Yvan Vandenplas
Editor

Gastroesophageal Reflux in Children

GER in Children

Springer

Gastroesophageal Reflux in Children

Yvan Vandenplas
Editor

Gastroesophageal Reflux in Children

GER in Children

Springer

Editor
Yvan Vandenplas
Universitair Ziekenhuis Brussel
Kidz Health Castle
Brussels
Belgium

ISBN 978-3-319-60677-4 ISBN 978-3-319-60678-1 (eBook)
DOI 10.1007/978-3-319-60678-1

Library of Congress Control Number: 2017951902

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The diagnosis and management of gastro-oesophageal reflux disease (GERD) remains a challenge. Each author of this book is a worldwide recognized authority in different aspects related to GERD. Therefore, we are convinced that this book will help our readers to better understand the debates about GERD and its diagnosis and management. Each chapter discusses a different topic or aspect of GERD, going from basic science to clinical data.

Up to now, such a book has never been written. At the best, there is a chapter on GERD in a book on GERD focusing on adults in order to highlight the differences between adults and children ("children are indeed not small adults"), or there is a chapter on GERD in a textbook of paediatric gastroenterology. We felt that there was a need for an in-depth book on different aspects of GERD in childhood.

Why is GERD in childhood such a debated topic? The changing spectrum of symptoms according to age is a major reason. Symptoms are non-specific in infants and young children. Regurgitation and crying are manifestations of GERD in infants, but most infants that regurgitate do not have GERD, and many infants that cry do not suffer from GERD. But when physiologic GER or regurgitation stops and when it becomes GERD are not clear. In fact, there is a continuum between physiologic reflux and disease. So, parental distress and compliance and the attitude of the healthcare provider will decide whether an infant is considered to have physiologic reflux or (mild) reflux disease. As a consequence, the diagnosis of GERD is also a matter of controversies. There is no golden standard technique, although 24-h multiple intraluminal impedance in combination with pH monitoring seems to be the best, certainly in patients that do not present with overt regurgitation and/or vomiting. Endoscopy with biopsies is recommended to rule out other diseases than GERD. If symptoms are non-specific, diagnostic techniques are debated; treatment is as well discussed. Nutritional treatment seems "on the winning hand" in these infants with physiologic regurgitation or those with not-severe GERD. While anti-acid medication is overused in distressed infants, there is only limited evidence for its efficacy in young children. Effective and safe medication enhancing motility and lower oesophageal sphincter function would be welcomed.

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published in 2009 and 2017 common guidelines on the diagnosis and management of GERD in children. While efforts

were made to make these recommendations as much as possible "evidence based", it is clear that evidence for many aspects is missing. A summary of the 2017 guidelines can be found at the end of this book.

We do hope that this book will help to better understand the actual knowledge and controversies on GERD in children.

We look forward to a successful and worldwide spreading of this book.

Brussels, Belgium Yvan Vandenplas

Acknowledgements

I am pleased and honoured that so many key opinion leaders contributed to this book. Thanks to their valuable input, this book will become the reference work on paediatric gastro-oesophageal reflux disease. This is the second book on this topic. The first one was published in 1992, *Oesophageal pH Monitoring for Gastro-Oesophageal Reflux in Infants and Children*, and was in fact my PhD thesis. This book was published 4 years after having obtained my certificate as a paediatrician, and now, in 2017, I am 4 years away from retirement. Thanks to the never-ending support of my family, it was possible to devote so much time to this passion.

Contents

Epidemiology

1

Silvia Salvatore and Yvan Vandenplas

Abstract

Determination of the exact prevalence of gastroesophageal reflux (GER) and GER disease (GERD) at any age is virtually impossible mainly because symptoms are not specific, not all patients seek medical help, many patients are not (fully) investigated, and prospective data are limited. Many epidemiologic studies evaluated in infancy the frequency of regurgitation which is a common physiologic symptom in the first months of life with a spontaneous recovery in nearly all infant. Many other esophageal and extraesophageal symptoms and signs of GER(D) have been reported, but sensitivity and specificity are low, the causal relation is uncertain, and there is a lack of diagnostic gold standard technique. While reflux occurs physiologically at all ages, there is also a continuum between physiologic GER and GERD leading to different manifestations and complications depending on individual sensitivity and perception, defense mechanisms, mucosal resistance, and possible genetic influence. In selected population such as children with neurological impairment, cystic fibrosis, and esophageal atresia, severe persisting GER and esophageal complications have been frequently reported. Whether early treatment of GER(D) significantly changes, the incidence or severity of symptoms and complications in adults is uncertain.

Keywords

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

S. Salvatore (✉)
Department of Paediatrics, Università dell'Insubria, Varese, Italy
e-mail: silvias.varese@gmail.com

Y. Vandenplas
Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussels, Brussels, Belgium

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_1

Introduction

Epidemiology of gastroesophageal reflux (GER) and GER disease (GERD) in infants and children is unclear because of several factors influencing both incidence and prevalence rates. Definition, age, clinical manifestations, selection of population, diagnostic criteria, nutrition, over-the-counter treatment, and parental and patient concern are all important determinants of the high heterogeneity in the literature data.

GER, the involuntary passage of gastric contents into the esophagus, occurs several times per day in every human, particularly after meals, and is a completely normal physiologic process [1–3]. Most reflux episodes are asymptomatic, of short duration, and limited to the distal esophagus. Regurgitation, also called spitting up, posseting, or spilling, is the passage of GER into the pharynx, mouth, or the perioral external area [1]. Regurgitation is frequent in healthy infants especially in the first months of life, with a peak incidence around 3–4 months, and after intake of large volumes of milk as happens in young infants. Vomiting is a forceful expulsion of gastric contents from the mouth, is a more complex coordinated motor response, and is a consequence of the activation of receptors both inside and outside the gastrointestinal tract, often confused with regurgitation [4, 5]. GERD occurs when GER causes troublesome symptoms and/or complications [2, 3]. Despite that the semantic difference between GER and GERD is clear, the clinical distinction is often challenging, even for physicians.

Pitfalls

The spectrum of GER symptoms is wide and unspecific (such as behavioral, respiratory, feeding, or sleeping problems with or without esophageal signs and symptoms such as regurgitation or vomiting) [1]. The presenting symptoms of GERD also differ according to age [6] and may be secondary to other conditions (cow's milk allergy, malformation, metabolic, renal, and neurologic disorders) [1].

GERD frequently causes an impaired quality of life, easy to report for adult patients but difficult to quantify in infancy and childhood when it is mainly determined by parental perception and coping.

The absence of a gold standard test for the diagnosis of GERD and the complementary results of all the available investigations hamper the difficulty to clarify the epidemiology of GERD.

Symptoms showed a poor correlation with pH monitoring or endoscopy results, especially in children [1]. Mucosal complications of GERD such as erosive esophagitis, stenosis, and Barrett's esophagus are less frequent in children than in adults, but the exact occurrence in pediatrics may be underestimated because of limited endoscopic approach in pediatric patients with GER(D) symptoms and because no symptom is predictive of esophagitis. The natural history, evolution,

and progression of GERD for an individual patient also depend on genetic, environmental, and mucosal factors [7].

In the last 10 years, different European and American guidelines on the diagnosis and management of GER in children have been published [1, 8, 9]. However, considering symptoms without investigations, overdiagnosis of GERD and thus overtreatment with medication (mainly acid inhibitors) are common especially in infants and young children [10].

GER(D) in Infants

The most frequently reported symptom of GER in infants is regurgitation but is neither sensitive nor specific to diagnosis of GERD.

Epidemiological data show that spilling or regurgitation in infancy is very common between 1 and 6 months of age, with a peak at the age of 3–4 months, and spontaneous and almost complete resolution (in 95% of cases) by 1 year of age with a similar figure all over the world [11–18] (Fig. 1.1).

The oldest epidemiological report dates from 1992 and is a cross-sectional retrospective study from France [19]. Chouhou reported that a history-based diagnosis of GER was made by a physician in 18% of a population of unselected infants younger than 10 months of age [19]. Since then, data from the USA, Australia, India, Indonesia, Italy, Japan, Spain, and Thailand have been reported

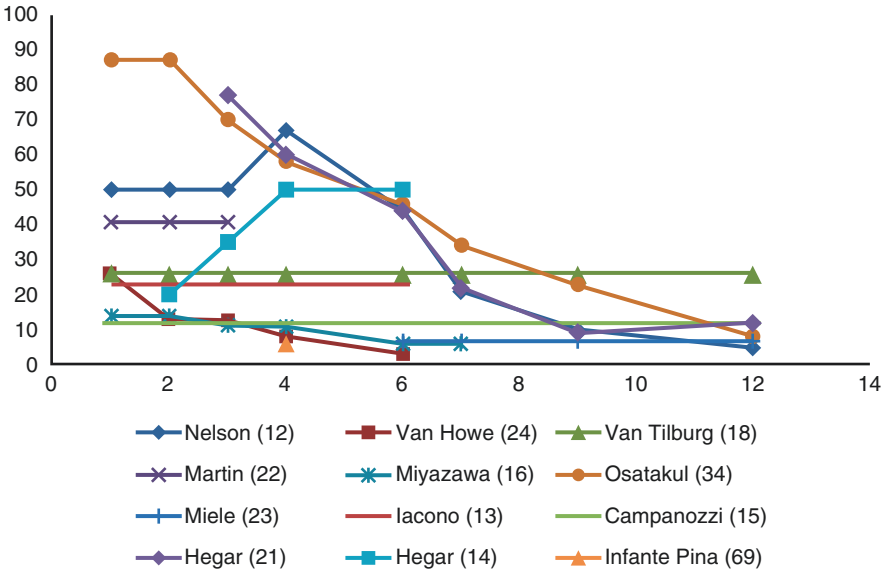


Fig. 1.1 Natural evolution of physiologic regurgitation in infants

Table 1.1 Summary of the studies reporting regurgitation in infancy (modified from [17])

Number of infants	Geographical area	Age (months)	Prevalence of regurgitation	Diagnostic criteria	References
948	USA	0–3 4 10–12	50% 67% 5%	≥1 episode per day	[12]
128	USA	1 2 4 6	26% 13% 8% 3%	I-GERQ-R	[24]
264 (0–3 years)	USA	0–12	26%	Rome III	[18]
693	Australia	3–4	41%	Spilling most feed each day	[22]
921	Japan	1 4 7	47–14% 29–11% 6–6%	≥1 to ≥3 episodes per day	[16]
216	Thailand	2 4 6 8 12	87% 70% 46% 23% 8%	Daily regurgitation	[34]
9660 children	Italy	0–12	7%	Rome II	[23]
2879	Italy	0–6	23%	Loss of most part of the meal without retching	[13]
2642	Italy	0–24	12%	Rome II	[15]
138	Indonesia	0–3 4–6 7–9 9–12	77% 44% 9% 12%	≥1 episode per day	[21]
130	Indonesia	0–2 1 5	20% 73% 50%	≥4 episodes per day ≥1 episode per day	[14]
3487	Spain	0–4	6%	Not specified	[69]

in cross-sectional or prospective studies with different frequencies of regurgitation considered (Table 1.1).

