 (77%) EndoCinch®-treated patients and in 20 of 23 patients treated by Enteryx® (87%, $p = 0.365$).

Approximately 25% of the patients in both groups required retreatment in an attempt to achieve symptom control. To date, an estimated 3800 patients have been treated with the Enteryx® device, which was approved in 2003 by the FDA. To date, there are no published records of its use in pediatrics. However, the FDA and Boston Scientific notified healthcare professionals and patients about serious adverse events, including death, occurring in patients treated with the Enteryx® device. Based upon reports filed with the FDA, patients suffered leakage, swelling, and ulcers in the esophagus. One elderly patient died after some of the polymers had been injected into the woman's aorta, which ruptured, causing her to bleed to death.

On September 23, 2005, Boston Scientific ordered a recall of all Enteryx® Procedure Kits and Enteryx® Injector Single Packs from commercial distribution. The company's recall notice stated that some doctors accidentally punctured the wall of the esophagus while injecting the substance, causing adverse events. Additionally, Boston Scientific suspended sales of its Enteryx® device after more than two dozen reports of problems. The notice was posted on the company's website during the week of September 19, 2005.

Conclusion

The most promising results seem to accrue in the mid-term with the suturing devices which attain full-thickness plications, increase the intra-abdominal portion of the esophagus (most likely by plication tags inserting through the diaphragmatic crura as well as the full thickness of the esophageal wall, i.e., actual change in anatomy), and raised intra-sphincteric length and resting pressure. However, a more "physiological" approach seems to occur with the Stretta device promoting hypertrophy of the patient's own esophageal muscle layers around the GOJ, with very good mid to long-term results emerging.

Endo-ultrasound may provide a more controlled and sophisticated approach to this technology in the future.

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Surgical Options to Treat GERD

29

Antoine De Backer

Abstract

Severe gastroesophageal reflux disease is an invalidating illness that can be treated with dietary and postural measures and with medication (antacids, prokinetics, PPIs). Medication however can only modify the refluxate to become less aggressive for the esophageal mucosa, but can never really prevent the gastric content to reflux into the esophagus. Only surgery is able to prevent reflux to occur. These operations however carry a certain morbidity, and the results are not always perfect, especially in the neurologically disabled and in children with esophageal atresia or other congenital anomalies. Therefore, the indications for surgery must be strict. In this chapter, we discuss the work-up before surgery, the indications for surgery, complications, and outcomes.

Keywords

Gastroesophageal reflux · Surgery · Fundoplication · Nissen · Esophagogastric dissociation

Introduction

In infants and children, gastroesophageal reflux (GER) is a frequently encountered condition, which is known to resolve spontaneously in most patients by 1–2 years of age [1, 2]. The prevalence of GER is estimated at 10% of the population [3].

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Recently, a Japanese study showed a significant increase in erosive esophagitis [4]. In symptomatic cases, GER can be treated adequately with postural and dietary measures, antacids, prokinetics, H2-blocking agents, or proton pump inhibitors (PPIs) [1–3]. Only a small number of patients have reflux that is so severe, so massive or gives rise to such serious complications (e.g., erosive esophagitis with occult blood loss, failure to thrive, brief resolved unexplained events (BRUE) (formerly known under the term ALTE), asthma, repeated pulmonary infections) that surgery is needed to treat the condition. We then speak about gastroesophageal reflux disease (GERD), with a prevalence estimated between 1.8% and 8.2% [3]. A number of examinations are at our disposal. Each of them examines another facet of reflux. Upper GI radiography (UGIS) for the detection of reflux has a low yield [5], but in my opinion, is important for the surgeon to study the esophagogastric anatomy prior to surgery. Also, esophageal endoscopy is not a good examination to diagnose reflux, but it can demonstrate the consequences or reflux (esophagitis). 24-hour pH-metry or even better, multiple intraluminal impedance monitoring (pH-MII) is the most accurate test to diagnose GERD, or to distinguish between patients with GER and patients with GERD [5–7]. Esophageal manometry is not an examination used to detect reflux, but to study the motility of the esophagus which in turn is important when surgery is considered [8]. Scintigraphy to study GERD is less sensitive but may be used whenever delayed emptying of the stomach is suspected [9]. The latter two examinations are of interest whenever surgery is taken into consideration. Of course, the recommendations of NASPGHAN and of ESPGHAN will help in establishing a diagnosis, work-up, and treatment [10]. However, a diagnostic evaluation will not always be conclusive, and a lot of common sense is often needed to come to a sound judgment regarding whether or not surgery is indicated.