In the Chicago area, regurgitation of at least one episode a day was reported in half of 0- to 3-month-olds [12]. Peak-reported regurgitation by Nelson and coworkers was 67% at 4 months; the prevalence of symptoms decreased dramatically from 61 to 21% between 6 and 7 months of age and to 5% at 10–12 months of age [12]. In India, 55% of the infants aged 1–6 months had daily regurgitation [20]. According to a cross-sectional survey in Indonesia, regurgitation (of at least once a day) was reported more frequently in the first 3 months of life and in 77% of infants younger than 3 months [21], with a reported peak prevalence of 81% during the first month

of life but with a sharp decrease between the 4–6- and 7–9-month-old groups (from 44 to 9%) reaching a rate similar to the other geographical reports [21].

Martin et al. performed a prospective follow-up study in the Adelaide area (Australia) in 836 infants followed for 2 years from birth with daily symptom diaries [22]. Spilling of most feeds each day was common in infancy and reached a peak incidence of 41% between 3 and 4 months of age and thereafter declined to less than 5% between 13 and 14 months of age [22].

In another cohort study in Japan, 47% of 1-month-old infants had one or more episodes of regurgitation or vomiting per day [16]. This proportion decreased to 29% at 4 months old and 6% at 7 months old [16].

Iacono and coworkers reported that regurgitation was the most common gastrointestinal complain in an unselected cohort of nearly 3000 Italian infants followed by about 150 pediatricians, with a cumulative incidence of 23% and an increased rate of 30% in infants with low birth weight [13]. In another study in Italy, 7% of infants had two or more episodes of regurgitation per day for 3 or more weeks. All had improved at 3-month follow-up and none had significant symptoms at 1 year [23]. From the same geographical area, 2642 infants were prospectively assessed with Rome II criteria and followed up to 2 years. Nearly 300 reported infant regurgitation, and at follow-up, 1 of the 210 patients who remained in the study had developed GERD with esophagitis, proven endoscopically and histologically; 9% had used antacids (alginate and/or aluminum hydroxide) and 3% prokinetics (domperidone) [15]. However, because of the high (33%) dropout in this population, a firm conclusion of the natural history of GER in infants cannot be drawn from this study.

In a prospective cohort study in a rural part of Michigan, 128 consecutive maternal-infant pairs were followed for 6 months and administered the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R). At least one episode of regurgitation was reported in the previous day in 82%, 77%, 83%, and 67% of infants at the 1-month, 2-month, 4-month, and 6-month visits, respectively. The regurgitation frequency remained fairly constant through the first 4 months of age (average regurgitations per day, 2.3 with SD = 1.9) and then dropped at 6 months of age (average regurgitations per day 1.5 (SD = 1.5)) [24].

According to a recent review on GER in infants, the regurgitation in infants has been reported with a wide range of prevalence from 3% to 87% and with a lack of good-quality data [17]. Prospective studies were limited, and the criteria used to define regurgitation varied widely, from one to four episodes per day; the Rome III criteria of two or more episodes a day for at least 3 weeks were used in only two studies, reporting prevalence of 17 and 26% [17].

There is a clinical significant discrepancy in the percentage of infants presenting with daily regurgitation in the first semester of life according to the population in which the research was performed, whereas from the age of 6 months onward, epidemiological data are comparable.

Based on a worldwide survey and expert consensus, the average worldwide prevalence of regurgitation is estimated to be of 30% (decreased to 23% when

considering more than four episodes of regurgitation a day), with respondents mainly using Rome III criteria or NASPGHAN/ESPGHAN guidelines [17].

Regurgitation is frequent in infants because of the large liquid volume intake, the limited capacity of the esophagus (10 ml in newborn infants), the horizontal position of infants, etc. [7].

A genetic influence on the prevalence of GER is supported by the finding that GER symptoms are more frequently encountered in the relatives of GERD patients [25]. Moreover, the concordance for GER is higher in monozygotic than dizygotic twins [26]. A locus on chromosome 13q, between microsatellites D13S171 and D13S263, has been linked with severe GER disease in five families with multigenerational histories [27], but the same abnormal locus was not found in five other families, possibly due to the genetic heterogeneity of GERD and different clinical presentations among patients studied [28]. Nevertheless, similar trends in prevalence of regurgitation in infancy can be recognized worldwide independent of genetic and racial background.

"Excessive regurgitation" is one of the symptoms of GERD, but the definition of "excessive" is subjective, and the terms regurgitation and GERD should not be used as synonyms. Furthermore, regurgitation is a characteristic symptom of reflux in infants but is neither necessary nor sufficient for a diagnosis of GERD.

In normal 3–4-month-old infants, three to four episodes of GER are detectable during 5 min of intermittent fluoroscopic evaluation [29]. According to esophageal pH monitoring, up to 31 ± 21 acid reflux episodes are recorded within a 24-h period in infants [30]. More recently, studies using esophageal impedance [31, 32] have reported up to 100 episodes and 70 episodes of reflux in 24 h in infants and children, respectively [31–33]. However, for ethical reasons, these investigations were performed in symptomatic children. Less than 10% of infants and children have (acid and troublesome) GERD [30].

The influence of different feedings on infantile regurgitation is not completely clarified. Hegar [14] reported a decreased prevalence of regurgitation in the exclusive breastfed group, but all dropouts because of excessive symptoms were in the partial breastfed group. Nevertheless, other authors did not find a difference in regurgitation and vomiting according to method of feeding [16, 22, 34]. The possible reasons of 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, in other infants, breast milk could be associated to an increased frequency of meals and a cause of overfeeding compared to a (more easily to quantify) formula intake.

Smoking avoidance is recommended based on a reported positive association with esophageal adenocarcinoma in adults [1] although not all pediatric studies found a positive association between smoking exposure and GER symptoms or GERD [15, 22, 24].

Reflux treatment is frequently administered to premature infants although diagnosis of GERD is much more often based on symptoms (desaturation, crying, vomiting, feeding problems) supposed to be related to GER than on investigations. Progression of GER from neonatal period to childhood and adulthood has never

been assessed, and the long-term risk of GERD in premature infants is unclear. One study [35] reported a greater than 11-fold increase in the incidence of esophageal adenocarcinoma in adults who were born preterm or small for gestational age. However, a subsequent nested case-control study did not confirm a strong association between risk of esophageal cancer and birth weight [36].

About 20–25% of parents seek medical advice because of frequent infantile regurgitation, which often does correspond to at least four episodes of regurgitation a day [12, 14].

Parental perception of regurgitation as a problem was associated with the frequency and volume of regurgitation, increased crying or fussiness, reported discomfort with spitting up, and frequent back arching [12, 16].

It is generally accepted that infants with regurgitation are thought to have an excellent long-term prognosis. It is classically stated that infant regurgitation is physiological and rarely requires medical intervention needing only explanation and reassurance. However, somewhere between 5 and 9% of infants have a pathological esophageal acid exposure at pH monitoring and/or ongoing and troublesome GERD [22, 30].

Regurgitating greater than five times per day had a specificity of GERD of 71% but a positive predictive value of only 22% [37]. However, in another study evaluating 100 infants through a 35-item questionnaire, pH monitoring, and endoscopy, no significant correlation was found among the results of the three diagnostic tools [38].

A prospective follow-up reported disappearance of regurgitation in all subjects before 12 months, although the prevalence of feeding refusal, duration of meals, parental feeding-related distress, and impaired quality of life was observed and was higher in those who presented with regurgitation (even after disappearance of symptoms) compared to those who never regurgitated [12]. Miyazawa [16] and Osatakul [34] reported that no infant needed treatment for GER in their retrospective cohorts of Japanese and Thai infants. In the report by Chouhou et al., treatment for GER was started in 14% of all infants [19]. According to the data from the Chicago area, reported treatment for regurgitation was started in 12% of the infants and included a change in the diet or a medication [12].

Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, it is not an indication for extensive testing [1]. The duration of crying is not related with acid reflux, measured with pH metry [37, 39], or with response to acid inhibitors [40–43]. Irritability and crying are common in healthy infants, are not specific symptoms of GERD, and should not be a reason for empirical pharmacological treatment [1, 8, 44].

Poor weight gain is not part of physiologic GER and represents a crucial warning sign that necessitates clinical management and a complete diagnostic workup before GERD or different gastroenterological or extraintestinal disorders can be appropriately diagnosed [1]. Although usually regurgitation causes little more than a nuisance, important regurgitation produces also caloric insufficiency and malnutrition in a minority. GERD is only one of the many etiologies of “feeding problems” in infancy [1, 8, 9].

GER(D) in Children

According to parents, regurgitation is reported to occur in 2.3%, and heartburn is present in 1.8% of 3–9-year-old healthy children, while 1.4% of them needs antiacid medication [45].

GER symptoms are more frequent at 9 years of age who had frequent regurgitations in infants [22] and in children (and young adults) who reported persistent regurgitation after 3 years of life [46] or constipation [47].

In an Italian survey of nearly 10,000 children enrolled with a mixed group of infants and children up to 12 years, 72 (37%) out of 194 children who met Rome II criteria for functional gastrointestinal disorders had infant regurgitation, and one showed reflux esophagitis after endoscopy performed because of hematemesis [23].

In older children, reflux symptoms are frequently relapsing, resistant to complete spontaneous resolution [48, 49].

Cough, feeding problems, and regurgitation/vomiting have been reported to be less severe and heartburn more severe in school-age children with erosive esophagitis compared to younger (1–5 years old) children with GERD [50]. A cohort of 207, a mix group of children and young adults with esophagitis without comorbid illnesses, were recalled nearly 10 years later to evaluate the presence of GERD symptoms and the use of GER treatment. Only 80 (39%) (mean age 20 years, range 10–40) completed the questionnaire, 64 (80%) reported at least monthly heartburn and/or acid regurgitation with 18 (23%) with at least weekly symptoms, 24 (30%) were currently taking H2 antagonists or proton pump inhibitors, and 19 had undergone fundoplication [46]. Because of the recruitment bias, the authors also recalculated the rate of persisting symptoms in their population assuming that all nonresponders were symptom-free at recall. They showed an incidence of 31% with monthly symptoms and of 9% of subjects with weekly symptoms highlighting that a high proportion of patients continue to have GERD symptoms [46].