For a Successful Surgical Treatment, Three Conditions Need to be Fulfilled: Careful Selection of the Candidates for Surgery After a Complete Pre-Operative Work-Up, and a Technically Correct Operation

Preoperative Work-Up for Anti-reflux Surgery

A complete work-up is necessary before taking a patient to surgery. Are the symptoms of the patient likely to be caused by reflux? How is the anatomy of the GE junction? Is there any mucosal damage (esophagitis) present, and if yes, how severe is the esophagitis? Is the peristalsis of the esophagus normal? Is the stomach emptying normally? All these questions are important and need to be answered. A good *anamnesis* is therefore of paramount importance. Before considering surgery, an appropriate medical treatment must be conducted over a sufficiently long period of time. In the presence of pathological reflux on pH-metry and a good response to PPI, but recurrence whenever treatment is stopped, it is likely that surgical fundoplication will be successful. The situation where no response on PPI on the symptoms occurs (“refractory GERD”) should warrant caution, as this might mean that the symptoms could be caused by other illnesses, such as achalasia for instance. *A*

barium swallow (upper gastrointestinal series) helps in studying the anatomy. For surgeons, this somewhat old-fashioned exam is important, because it shows the anatomy of the esophagus, the esophagogastric junction, the stomach, and gastric emptying. Hiatal hernia is only rarely present in children that are presented for fundoplication. *Upper gastrointestinal endoscopy* is the most sensitive examination to detect whether or not esophageal mucosal damage (esophagitis) is present, as well as the severity of the esophagitis. *Esophageal manometry* provides useful information about the peristalsis of the esophagus. Finally, *ambulatory 24-hour pH-monitoring or pH-MII* is the gold standard for detecting the presence and severity of reflux (acid, non-acid or mixed), as is the association between reflux and symptoms.

Indications for Anti-Reflux: Surgery

GERD is a complex disease with multiple factors involved. As a consequence, there is not always an agreement on the indications for surgery. Nevertheless, there are a number of indications that are almost universally accepted.

1. *Children with anatomical alterations of the esophagogastric junction:*
   Patients with hiatal hernia, with part of the stomach intrathoracically, will benefit from surgical restoration of the hernia, repair of the hiatal opening in the diaphragm and fundoplication. Children in whom the intra-abdominal length of the esophagus is either too short or absent (such as in esophageal atresia with or without tracheo-esophageal fistula or in congenital diaphragmatic hernia (Bochdalek)) who suffer from GERD, will also benefit from fundoplication.
2. Children with *gastroesophageal reflux (disease) without anatomical alterations, whose complaints (pain) do not diminish significantly or disappear with optimal medical treatment, or if there is recurrence each time that the medication is stopped.*
   The minimal time period of optimal medical treatment before surgery should be considered, is never communicated in the literature, but 3–6 months seems a minimum. In children who respond well to medication, but whose symptoms recur if the medication is stopped, and/or who do not want to continue with medication for the rest of their life (taking into account the adverse effects of long-term treatment), surgery certainly is a good option.
3. Children with *severe esophagitis*, associated or not with occult blood loss
4. Children with *peptic stenosis*
5. Children with *Barrett's esophagus*
6. Children with *repetitive pulmonary infections* or with severe non-allergic asthma [11]
7. Children with *failure to thrive* (because of the vomiting, or because of the pain during deglutition due to esophagitis)
8. Young children with *brief resolved unexplained events (BRUE)* due to massive reflux of the gastric content and aspiration into the airway
9. A relative indication is tho*se infants (neurologically handicapped or not) who need a gastrostomy*. Neurologically impaired patients frequently have GERD. Those patients have alterations in LES pressure and relaxation, are

often in a recumbent position, disturbed regulation of intestinal motility, respiratory problems, spasticity and constipation with increased intra-abdominal pressure. Some suffer serious scoliosis which distorts the hiatal region. For all these reasons, those patients frequently are sent to the surgeon. Another reason for neurologically handicapped is that from some day on they need feeding via a feeding tube or gastrostomy, and this is known to increase reflux. Therefore, during a certain period it was believed that, when a neurologically handicapped needed a gastrostomy, it was best to add a Nissen. This way of thinking, however, has been abandoned as a general rule, in favor of an individual tailored approach [12, 13].