The rapidly increasing prevalence of obesity is causing a rising prevalence of GERD [3]. The risk of GERD symptoms is associated with the increase in body mass index and waist circumference in obese but even in normal-weight children [51].

Epigastric pain, nausea, flatulence, hiccups, chronic cough, asthma, chest pain, and hoarseness account for 30–60% of presentations of GERD [1, 52]. Possible associations exist between GERD and asthma, pneumonia, bronchiectasis, laryngotracheitis, sinusitis, and dental erosion, but the exact prevalence is unclear, and causality or temporal association is not well established [1, 52].

The accuracy of diagnostic tests (laryngoscopy, endoscopy, and pH or pH-impedance monitoring) for patients with suspected extraesophageal manifestations of GERD is suboptimal [53]. Data from several placebo-controlled studies and meta-analyses uniformly have shown no effect of antireflux therapy on upper airway symptoms or signs [1]. However, well-designed, prospective, placebo-controlled, blinded studies are limited [1, 9, 54]. There is currently still little or no evidence on which to base the correlation between laryngeal findings and GERD, particularly in the pediatric age [1]. The paucity of studies, small sample sizes, and varying disease definitions do not allow to draw firm conclusions about this correlation [52].

Little is known about GER symptoms during childhood in adults with GERD. According to one retrospective study, GER symptoms during childhood were reported significantly more frequently (63% vs. 35%) in 225 adults with GERD than in 154 non-refluxer adults [55]. However, this interesting difference may be influenced by recall bias in current symptomatic patients.

GER(D) in Adolescents

According to parents, heartburn is present in 1.8% of 3–9-year-old healthy children and 3.5% of 10–17-year-old adolescents; regurgitation is reported to occur in 2.3 and 1.4%, respectively, and 0.5 and 1.9% need antiacid medication [45]. According to self-reports, adolescents complain about heartburn in 5.2% and regurgitation in up to 8.2%, while antiacids are taken by 2.3% and histamine2 receptor antagonists by 1.3%, suggesting that symptoms of GER are not rare during childhood and are underreported by parents or overestimated by adolescents [45].

GERD in adolescents is more adult-like, and heartburn is a common symptom of GERD with or without esophagitis, in most cases responsive to PPI [1, 9].

Esophageal Complications

Complications of GER can be divided according to those related to lesions of the esophageal mucosa (esophagitis, anemia, weight loss, Barrett's, esophageal stenosis, etc.) and consequences independent of the esophageal lesion (feeding and sleeping disturbances, chronic respiratory symptoms, impaired quality of life). No clear-cut temporal progression exists between successive grades of disease severity, as the most severe grade of GERD may be detected at the first presentation.

Children with GER symptoms present reflux esophagitis in 2 up to 62%, Barrett's esophagus in 0.1–3%, and refractory GERD requiring surgery in 6–13% [1, 49, 56]. The huge variation in the prevalence of GERD is determined by patient recruitment, limited investigations and follow-up, dropout rate in the (few) prospective studies, differences of definition of esophagitis, and availability of self-treatment.

Nearly 40 years ago, in the absence of reflux treatment, esophageal strictures were reported in about 5% of children with reflux symptoms [57]. Nowadays, esophageal stenosis and ulceration in children have become extremely rare. The development of strictures is likely to be related to delay in diagnosis, as what occurs in neurologically impaired children, or other causes than GERD.

Indian infants' esophageal biopsies were taken in 25 of 31 cases selected by a positive questionnaire score and showed histological evidence of reflux esophagitis in 23 (92%) [20].

More recently, erosive esophagitis has been reported in 12.4% of 0–17-year-old children with GERD symptoms, increasing with age and limited to 5.5% in those younger than 1 year, and more frequent in patients with hiatal hernia [58]. This

finding is in sharp contrast with the extremely high prescription rate of acid inhibitors, even in neonates [59] and children [10].

Esophagitis, identified by histology, occurs in 61–83% of (investigated) infants with reflux symptoms severe enough to perform endoscopy. Although esophagitis may present with pain, it can also be asymptomatic [60].

Barrett's esophagus, strictures, and esophageal adenocarcinoma are complications of chronic severe GERD. Barrett's esophagus is not rare in adolescents with chronic GERD [1]. Barrett's esophagus is a premalignant condition in which metaplastic specialized columnar epithelium with goblet cells is present in the tubular esophagus. Differences in esophageal mucosal resistance and genetic factors may partially explain the diversity of lesions and symptoms. Barrett's has a male predominance and increases with age. There is a genetic predisposition in families in patients with Barrett's esophagus and esophageal carcinoma [1]. Reflux symptoms during childhood were not different in adults without than in adults with Barrett's [61]. Patients with short segments of columnar-lined esophagus and intestinal metaplasia have similar esophageal acid exposure but significantly higher frequency of abnormal bilirubin exposure and longer median duration of reflux symptoms than patients without intestinal metaplasia [62]. In a series including 402 children with GERD without neurological or congenital anomalies, no case of Barrett's esophagus was detected [56]. In another series including 103 children with long-lasting GERD and not previously treated with H2RAs or a proton pump inhibitors (PPIs), Barrett's esophagus was detected in 13%, and esophageal stricture was present in 5 of the 13 patients with Barrett's (38%) [63].

Children with neurological impairment, cystic fibrosis (CF), and esophageal atresia are known to be children at risk for severe reflux and subsequent complications [1].

Young CF patients do have a high prevalence of acid GER, even before respiratory symptoms developed [64]. CF patients also suffer from duodenogastroesophageal reflux of bile acids [65, 66]. It is likely that both acid and bile reflux aggravate the respiratory symptoms and that the respiratory symptoms aggravate the reflux.

Despite the above reported groups at risk for GERD, the natural history such as persistence of symptoms and progression to complications is unpredictable for the individual patient. Overall, the correlation between the severity of symptoms and the results of investigations is poor both in infants and in children [1, 38, 60].

There are no data in literature to suggest that preterms suffer from GERD more often than term babies, although preterms are frequently treated with antiacid medication.

Esophageal peptic ulcer caused by GERD and esophageal and gastric neoplastic changes are extremely seldom in children and adolescents. In adults, over the last 30 years, a decreased prevalence of gastric cancer and peptic ulcer with an opposite increase of esophageal adenocarcinoma and GERD has been noted [67, 68]. This has been attributed to independent factors, among which are changes in dietary habits such as a higher fat intake, an increased incidence of obesity, and a decreased

incidence of *Helicobacter pylori* infection [67, 68]. Frequency, severity, and duration of reflux symptoms have been related to the risk to develop esophageal cancer. Among adults with long-standing and severe reflux, the odds ratios are 43.5 for esophageal adenocarcinoma and 4.4 for adenocarcinoma at the cardia [67]. Whether better and/or earlier diagnosis and treatment of pediatric GERD play a role in these findings is not known.

Conclusion

The prevalence of GERD in infants and children is unknown since it is unethical to investigate asymptomatic children, symptoms of GERD are neither sensitive nor specific, empirical treatment is frequent, investigations are differently performed depending on technical facilities and clinical judgment, and gold standard diagnostic tool does not exist. There is a wide spectrum of symptoms and signs both for GER and GERD, with both esophageal and extraesophageal manifestations, partially age dependent, and with a difficult-to-prove causal relation. Symptoms are not specific and not sensitive. Regurgitation is the most reported symptom of GER in infancy and is a common condition in healthy infants with spontaneous disappearance with increasing age. Except regurgitation, little is known about the natural evolution of pediatric GER and GERD, but at-risk population (patients with severe neurological disorders, cystic fibrosis, esophageal atresia, etc.) have been identified. Complications of GERD may be severe and even life threatening, such as esophageal stenosis and Barrett's esophagus, although these are very seldom in children.

Alarm symptoms and signs are difficult to recognize clinically, and many unsettled issues in GER(D) are encountered in its natural course and clinical presentation.

References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the north American society of pediatric gastroenterology, hepatology, and nutrition and the European society of pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr. 2009;49:498–5472.
2. Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, Orenstein S, Rudolph C, Vakil N, Vandenplas Y. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104:1278–95.
3. Bredenoord AJ, Pandolfino JE, Smout AJPM. Gastro-oesophageal reflux disease. Lancet. 2013;381:933–42.
4. Stanford EA, Chambers CT, Craig KD. The role of developmental factors in predicting young children's use of a self-report scale for pain. Pain. 2006;120:16–23.
5. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain. 2007;127:140–50.
6. Salvatore S, Hauser B, Vandenplas Y. The natural course of gastro-oesophageal reflux. Acta Paediatr. 2004;93(8):1063–9.
7. Vandenplas Y, Hassall E. Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2002;35:119–36.

8. Lightdale JR, Gremse DA. Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013;131:e1684–95.
9. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people. Clinical Guideline 193. 2015. www.nice.org.uk/guidance/NG1.
10. Quitadamo P, Papadopoulou A, Wenzl T, et al. European pediatricians' approach to children with GER symptoms: survey on the implementation of 2009 NASPGHAN-ESPGHAN Guidelines. J Pediatr Gastroenterol Nutr. 2014;58(4):505–9.
11. Orenstein SR, Shalaby TM, Cohn J. Reflux symptoms in 100 normal infants: diagnostic validity of the Infant Gastroesophageal Reflux Questionnaire. Clin Pediatr. 1996;332:607–14.
12. Nelson SP, Chen EH, Syniar GM. Prevalence of symptoms of gastroesophageal reflux in infancy. Arch Pediatr Adolesc Med. 1997;151:569–72.
13. Iacono G, Merolla R, D'Amico D, et al. Gastrointestinal symptoms in infancy: a population-based prospective study. Dig Liver Dis. 2005;37(6):432–8.
14. Hegar B, Dewanti NR, Kadim M, Alatas S, Firmansyah A, Vandenplas Y. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009;98:1189–93.
15. Campanozzi A, Boccia G, Pensabene L, et al. Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey. Pediatrics. 2009;123:779–83.
16. Miyazawa R, Tomomasa T, Kaneko H, et al. Prevalence of gastro-esophageal reflux related symptoms in Japanese infants. Pediatr Int. 2002;44:513–6.
17. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Çokura F, Harb T, Hegar B, Lifschitz C, Ludwig T, Miqdady M, de Morais MB, Osatakul S, Salvatore S, Shamir R, Staiano A, Szajewska H, Thapar N. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. J Pediatr Gastroenterol Nutr. 2015;61(5):531–7.
18. van Tilburg MA, Hyman PE, Walker L, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. J Pediatr. 2015;166:684–9.
19. Chouhou D, Rossignol C, Bernard FL, Dupont C. Le reflux gastro-oesophagien dans les centres de bilan de santé de l'enfant de moins de 4 ans. Arch Fr Pediatr. 1992;49:843–5.
20. De S, Rajeshwari K, Kalra KK, Gondal R, Malhotra V, Mittal SK. Gastrooesophageal reflux in infants and children in north India. Trop Gastroenterol. 2001;22:99–102.
21. Hegar B, Boediarso A, Firmansyah A, Vandenplas Y. Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. World J Gastroenterol. 2004;10:1795–7.
22. Martin AJ, Pratt N, Kennedy JD, Ryan P, Ruffin RE, Miles H, Marley J. Natural history and familial relationships of infant spilling to 9 years of age. Pediatrics. 2002;109:1061–7.
23. Miele E, Simeone D, Marino A, et al. Functional gastrointestinal disorders in children: an Italian prospective survey. Pediatrics. 2004;114:73–8.
24. Van Howe RS, Storms MR. Gastroesophageal reflux symptoms in infants in a rural population: longitudinal data over the first six months. BMC Pediatr. 2010;10:7.
25. Trudgill NJ, Kapur KC, Riley SA. Familial clustering of reflux symptoms. Am J Gastroenterol. 1999;94:1172–8.
26. Cameron AJ, Lagergren J, Henriksson C. Gastroesophageal reflux disease in monozygotic and dizygotic twins. Gastroenterology. 2002;122:55–9.
27. FZ H, Preston RA, Post JC. Mapping of a gene for severe pediatric gastroesophageal reflux to chromosome 13q14. JAMA. 2000;284:325–34.
28. Orenstein SR, Shalaby TM, Barmada MM, Whitcomb DC. Genetics of gastroesophageal reflux disease: a review. J Pediatr Gastroenterol Nutr. 2002;34:506–10.
29. Cleveland RH, Kushner DC, Schwartz AN. Gastroesophageal reflux in children: results of a standardized fluoroscopic approach. Am J Roentgenol. 1983;141:53–6.
30. Vandenplas Y, Goyvaerts H, Helven R. Gastroesophageal reflux, as measured by 24-hours pH-monitoring, in 509 healthy infants screened for risk of sudden infants death syndrome. Pediatrics. 1991;88:834–40.
31. Pilic D, Fröhlich T, Nöh F, Pappas A, Schmidt-Choudhury A, Köhler H, Skopnik H, Wenzl TG. Detection of gastroesophageal reflux in children using combined multichannel intraluminal

impedance and pH measurement: data from the German Pediatric Impedance Group. J Pediatr. 2011;158:650–654.e1.
32. Di Pace MR, Caruso AM, Catalano P, Casuccio A, De Grazia E. Evaluation of esophageal motility using multichannel intraluminal impedance in healthy children and children with gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2011;52:26–30.
33. Mousa H, Machado R, Orsi M, Chao CS, Alhajj T, Alhajj M, et al. Combined multichannel intraluminal impedance-pH (MII-pH): multicenter report of normal values from 117 children. Curr Gastroenterol Rep. 2014;16(8):400.
34. Osatakul S, Sriplung H, Puetpaiboon A, et al. Prevalence and natural course of gastroesophageal reflux symptoms: a 1-year cohort study in Thai infants. J Pediatr Gastroenterol Nutr. 2002;34:63–7.
35. Kaijser M, Akre O, Cnattingius S, et al. Preterm birth, low birth weight, and risk for esophageal adenocarcinoma. Gastroenterology. 2005;128:607–9.
36. Akre O, Forssell L, Kaijser M, et al. Perinatal risk factors for cancer of the esophagus and gastric cardia: a nested casecontrol study. Cancer Epidemiol Biomark Prev. 2006;15:867–71.
37. Heine RG, Jordan B, Lubitz L, Meehan M, Catto-Smith AG. Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health. 2006;42:134–9.
38. Salvatore S, Hauser B, Vandemaele K, Novario R, Vandenplas Y. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr. 2005;40:210–5.
39. Heine RG, Jaquiery A, Lubitz L. Role of gastro-oesophageal reflux in infant irritability. Arch Dis Child. 1995;73:121–5.
40. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154:514–520.e4.
41. Chen IL, Gao WY, Johnson AP, Niak A, Troiani J, Korvick J, Snow N, Estes K, Taylor A, Griebel D. Proton pump inhibitor use in infants: FDA reviewer experience. J Pediatr Gastroenterol Nutr. 2012;54:8–14.
42. Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the treatment of GERD in infants ages 1–11 months. J Pediatr Gastroenterol Nutr. 2012;55:14–20.
43. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, Illueca M. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. J Pediatr. 2013;163:692–8.
44. Salvatore S, Barberi S, Borrelli O, et al. SIPPS Working Group on FGIDs. Pharmacological interventions on early functional gastrointestinal disorders. Ital J Pediatr. 2016;42(1):68.
45. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood. Arch Pediatr Adolesc Med. 2000;154:150–4.
46. El-Serag HB, Gilger M, Carter J, Gentra RM, Rabeneck L. Childhood GERD is a risk factor GERD in adolescents and young adults. Am J Gastroenetrology. 2004;100:806–12.
47. Baran M, Özgenç F, Arikan Ç, Çakir M, Ecevıt ÇÖ, Aydoğdu S, Yağci RV. Gastroesophageal reflux in children with functional constipation. Turk J Gastroenterol. 2012;23(6):634–8.
48. Treem W, Davis P, Hyams J. Gastroesophageal reflux in the older child: presentation, response to treatment, and long-term follow-up. Clin Pediatr. 1991;30:435–40.
49. Lee WS, Beattie RM, Meadows N, Walker-Smith JA. Gastro-oesophageal reflux: clinical profiles and outcome. J Paediatr Child Health. 1999;35:568–57.
50. Gupta SK. Presenting symptoms of non-erosive and erosive esophagitis in pediatric patients. Dig Dis Sci. 2006;51(5):858–63.
51. Quitadamo P, Buonavolontà R, Miele E, Masi P, Coccorullo P, Staiano A. Total and abdominal obesity are risk factors for gastroesophageal reflux symptoms in children. J Pediatr Gastroenterol Nutr. 2012;55:72–5.
52. Tolia V, Vandenplas Y. Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. Aliment Pharmacol Ther. 2009;29:258–72.

53. Kahrilas PJ, Smith JA, Dicpinigaitis PV. A causal relationship between cough and gastroesophageal reflux disease (GERD) has been established: a pro/con debate. Lung. 2014;192:39–46.
54. Writing Committee for the American Lung Association Asthma Clinical Research Centers, Holbrook JT, Wise RA, Gold BD, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307:373–81.
55. Waring JP, Feiler MJ, Hunter JG, et al. Childhood gastroesophageal reflux symptoms in adult patients. J Pediatr Gastroenterol Nutr. 2002;35:334–8.
56. El-Serag HB, Bailey NR, Gilger M, Rabeneck L. Endoscopic manifestations of gastroesophageal reflux disease in patients between 18 months and 25 years without neurological deficits. Am J Gastroenterol. 2002;97:1635–9.
57. Carre I. The natural history of the partial thoracic stomach ("hiatal hernia") in children. Arch Dis Child. 1959;34:344–53.
58. Gilger MA, El-Serag HB, Gold BD, Dietrich CL, Tsou V, McDuffie A, Shub MD. Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study. J Pediatr Gastroenterol Nutr. 2008;47:141–6.
59. Malcolm WF, Gantz M, Martin RJ, et al. National institute of child health and human development neonatal research network. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. Pediatrics. 2008;121:22–7.
60. Volonaki E, Sebire NJ, Borrelli O, et al. Gastrointestinal endoscopy and mucosal biopsy in the first year of life: indications and outcome. J Pediatr Gastroenterol Nutr. 2012;55:62–5.
61. Hassall E. Barrett's esophagus: new definitions and approaches in children. J Pediatr Gastroenterol Nutr. 1993;16:345–64.
62. Oberg S, Peters JH, DeMeester TR, et al. Determinants of intestinal metaplasia within the columnar-lined esophagus. Arch Surg. 2000;135:651–6.
63. Krug E, Bergmeijer JH, Dees J. Gastroesophageal reflux and Barrett's esophagus in adults born with esophageal atresia. Am J Gastroenterol. 1999;94:2825–8.
64. Blondeau K, Pauwels A, Dupont L, Mertens V, Proesmans M, Orel R, Brecelj J, López-Alonso M, Moya M, Malfroot A, De Wachter E, Vandenplas Y, Hauser B, Sifrim D. Characteristics of gastroesophageal reflux and potential risk of gastric content aspiration in children with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;50:161–6.
65. Pauwels A, Decraene A, Blondeau K, Mertens V, Farre R, Proesmans M, Van Bleyenbergh P, Sifrim D, Dupont LJ. Bile acids in sputum and increased airway inflammation in patients with cystic fibrosis. Chest. 2012;141:1568–74.
66. Woodley FW, Machado RS, Hayes D Jr, Di Lorenzo C, Kaul A, Skaggs B, McCoy K, Patel A, Mousa H. Children with cystic fibrosis have prolonged chemical clearance of acid reflux compared to symptomatic children without cystic fibrosis. Dig Dis Sci. 2013;59(3):623–30.
67. Lagergren J, Bergstrom R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340:825–31.
68. Dubecz A, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the incidence of adenocarcinoma of the esophagus and gastric cardia continue to rise in the twenty-first century?—a SEER database analysis. J Gastrointest Surg. 2013;18:124–9.
69. Infante Pina D, et al. Prevalence and dietetic management of mild gastrointestinal disorders in milk-fed infants. World J Gastroenterol. 2008;14(2):248–54.

Pathophysiology of Gastroesophageal Reflux Disease

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].

S. Nurko
Center for Motility and Functional Gastrointestinal Disorders, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02155, USA
e-mail: samuel.nurko@childrens.harvard.edu

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_2

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 and a supine position that predisposes to a common immersion of the gastroesophageal junction, compounded by a small esophageal capacity to hold fluids [2].