10. Although not an indication in itself, *patients with esophageal atresia and treacheo-esophageal fistula, with congenital diaphragmatic hernia and with abdominal wall defects* should be mentioned here. These children have a congenital anomaly that facilitates reflux as a consequence of the anatomical alterations. They need a close follow-up from birth; most will be prescribed PPIs in the first years of life, and some will eventually need surgery to control their reflux [14].

Surgical Technique

The History of Anti-Reflux Surgery [15]

The very first operations to cure hiatal (diaphragmatic) hernia were performed at the beginning of the twentieth century. In 1946, and a few years later in 1951, Allison published bilateral truncal vagotomy, restoration of an abdominal segment of the esophagus, and post-crural repair to treat gastroesophageal reflux by using a left thoracotomy. By then, he made aware that reflux was the problem, and esophagitis the consequence of reflux. From then on, many surgeons started to publish their vision upon, and their operations for GERD. Rudolph Nissen, in 1956, was the first to publish a total 360° fundic wrap around the distal esophagus, as a treatment for GERD. Many modifications followed. In 1963 Toupet's partial fundoplication, in 1967 the posterior gastropexy (Hill) and Belsey's operation (Belsey Mark IV), in 1968 Collis operation, later Collis-Nissen, in 1978 prosthetic repair (Angelchik), and in 1993 the first laparoscopic fundoplications in children.

Nowadays, the standard surgical technique which is most widespread is the laparoscopic Nissen fundoplication. Difficult to say exactly, but we may assume that 90% of all anti-reflux procedures performed worldwide are Nissens, and the majority are done laparoscopically.

Laparoscopic Fundoplication (Nissen Procedure)

This procedure can be done at all ages. We prefer to have a naso-gastric tube in situ. Depending on the size of the patient, the trocar diameters used are 5 mm or even 3 mm in babies. The patient is positioned on the back, with a cushion under the back and thorax. In my institution, we have always promoted open laparoscopy. A small incision is made around the umbilicus, and a first trocar is inserted. Pneumoperitoneum

is created to a pressure of 10–12 mm Hg. A 30° angled telescope is introduced. Under vision, the second and third trocars, which are the working ports, are inserted in the left and right epigastrium. Then, a liver retractor is inserted. We prefer using a Nathanson liver retractor which is available in several sizes and is in our opinion a very safe instrument. The cardio-esophageal junction is exposed. The phreno-esophageal ligament and gastrohepatic omentum overlying the right crus are opened with hook diathermy. The anterior esophagus is now identified, as well as the right crus. The edge of the right crus is separated from the esophagus, and the intra-abdominal part of the esophagus is separated from its surrounding adventitia. We then dissect behind the esophagus until we encounter the edge of the left crus. Once we open the visceral peritoneum, the fundus comes in sight. Only the most cranial short gastric vessels are divided. It is rather exceptional to divide more of the short gastrics in order to be able to perform fundoplication. We now have to check if the posterior esophageal window is wide enough to accommodate the fundic wrap. If judged necessary, the esophageal hiatus is narrowed by one or two stitches with non-absorbable monofilament sutures. Then, the fundus is grasped and brought through the posterior window. Fundoplication is done by suturing the wrap with non-absorbable monofilament sutures. Usually, three stitches are sufficient as to create a loose wrap ("floppy Nissen"). Before we take out the telescope, the naso-gastric tube is removed.

More recently, in order to reduce the percentage of transmigration of the fundoplication wrap and of redo-surgery, some authors [16] advocate not to incise the phreno-esophageal membrane. They advocate only minimal mobilization of the esophagus, leaving the phreno-esophageal membrane intact. A retro-esophageal window is created by incising the gastrohepatic ligament on the right side and dissecting behind the esophagus. Moreover, these authors advocate reducing the esophageal hiatus with one or two stitches.