The pathophysiology of GERD is multifactorial. It is related on the one hand to lower esophageal sphincter (LES) function and on the other to esophageal events that lead to reflux clearance, mucosal damage, and perception of the refluxate. 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 or (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, 3].

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

LES Function

An important part of the study of the pathophysiology of GERD in children has focused on understanding the role that the LES plays [4]. 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.

It has now been shown in multiple studies that contrary to the initial hypothesis, in the vast majority of children, GER is not related to a decreased tone of the LES [2–6]. 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, 6].

It is now known that the predominant mechanism through which GER occurs is by transient lower esophageal sphincter relaxations (TLSERs) (Fig. 2.1) [2–4] which are relaxations of the LES that are not preceded by swallowing. High-resolution manometry is the new gold standard to detect TLSERs. Using HRM, TLESR might be defined as LES relaxation occurring in the absence of swallowing, lasting more than 10 s and associated with inhibition of the crural diaphragm [7, 8] (Fig. 2.1). Gastric distension is a potent stimulus for TLESR, via vago-vagal pathways [9]. In infants more TLESRs were triggered when feedings are administered in the right lower position, as compared with the left lateral position [9].

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 [10, 11]. However, in patients with GERD, the TLSERs are more likely to be associated with reflux as compared to healthy controls [12, 13]. The mechanism behind this phenomenon remains largely unknown. The frequency of TLSERs that are associated with more reflux

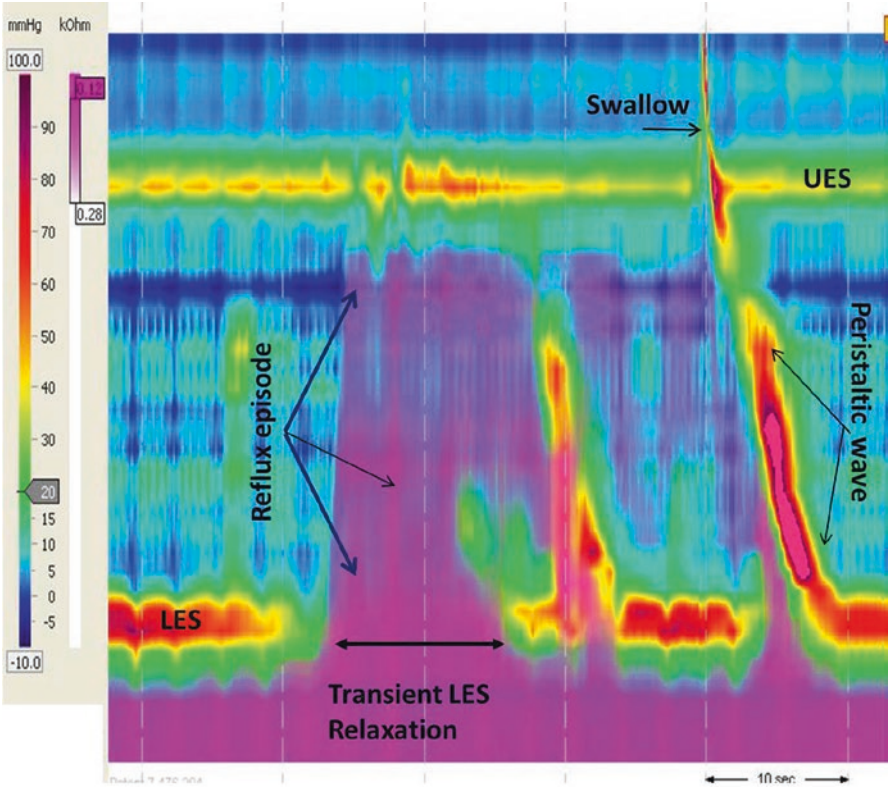


Fig. 2.1 Transient lower esophageal sphincter relaxation (TLSER) with a reflux event. The figure shows a tracing from a high-resolution esophageal manometry with impedance during an episode of gastroesophageal reflux (*pink color*). The episode is occurring after there is a relaxation of the lower esophageal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

is higher when the osmolarity and volume of the meals increases [11]. 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 [14]. The acid pocket forms due to the buffering effect of food within the stomach. The acidity falls within the main stomach body where 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 [14]. The lack of mixing will also allow gastric juice to pool and form a layer of acid on top of the gastric contents. Therefore increased 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 [14, 15].

Delayed gastric emptying has been suggested as another factor that can increase TLSERs and reflux [15], although the evidence that there is an association is controversial, and most studies in children do not show a correlation [2, 16].

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 [17]. Ingestion of medications or other substances (nonsteroidals, antibiotics, 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 [18], and in a very small percent 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 [20].

Other Structural Abnormalities

The antireflux barrier is not only comprised of the LES. 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. Therefore there are other structural and physiologic antireflux mechanisms at the gastroesophageal junction, like the diaphragm and the phrenoesophageal ligament. 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 [19]. There is also an increased number of TLSERs [20]. 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].

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].

Esophageal clearance of refluxate is directly related to the presence of normal esophageal motility. 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 [3]. There has been some controversy 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 [5, 21]. Theoretically esophageal mucosal inflammation may affect nerves and muscle that alter LES function and esophageal body motility. A vicious cycle of inflammation and impaired motility may cause progressive disease [5, 21]. It has been shown that in patients with GERD, there may be subtle alterations in esophageal peristalsis [5], 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 [5, 21]. In patients with severe motility dysfunction as is observed in children with esophageal atresia [22] or patients with scleroderma [23], the abnormal motility predisposes to delayed clearance and more esophagitis.

Esophageal chemical clearance with saliva has recently been measured with impedance monitoring by using the postreflux swallow-induced peristaltic wave (PSPW), 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 [24]. 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. 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 [25]. 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 [26, 27]. Recent animal studies have shown that bile produces dilatation of the intracellular spaces in esophageal epithelium [26–28].

Mucosal Integrity

Problems in mucosal integrity have been identified histologically by measuring intercellular space [29], in vitro [30] by measuring permeability and electrical resistance, and by using baseline esophageal impedance values in vivo [32].

The impaired mucosal integrity was initially suggesting histological findings that showed dilated esophageal intercellular spaces (ISD) in patients with GERD. Increased ISD has been shown to represent an early morphological marker of reflux injury in the esophageal epithelium [29–32]. Changes have been shown to be independent of visible erosions and have been shown both in erosive (ERD) and nonerosive reflux disease (NERD) [29–33]. Experimental models initially showed that DIS dilation occurred as a consequence of acid peptic injury to the esophageal epithelial cells [26]. 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 [26]. Abnormal DIS in patients with erosive esophagitis has been shown to normalize following antisecretory therapy [31].

In vitro measurements of mucosal integrity using different methodologies have shown abnormalities in animal models and patients with GERD [30]. 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 [26, 28] and are reversible with successful therapy [30].

Baseline esophageal impedance values have been correlated with in vitro measurement of mucosal integrity using a Ussing chamber, so they provide a validated tool [33]. 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. Baseline impedance values correlate with esophageal acid exposure time, and low impedance values have been shown in patients with severe esophagitis, Barrett's esophagus, and nonerosive reflux disease

[32–34]. More importantly previous findings have shown that the baseline impedance levels increase in response to PPI treatment [29–32].

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 [32], 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. The mechanisms that lead to the perception of the refluxate or to symptoms are not well understood, but multiple factors may influence them. 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 [30, 32, 34, 35]. It has become evident that an important underlying mechanism in patients with esophageal symptoms is the presence of esophageal hypersensitivity [30, 32, 34, 35].

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 [30–32]. 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 [29, 30, 33]. 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 [34, 35]. For example, the infusion of acid reduced the esophageal pain threshold in patients with non-cardiac 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 [36]. Furthermore, the decreased pain threshold in patients with GERD-related non-cardiac chest pain was increased after proton pump inhibitor (PPI) treatment [36].

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-sensitive ion channels, and the purinergic (P2X) receptors [37]. 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 [37], which are pro-inflammatory mediators, thus promoting further inflammation which could lead to an increased mucosal permeability and further peripheral sensitization [35].

It is important to note that in recent studies both in children [29, 33] and adults [30], 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 [30].

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* [38]. Acid stimulation of the esophagus can sensitize the insula and cingulate cortex to subliminal and liminal non-painful mechanical stimulations [35, 38]. 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 [35, 38]. Interestingly, using fMRI it was found that the same stimulus was perceived more intensely during a negative emotional context and was associated with an increased cortical activity in the anterior insula and the dorsal anterior cingulate gyri than during a neutral emotional context [39]. Moreover, it has been demonstrated that acid exposure in GERD patients leads to a more rapid and greater cerebral activity than in healthy controls [35].

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 [41].

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, cerebral palsy in particular, is one of the most common conditions that predispose patients to severe GERD [40, 41]. Several studies confirmed the high prevalence of reflux esophagitis and pathological pH monitoring in NI children [5, 40, 41]. Some chromosomal abnormalities, like Cornelia de Lange [42], 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 [43]. An increased prevalence of GERD and its complications have also been reported in patients with chronic pulmonary disease, including cystic fibrosis [44].

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 [45, 46]. Pathophysiological mechanisms in obesity include lower esophageal sphincter abnormalities, increased risk of hiatal hernia, and increased intragastric pressure [48].

Conclusions

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.

References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
2. Singendonk MM, Rommel N, Omari TI, Benninga MA, van Wijk MP. Upper gastrointestinal motility: prenatal development and problems in infancy. Nat Rev Gastroenterol Hepatol. 2014;11(9):545–55.
3. Pena EM, Parks VN, Peng J, Fernandez SA, Di Lorenzo C, Shaker R, et al. Lower esophageal sphincter relaxation reflex kinetics: effects of peristaltic reflexes and maturation in human premature neonates. Am J Physiol Gastrointest Liver Physiol. 2010;299(6):G1386–95.
4. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. Gastroenterology. 1997;113(2):399–408.
5. Hoffman I, De Greef T, Haesendonck N, Tack J. Esophageal motility in children with suspected gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2010;50(6):601–8.
6. Omari TI, Benninga MA, Barnett CP, Haslam RR, Davidson GP, Dent J. Characterization of esophageal body and lower esophageal sphincter motor function in the very premature neonate. J Pediatr. 1999;135(4):517–21.
7. Roman S, Holloway R, Keller J, Herbella F, Zerbib F, Xiao Y, et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neurogastroenterol Motil. 2016;29:e12920.
8. Roman S, Zerbib F, Bruley des Varannes S, Mion F. Esophageal high resolution manometry: a new gold standard for the detection of transient lower esophageal sphincter relaxations? Neurogastroenterol Motil. 2012;24(5):498–9. Author reply 500.
9. van Wijk MP, Benninga MA, Davidson GP, Haslam R, Omari TI. Small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral position in infants. J Pediatr. 2010;156(5):744–8. 8 e1.
10. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol. 2001;96(9):2569–74.
11. Salvia G, De Vizia B, Manguso F, Iula VD, Terrin G, Spadaro R, et al. Effect of intragastric volume and osmolality on mechanisms of gastroesophageal reflux in children with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96(6):1725–32.
12. Sifrim D, Holloway R. Transient lower esophageal sphincter relaxations: how many or how harmful? Am J Gastroenterol. 2001;96(9):2529–32.
13. Sifrim D, Holloway R, Silny J, Tack J, Lerut A, Janssens J. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96(3):647–55.
14. Mitchell DR, Derakhshan MH, Robertson EV, McColl KE. The role of the acid pocket in gastroesophageal reflux disease. J Clin Gastroenterol. 2016;50(2):111–9.
15. Penagini R, Bravi I. The role of delayed gastric emptying and impaired oesophageal body motility. Best Pract Res Clin Gastroenterol. 2010;24(6):831–45.

16. Knatten CK, Avitsland TL, Medhus AW, Fjeld JG, Pripp AH, Emblem R, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. J Pediatr Surg. 2013;48(9):1856–61.
17. Herregods TV, van Hoeij FB, Oors JM, Bredenoord AJ, Smout AJ. Effect of running on gastroesophageal reflux and reflux mechanisms. Am J Gastroenterol. 2016;111(7):940–6.
18. Guan J, Mao C, Feng X, Zhang H, Xu F, Geng C, et al. Fetal development of regulatory mechanisms for body fluid homeostasis. Braz J Med Biol Res. 2008;41(6):446–54.
19. Vandenplas Y, Hassall E. Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2002;35(2):119–36.
20. Murray JA, Camilleri M. The fall and rise of the hiatal hernia. Gastroenterology. 2000;119(6):1779–81.
21. Chitkara DK, Fortunato C, Nurko S. Esophageal motor activity in children with gastroesophageal reflux disease and esophagitis. J Pediatr Gastroenterol Nutr. 2005;40(1):70–5.
22. Iwanczak BM, Kosmowska-Miskow A, Kofla-Dlubacz A, Palczewski M, Grabinski M, Pawlowska K, et al. Assessment of clinical symptoms and multichannel intraluminal impedance and pH monitoring in children after thoracoscopic repair of esophageal atresia and distal tracheoesophageal fistula. Adv Clin Exp Med. 2016;25(5):917–22.
23. Crowell MD, Umar SB, Griffing WL, DiBaise JK, Lacy BE, Vela MF. Esophageal motor abnormalities in patients with scleroderma: heterogeneity, risk factors, and effects on quality of life. Clin Gastroenterol Hepatol. 2017;15(2):207–213.e1.
24. Frazzoni M, de Bortoli N, Frazzoni L, Furnari M, Martinucci I, Tolone S, et al. Impairment of chemical clearance and mucosal integrity distinguishes hypersensitive esophagus from functional heartburn. J Gastroenterol. 2017;52(4):444–51.
25. Hirschowitz BI. A critical analysis, with appropriate controls, of gastric acid and pepsin secretion in clinical esophagitis. Gastroenterology. 1991;101(5):1149–58.
26. Farre R, van Malenstein H, De Vos R, Geboes K, Depoortere I, Vanden Berghe P, et al. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. Gut. 2008;57(10):1366–74.
27. Pardon NA, Vicario M, Vanheel H, Vanuytsel T, Ceulemans LJ, Vieth M, et al. A weakly acidic solution containing deoxycholic acid induces esophageal epithelial apoptosis and impairs integrity in an in vivo perfusion rabbit model. Am J Physiol Gastrointest Liver Physiol. 2016;310(7):G487–96.
28. Ghatak S, Reveiller M, Toia L, Ivanov AI, Zhou Z, Redmond EM, et al. Bile salts at low pH cause dilation of intercellular spaces in in vitro stratified primary esophageal cells, possibly by modulating Wnt signaling. J Gastrointest Surg. 2016;20(3):500–9.
29. Quitadamo P, Di Nardo G, Miele E, Campione S, Mancusi V, Oliva S, et al. Gastroesophageal reflux in young children and adolescents: is there a relation between symptom severity and esophageal histological grade? J Pediatr Gastroenterol Nutr. 2015;60(3):318–21.
30. van Hoeij FB, Weijenborg PW, van den Bergh Weerman MA, van den Wijngaard RM, Verheij J, Smout AJ, et al. Mucosal integrity and sensitivity to acid in the proximal esophagus in patients with gastroesophageal reflux disease. Am J Physiol Gastrointest Liver Physiol. 2016;311(1):G117–22.
31. Borrelli O, Mancini V, Thapar N, Ribolsi M, Emerenziani S, de'Angelis G, et al. Dilated intercellular space diameter as marker of reflux-related mucosal injury in children with chronic cough and gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2014;39(7):733–42.
32. Borrelli O, Salvatore S, Mancini V, Ribolsi M, Gentile M, Bizzarri B, et al. Relationship between baseline impedance levels and esophageal mucosal integrity in children with erosive and non-erosive reflux disease. Neurogastroenterol Motil. 2012;24(9):828–e394.
33. Mauritz FA, Rinsma NF, van Heurn EL, Sloots CE, Siersema PD, Houwen RH, et al. Esophageal mucosal integrity improves after laparoscopic antireflux surgery in children with gastroesophageal reflux disease. Surg Endosc. 2016; doi:10.1007/s00464-016-5304-0.
34. Kandulski A, Weigt J, Caro C, Jechorek D, Wex T, Malfertheiner P. Esophageal intraluminal baseline impedance differentiates gastroesophageal reflux disease from functional heartburn. Clin Gastroenterol Hepatol. 2015;13(6):1075–81.

35. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil. 2015;27(9):1202–13.
36. Coss-Adame E, Rao SSA. Review of esophageal chest pain. Gastroenterol Hepatol. 2015;11(11):759–66.
37. Shieh KR, Yang SC, Tseng HL, Yi CH, Liu TT, Chen CL. Evidence for up-regulation of purinergic receptor genes associating with TRPV1 receptors and neurotrophic factors in the inflamed human esophagus. Curr Mol Med. 2014;14(9):1205–14.
38. Lawal A, Kern M, Sanjeevi A, Antonik S, Mepani R, Rittmann T, et al. Neurocognitive processing of esophageal central sensitization in the insula and cingulate gyrus. Am J Physiol Gastrointest Liver Physiol. 2008;294(3):G787–94.
39. Phillips ML, Gregory LJ, Cullen S, Coen S, Ng V, Andrew C, et al. The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. Brain. 2003;126(Pt 3):669–84.
40. Campanozzi A, Staiano A. Impact of malnutrition on gastrointestinal disorders and gross motor abilities in children with cerebral palsy. Brain Dev. 2010;32(2):168.
41. Del Giudice E, Staiano A, Capano G, Romano A, Florimonte L, Miele E, et al. Gastrointestinal manifestations in children with cerebral palsy. Brain Dev. 1999;21(5):307–11.
42. Vincent MV, Duncan ND. Gastroesophageal reflux and reflux oesophageal strictures in children with Cornelia de Lange syndrome. West Indian Med J. 2013;62(2):161–4.
43. Sistonen SJ, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, et al. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. Ann Surg. 2010;251(6):1167–73.
44. Alexander CL, Urbanski SJ, Hilsden R, Rabin H, MacNaughton WK, Beck PL. The risk of gastrointestinal malignancies in cystic fibrosis: case report of a patient with a near obstructing villous adenoma found on colon cancer screening and Barrett's esophagus. J Cyst Fibros. 2008;7(1):1–6.
45. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol. 2005;100(6):1243–50.
46. Nam SY. Obesity-related digestive diseases and their pathophysiology. Gut Liver. 2017;11(3):323–34.
47. Lee YY, McColl KE. Pathophysiology of gastroesophageal reflux disease. Best Pract Res Clin Gastroenterol. 2013;27(3):339–51.
48. Viazis N, Keyoglou A, Kanellopoulos AK, Karamanolis G, Vlachogiannakos J, Triantafyllou K, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. Am J Gastroenterol. 2012;107(11):1662–7.

Esophageal Clearance in Gastroesophageal Reflux

3

Maheen Hassan, Frederick W. Woodley, and Hayat Mousa

Abstract

Gastroesophageal reflux is a normal physiologic process, with multiple mechanisms in place to prevent physiologic reflux from becoming pathologic. One such mechanism is esophageal clearance. Esophageal clearance is composed of two distinct phases: volume clearance and chemical clearance. Volume clearance utilizes swallowing and esophageal peristalsis to empty the esophagus of reflux bolus and virtually all acid. Chemical clearance neutralizes the residual acid film by saliva, either swallowed or secreted by the esophagus. Combined pH-multichannel intraluminal impedance is the best technique to measure both phases of clearance. Normal values for children have been established. If either phase of esophageal clearance is prolonged, the esophagus experiences increased acid exposure, and this can result in secondary complications. There are physiologic and disease states which can impact either or both of the clearance phases. They do so by impacting the swallow, esophageal peristalsis, esophageal motility, and composition or quantity of saliva. As a result, these patients are predisposed to gastroesophageal reflux disease.

Keywords

Gastroesophageal reflux • Acid reflux • Esophageal clearance • Volume clearance • Bolus transit • Chemical clearance • Impedance • Normal values • Sleep • Body position • Pathophysiology • Pediatrics

The original version of this chapter was revised. An erratum to this chapter can be found at https://doi.org/10.1007/978-3-319-60678-1_27

M. Hassan • H. Mousa (✉)
Department of Pediatric Gastroenterology, University of California, San Diego, CA 92123, USA
e-mail: hmousa@rchsd.org

F. W. Woodley
Department of Pediatric Gastroenterology, Nationwide Children's Hospital, Columbus, OH 43205, USA

Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH 43205, USA

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_3

Gastroesophageal reflux (GER) is a normal physiologic process. It is defined as the involuntary flow of stomach content back into the esophagus [1]. Most episodes of reflux are into the distal esophagus, brief, and asymptomatic. Gastroesophageal reflux disease (GERD) occurs when reflux causes troublesome symptoms or complications [2]. It's estimated that 10% of all children have GER [3] and 1.8–8.2% have GERD [3, 4]. Inappropriate transient lower esophageal sphincter relaxation (TLESR) is the most important cause of GERD in children [5, 6]. However, we also know that mechanisms other than the lower esophageal sphincter (LES) are at play in the development of GERD, one of which includes esophageal clearance [7].