Rarely, it is necessary to use prosthetic material (with GoreTex® or with a biological patch) to reinforce the hiatal diaphragmatic opening. Only in redo surgery, this might be useful.

Some Special Considerations

Some of the *patients with a neurologic handicap* have a serious kyphoscoliosis, which makes the surgery more difficult; caution is warranted in these patients. But it is essentially the same intervention.

Whenever indicated, a *gastrostomy* can be added to the fundoplication.

In patients who already have a (percutaneous endoscopic) gastrostomy, laparoscopic fundoplication is possible; sometimes the gastrostomy does not need to be detached, in other patients, the gastrostomy must be divided, and reconstructed after the Nissen. After percutaneous endoscopic gastrostomy placement, GERD appeared in 10% of (neurologically handicapped) patients, and worsened/aggravated already existing reflux in 25% of patients [13]. The question has been raised about whether it is necessary to systematically perform an anti-reflux procedure whenever a PEG is placed [12]. At present, however, there is insufficient evidence to systematically

perform an anti-reflux procedure whenever a PEG is placed in neurologically impaired patients [13].

In most cases, redo surgery after laparoscopic Nissen is not too complicated because the adhesions are minimal. After open Nissen fundoplication, on the other hand, adhesions between the liver and the esophago-gastric junction might be very dense and difficult to free.

Partial Fundoplication

As written previously, in the past 70 years, many other operations (mostly partial fundoplications) have been proposed. In children, the ones that are still carried out in a (small) number of patients are the partial anterior hemi-fundoplication (THAL procedure), and the partial posterior fundoplication (TOUPET). Those procedures can still be interesting in case of small fundus, or short esophagus. In the latter condition, a so-called COLLIS-NISSEN procedure could be more interesting (this procedure consists of stapling the junction along the axis of the esophagus at his left border which lengthens the esophagus and creates a new angle of HIS, and a fundoplication).

Esophagogastric Disconnection

This is a radical procedure used in neurologically handicapped children, or after the failure of multiple anti-reflux procedures. This operation was described for the first time by Adrian Bianchi in 1997 [17]. This intervention consists of dividing the lower esophagus from the stomach, closure of the stomach, creating a loop of small intestine in a Roux-en-Y fashion, and anastomosing the distal esophageal end to the small intestinal loop plus creating a gastrostomy. After this procedure, the gastric acid and biliopancreatic juices are diverted into the small intestine far from the esophagus, eliminating any possible reflux. In the meantime, several reports have been published on a few hundreds of patients with good results reported taken in consideration the complexity of surgery in these "difficult" patients. The article by Tanaka gives a good overview of early complications (15%), late complications (20%), and mortality rate (20% overall, about half unrelated to the surgery) [18–22]. Parent and caregiver's perceptions were very positive [23]. This technique clearly carries a certain mortality as well as early and late complications, and therefore has to be reserved for the worst cases.

Additional (Concomitant) Procedures

Gastrostomy and *pyloroplasty or pyloromyotomy* are sometimes associated with fundoplication. Pyloroplasty/pyloromyotomy has been performed together with fundoplication in former years [24], but at present, there is not really a good indication for a systematical addition of pyloroplasty to fundoplication. Gastrostomy on the other hand can be very useful in patients who cannot be fed per os for various reasons. This is particularly the case in neurologically handicapped, and in children with EA/TEF.

Complications of Anti-reflux Surgery

Intra-Operative Complications

Every surgical procedure carries risks of complications. It is true that comparing laparoscopic fundoplication with the open procedures that we used to perform more than 20 years ago, it appears that laparoscopic fundoplication looks like a very simple and innocent procedure. But it is not! Several complications may be encountered, although most are treatable without consequences. *Bleeding* from the short gastric vessels may occur, although it is rarely a problem, especially since the widespread use of the ultrasonic scalpel. *Damage to the posterior vagal trunk* has been reported, but this can be avoided by keeping the vagus nerve on the surface of the esophagus. Very rarely, when dealing with a huge hiatal hernia, the inadvertent opening of the pleura has been reported. This should however not be a problem if the pleural opening is closed and the air from the thoracic space aspirated before ending the operation. Tears in the esophagus, the stomach, and the small intestine have also been described.