Clearance of Gastroesophageal Reflux

Efficient clearance of refluxed material following a gastroesophageal reflux episode is a major defense mechanism against esophageal mucosal damage. Clearance involves the complete removal of both the bolus and the refluxate residuals that include pepsin, hydrogen ions, and possibly bile acids. Efficiency of esophageal clearance can be assessed by using pH monitoring, manometry, scintigraphy, videofluoroscopy, and impedance. Dual pH-impedance technique has demonstrated that clearance of acid reflux is a two-step process [8–14]: a rapid volume clearance involving primary and secondary peristalsis and slow chemical clearance that neutralizes acid (Fig. 3.1).

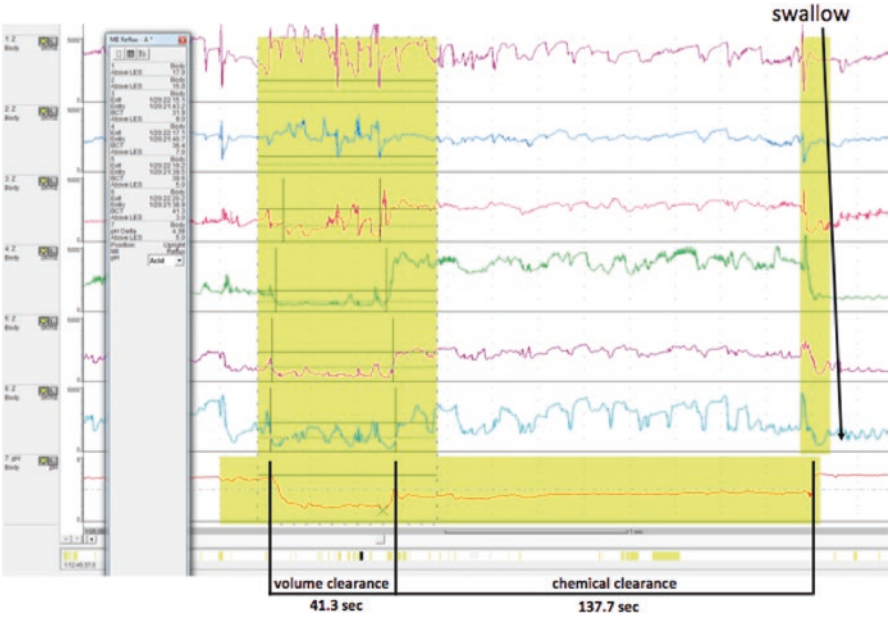


Fig. 3.1 Impedance-pH tracing illustrating both prolonged volume and chemical clearance. Upper limit (95% percentile) for volume clearance is 36 s (*upright*) [27] and for chemical clearance is 114.4 s [28]

Volume Clearance

Primary Peristalsis

The act of swallowing initiates primary peristalsis [15]. A rapidly progressing pharyngeal contraction wave transfers the bolus through the relaxed upper esophageal sphincter (UES) into the esophageal body, and a progressive circular contraction begins in the upper esophagus and proceeds distally along the esophageal body to propel the bolus through the relaxed LES [16]. Primary peristalsis clears the majority of content into the esophagus, though with ineffective peristalsis, they may be residual remains in the esophagus. Primary peristalsis is the most common motor event after reflux, making up to 90% of motor activity [17]. It is the most effective mechanism in clearing reflux episodes, demonstrating clearance in 83–90% of reflux episodes as compared to clearance of <1–6% reflux episodes with secondary peristalsis [15, 17, 18].

Secondary Peristalsis

Secondary peristalsis is regulated by mechanoreceptors in the esophageal wall that are excited by distention [16]. The presence of refluxate in the esophageal lumen stimulates, via mechanoreceptors, distention-induced secondary peristalsis which rapidly propels the bulk of the refluxed bolus back into the stomach.

Chemical Clearance

While volume clearance is known to be accomplished by esophageal peristalsis, chemical clearance is known to be accomplished primarily by bicarbonate-rich saliva that neutralizes acid and washes the esophageal walls of gastric and duodenal debris [9]. Contents of this debris include hydrogen ions, pepsin, and bile acids [9, 19, 20]. Salivary volume dilutes intraluminal acid and pepsin within gastroesophageal reflux and carries it back to the stomach [21]. Chemical clearance can last at least twice as long as volume clearance [8, 22], and, in infants, chemical clearance can persist up to six times longer [8].

Since the groundbreaking study performed by Helm and colleagues in 1984 demonstrated the two-phase clearance of reflux, other groups have conducted research directed toward the study of esophageal submucosal glands and their potential impact on the neutralization of refluxed esophageal acid. In 1980, Boyd and colleagues were the first to demonstrate alkaline secretion in the esophagi of both the opossum and the rabbit [23]. A comparison of the two animal models showed that, despite similarities in epithelial structure, ion permeability, and transport function, the opossum esophagus is superior in its alkaline secretion (20-fold greater) and acid clearance (fivefold greater), revealing a structure in the opossum esophagus that was not present in the rabbit, i.e., the esophageal

submucosal gland. In a later study, another group was able to detect secretion of bicarbonate ions in the human esophagus [24]. Their study showed that, in humans, submucosal glands secrete bicarbonate in amounts sufficient to neutralize residual acid in the esophagus following volume clearance. They found that bicarbonate secretion approached the secretion levels of salivary glands at rest [20, 24]. It is now clear that acid neutralization during chemical clearance is accomplished at least in part due to submucosal glands secreting bicarbonate directly into the lumen of the esophagus.

Measuring Volume Clearance

Volume clearance is the first step in the clearance of a gastroesophageal reflux event. In modern times, it is typically measured using multichannel intraluminal impedance (MII). The basic principle of this methodology rests on the change in electrical impedance that occurs as a bolus moves in either antegrade of retrograde direction within the esophageal lumen. The electrical conductivity of air is close to zero, while that of a liquid bolus is relatively high when compared to the low conductivity of the lumen wall. As liquid bolus moves proximally within the esophageal column, as with a reflux event, the electrical impedance (roughly equal to the inverse of conductivity) decreases. The classic impedance catheter, containing usually seven impedance electrodes and thus creating six impedance channels, permits the tracking of the bolus as it ascends the column of the esophagus. A reflux event that effects a drop in impedance in the proximal-most impedance channel (channel 6) is deemed to have reached the area of the esophagus nearest the upper esophageal sphincter.

Typically impedance catheters will contain an antimony pH electrode located in the center of one of the distal channels. For the infant catheter, this electrode is located within the distal-most channel (channel 1). For children, adolescents, and/or adults, it is located within the second channel nearest the LES (channel 2). The distance between adjacent impedance electrodes along the length of the catheter is 1.5 cm for the infant and pediatric catheters and 2.0 cm for the adolescent/adult catheter. Insertion of the catheter is generally performed transnasally, although craniofacial abnormalities may necessitate oral insertion. The Strobel formula ([(height × 0.252) + 5] × 0.87) is generally used to estimate the depth (cm) at which the catheter is inserted [25]. Proper positioning is then confirmed by radiography and subsequently adjusted, as necessary, so as to ensure that the pH electrode is positioned above the LES by 13% of the total distance between the nostrils and the LES.

The efficiency of volume clearance of a reflux episode is generally assessed using the most distal impedance channel (channel 1). By definition, the presence of the refluxate is evidenced when the impedance waveform drops to 50% of the pre-reflux impedance baseline. The bolus is cleared from the distal esophagus when the impedance waveform again reaches 50% of impedance baseline [26]. The presence of six impedance channels permits assessment of bolus exposure times in all

channels in which the impedance has dropped below and then extends to and beyond 50% of baseline.

Esophageal manometry is often used in conjunction with MII so that defects in esophageal motor function can be temporally correlated with volume clearance.

Measuring Chemical Clearance

As mentioned previously, chemical clearance is the period that immediately follows volume clearance; during this time, the esophageal mucosa is being returned to pre-reflux conditions. Events that must occur include (1) return of gastric and duodenal molecules back to the stomach and (2) in the case of acid reflux, neutralization of the refluxed acid to pre-reflux physiological pH. The trace numbers of gastric and duodenal molecules are transported back to the stomach by swallowed saliva. Neutralization of refluxed acid is accomplished by the bicarbonate and protein present in saliva, in addition to the bicarbonate that is secreted directly into the esophageal lumen from submucosal glands.

While some groups have considered all periods during which neutralization of esophageal acidification is occurring to be examples of chemical clearance, ignoring the fact that volume clearance may be occurring simultaneously, to date, only one group has attempted to assess chemical clearance efficiency, independent of volume clearance, using combined multichannel intraluminal impedance and pH monitoring (MII/pH).

Chemical Clearance Duration and Rate Calculations In 2007, Woodley and Mousa reported the results of a study in which they assessed the efficiency of chemical clearance over the course of a 24-h period in formula-fed symptomatic infants, birth to 12 months [8]. In their study, chemical clearance was defined as the duration of esophageal acidification (determined by pH monitoring) that immediately followed the end of volume clearance (determined by impedance). Chemical clearance began the moment the impedance waveform in channel 6 (distal channel) returned to 50% of baseline and ended when the pH waveform reached pH 4. Their study showed that chemical clearance is significantly prolonged during fasting in infants.

In 2014, Woodley and Mousa used MII/pH to characterize gastroesophageal reflux in symptomatic children, aged 3–18 years, with and without cystic fibrosis (CF) [27]. The results showed that while CF patients do not have more frequent reflux, or reflux that reached the hypopharynx, chemical clearance was significantly prolonged, as evidenced by the significantly higher nadir pH. The average duration of chemical clearance was approximately 123 s for the CF children and 66 s for the children without CF. In spite of the fact that the difference in chemical clearance duration was significantly prolonged in the CF children, it was not clear as to whether 123 s or 66 s was outside the normal range.