Postoperative Complications

Temporary dysphagia and retching following a Nissen procedure is reported to occur in 4.2–31.6% of patients, but this phenomenon usually resolves after a few days/weeks [28, 31].

A *too-tight fundic wrap* is theoretically possible, leading to severe dysphagia, but this should not occur if the principles of the "floppy Nissen" technique are meticulously followed. Balloon dilatations may be the treatment.

Recurrence of the complaints, recurrence of GERD, due to *dehiscence of the wrap* or not, is a serious complication that will be dealt with in the next paragraph.

Gas bloat symptoms: the accumulation of ingested air during the meal creates an unpleasant sensation of fullness while being unable to burp.

Results of Anti-reflux Surgery

The literature on the results of anti-reflux surgery is abundant. In spite of this, definitive conclusions on the effectiveness of fundoplication are limited by the heterogeneity of the patient cohorts, lack of consensus about indications for surgery, lack of reporting of preoperative findings, operative technique, and outcome measures. Longitudinal patient-reported outcomes are rather scarce. it is not easy at all to simply summarize the results. Some series include neurologically handicapped patients and patients with EA whereas others do not. Some compare open Nissen with laparoscopic Nissen fundoplication, including 360° as well as partial fundoplications, and the outcome parameters are different (control of reflux, the use of PPI after surgery, herniation of the wrap, dehiscence of the wrap, percentage of redo surgery, etc.). In other words, the literature on outcomes after anti-reflux surgery, although abundant, is confusing and high-quality evidence is lacking.

In almost every reported series, *mortality* is reported in the first year(s) after surgery, although in most cases not due to the operation itself, but to the underlying condition, i.e. the neurological disability. Mortality ranges from 0.07% to 41% in the literature [26–31]. In a personal unpublished series of 233 patients, of whom 37% were neurologically disabled, overall mortality was 5%. However, only one patient died as a consequence of the procedure (unrecognized leakage of a concomitant gastrostomy), which brought the procedure-related mortality to 0.4%. A child without neurological handicap should not die following a fundoplication. Neurologically disabled on the other hand are more at risk, the worst categories more than the others.

An important parameter to judge the outcome of fundoplication is the *control of the symptoms* judged by the parents or/and caregivers. A systematic review by the American Pediatric Surgical Association [25] concluded that there was little evidence in the literature. However, many studies reported between 65% and 87% resolution of GI symptoms. Fundoplication performed for the indication "recurrent aspiration pneumonias, apnea or BRUEU" appeared not to affect the rate of hospitalizations for aspiration pneumonia or apnea and might decrease the risk of BRUE. Furthermore, fundoplication may result in subjective resolution of GI symptoms of gastric reflux in patients who have failed medical management but does not affect the rate of hospitalization. Fundoplication is effective in reducing all parameters of esophageal acid exposure and improves gastric emptying [10, 25, 28]. Fundoplication appears as effective in neonates and infants when compared to older age groups [28].

Another parameter to estimate the outcomes is the *number of patients that have restarted PPI* again a certain time lapse after the surgery. There is a huge variation between studies, from 25% to 71.8% [26–28].

The percentage of *redo-surgery* also is a valuable parameter in this respect. Data between 4.5% [29] and 13% [30] have been reported. In my personal series, we also came to 4.5% of the patients that had to be operated. The redo procedures were performed between 4 months and 11 years after the first fundoplication.

All the above data mean that fundoplication surgery is effective in controlling reflux in a considerable number of patients, but that there is also a subset of patients who suffer complications, whose symptoms are not controlled, or who need to be reoperated.

It is my belief that the results are worse in neurologically disabled children when compared to those who are neurologically normal. This tendency is also observed in the literature, but some studies deny this [31]. The same is true in children with esophageal atresia and short esophagus. When children without a neurological handicap and without a short esophagus are considered, the results of laparoscopic Nissen fundoplication are (very) good. This means that over 90% of the children's overall condition had improved and that the symptoms have diminished or disappeared.

Conclusion

The only treatment capable of eliminating reflux is by surgery. At present, laparoscopic fundoplication is the procedure of choice. However, one must not forget that this procedure is associated with a certain morbidity. Therefore, a correct selection of patients submitted to surgery is mandatory.

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