To address the question of physiological norms, Woodley and Mousa (2015) derived reference values for acid neutralization during chemical clearance for two groups: (1) infants, age birth to 12 months, and (2) children, aged >12 months to

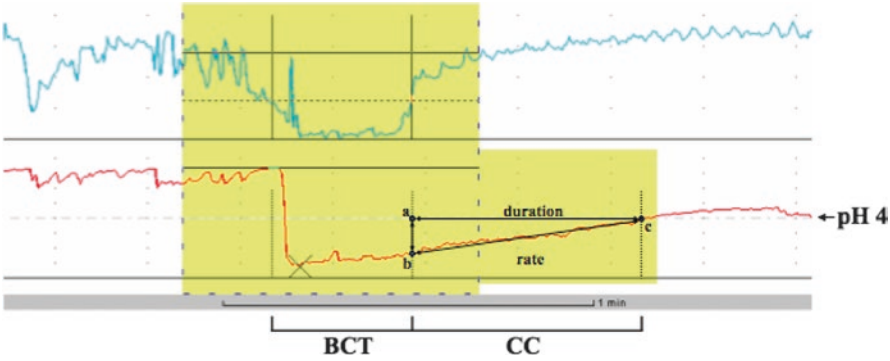


Fig. 3.2 Calculating chemical clearance rates

<18 years [28]. In their retrospective study, the authors enrolled patients who (1) had not had a fundoplication, (2) had no positive reflux-symptom associations, and (3) were not taking anti-reflux medications at the time of the study, (4) had impedance studies in the past 18 years, (5) and had AGER indices ≤3% for the children and ≤6% for the infants. Ethical considerations prevented the use of healthy subjects. In addition to calculating chemical clearance "duration" (seconds) for these two groups, they also reported the chemical clearance "rate." The chemical clearance rate was defined as the number of pH units that were neutralized per second. Chemical clearance rate for each two-phase acidic event was calculated by determining the nadir pH at the beginning of chemical clearance and subtracting from pH 4 (the pH at which the esophagus is no longer considered acidic) to generate the pH. pH was then divided by the number of seconds (number of pH units/second) (Fig. 3.2). The upper end of physiological chemical clearance duration was reported at 95% percentile (148.5 s for infants and 114.4 s for children), while the lower end of physiological chemical clearance rate was reported at the 5% percentile (0.0088 pH units/s for infants and 0.0465 pH units/s for children) [28].

PSPW Index

The post-reflux swallow-induced peristaltic wave (PSPW) Index is another means of assessing chemical clearance. It has recently been developed and has been used to show that impairment of esophageal chemical clearance represents a primary pathophysiological mechanism in gastroesophageal reflux disease (GERD) [29].

PSPW is defined as a 50% drop in impedance, relative to baseline, in the most proximal impedance channel, and extending similarly to all of the distal impedance channels [29, 30]. Those swallows not reaching the distal-most channel are excluded. Only those PSPWs that occur within 30 s from the end of a reflux episode are counted, in an attempt to limit overlap with spontaneous swallows and

considering the latency of saliva secretion in response to esophageal acidification [29]. The PSPW index then is calculated by dividing the total number of valid PSPWs per tracing by the number of total number of impedance-detected reflux events. The greater the PSPW index, the greater the chemical clearance efficiency.

The theory behind this novel impedance metric is that esophageal clearance depends on volume clearance and chemical clearance; volume clearance depends on a secondary peristaltic wave, which removes the vast bulk of the refluxate, while removal of trace amounts of gastric and duodenal debris and acid neutralization occurs only after saliva is transported by a swallow-induced peristaltic wave [31]. Early use of the PSPW index by Frazzoni and colleagues [29] with erosive reflux disease (ERD) patients, nonerosive reflux disease (NERD) patients, and controls showed that the PSPW index was significantly lower in 31 ERD patients (15%) and 44 NERD patients (33%) off-proton pump inhibitors (PPI) compared to 30 controls (75%). The PSPW index was also significantly lower in 18 ERD patients (16%) and 48 NERD patients (31%) on-PPI compared to 26 on-PPI functional heartburn patients (67%). In 29 PPI-refractory patients, the PSPW index was unaffected by fundoplication: 21% for preoperative and 20% for postoperative. The overall sensitivity, specificity, and positive and negative predictive values of the PSPW index for identifying GERD patients in this study were 97, 89, 96, and 93%, respectively [29]. The PSPW index also correlates with GERD symptoms. In a retrospective study of 143 patients, the PSPW index was significantly lower in patients with heartburn and negatively correlated with heartburn; it did not correlate with dysphagia symptoms [32]. This showed patients with delayed clearance had a complaint of heartburn more than dysphasia.

Remarkably, the PSPW index is calculated by considering both acid (pH <4) and nonacid (pH ≥4) reflux episodes. Classic considerations of chemical clearance were directed toward acid reflux events and ensuing acid neutralization that occurred following the volume clearance of these episodes [10]. The reality is that all gastroesophageal reflux events have a chemical clearance component independent of pH and, indeed, the damaging effects of prolonged acid exposure is only one consideration when contemplating the hazards of delayed or prolonged chemical clearance. All refluxates contain pepsin, a proteolytic enzyme that will damage esophageal epithelial cells at pH levels within the physiological range of the pre- and postreflux esophageal milieu. Prolonged chemical clearance of nonacid (pH 4) can have severe clinical implications.

Toward this end, Woodley and colleagues [33], having originally detected prolonged neutralization of acid during chemical clearance of acid reflux episodes in children with CF, used the PSPW index to assess the efficiency of nonacid chemical clearance in symptomatic children with and without CF. Their data showed that chemical clearance during nonacid reflux events was significantly more efficient in children without CF (89% vs 32%). The ability to assess the chemical clearance of both and nonacid reflux events suggests that the PSPW index may be a superior method for assessing chemical clearance of gastroesophageal reflux types.

Physiologic Influences on Esophageal Clearance

The process of esophageal clearance can generally be separated into two discrete phases. First, with volume clearance, the bolus and virtually all the acid are emptied from the esophagus by swallowing and peristalsis [8, 9]. Second, with chemical clearance, the residual acid film is neutralized by swallowed saliva, which is bicarbonate rich [9, 10]. Thus, the process of esophageal clearance may be prolonged by either abnormal esophageal emptying or impaired salivation. There are physiologic states and disease processes that can impact either of these steps and lead to delayed esophageal clearance.

Sleep

Esophageal clearance has been documented in multiple adult studies to be prolonged in the sleep state as opposed to the awake state [34–37], whether it be in those with known gastroesophageal reflux disease or controls [38]. Similar findings are seen in infants. In a study on infants under 12 months old [39], which included both a gastroesophageal reflux group and control group, acid clearance was equivalent between the two groups while awake. In the sleep state, acid clearance was unchanged in the control group, while 500% greater in the gastroesophageal reflux group.

In adults, clearance times are not affected by the degree of acidity, as shown in one study which showed similar esophageal clearance times during sleep with infusions of pH 3.0 and 1.2 [36] and in another study which showed acid clearance 2.5–3 times greater in the sleep state regardless of the acid reflux index (ARI) being $\leq$7% or >7% [33]. Esophageal peristaltic parameters of amplitude, velocity, and duration also did not differ between the sleep and awake states [34]. Similarly, in infants, there was no difference in the following that explained the difference in sleep acid clearance: minimum pH during sleep, the percentage of swallows resulting in esophageal peristalsis, or frequency of secondary peristaltic waves [39].

The decrease in esophageal clearance during sleep is thought to be multifactorial. During sleep, there is a reduction in the frequency of swallowing, which decreases volume clearance. In infants with pathological reflux, swallowing rate decreased from 4 times per minute in the awake state to 0.1 time per minute in the sleep state [39]. In adults, the swallowing rate decreases from 25 times an hour in the awake state to 5 times an hour in the sleep state [40]. Sleep also suppresses pharyngeal muscle activity, which may further contribute to decreased ability to swallow [41]. There is also significantly reduced saliva production during sleep, which will lead to delayed chemical clearance [41, 42].

There are few studies to date that have examined the efficiency of esophageal clearance over the course of a 24-h period. In 2016, Sankaran et al. reported the results of a study in which they examined the pattern of GER events in the sleep and awake states [33]. They tested infants with 24-h pH-impedance studies with concurrent video-polysomnography for 6 h. They found that increasing acid reflux index

(defined as % duration that esophageal pH is <4) was associated with an increased frequency of acidic events and increased clearance time. Consistent with the group's prior study [43], there were more GER events in the awake state, including both weakly acidic and acidic impedance events. This was attributed to a higher frequency of transient LES relaxation and postprandial gastric distention during awake state. Similar to prior studies, acid clearance was significantly longer in the sleep state versus the awake state. However, when they compared the ARI >7% group to the ARI ≥3 to ≤7%, they found that the number of reflux events, acid clearance time, and symptom index was higher in the former, only in the awake state and not in the sleep state. When they pooled their data, they found that for each unit increase in ARI, the rate of change in acid clearance time was less in the sleep state versus the awake state. This could suggest that at higher ARI, sleep and supine positions may have a protective reflex to prevent excessive acid exposure. These may include rapidly neutralizing acid, increasing frequency of swallowing, increased esophageal peristalsis, or higher threshold for LES relaxation when exposed to acidity. The conclusion that was drawn was that, over 24 h, the greater magnitude of esophageal acidification is secondary to increased frequency of reflux during the awake state.

Body Position

There have been conflicting studies regarding body positioning impacting esophageal clearance. Two studies noted improvement in esophageal clearance when going from a supine to sitting position, though the change was not statistically significant [10, 37]. Another study noted significant improvement in esophageal clearance with a 30-degree bed elevation as compared to supine [44]. In this study, the improvement in esophageal clearance correlated significantly with relief of heartburn and sleep disturbance. When comparing left and right lateral decubitus position, there is increased exposure to pH <4 in the right lateral decubitus position, both due to increased reflux episodes and prolonged clearance [45].

Gravity is thought to play a role in body position affecting clearance, with the supine positioning allowing material to stay in the esophagus longer given that gravity is not opposing it [44]. However, given inconsistencies in significant findings correlating the two parameters, it is unlikely that gravity contributes significantly to esophageal clearance in the presence of normal esophageal peristalsis. Esophageal motility also differs based on body positioning. When comparing patient swallows in the supine versus upright position using high-resolution manometry (HRM), solid swallows while supine occurred with more hypotensive peristalsis [46]. Liquid swallows showed a faster peristaltic wave velocity in the upright position, with reductions in amplitude and duration of contractions [47–50]. In a study aiming to evaluate the impact of motility in esophageal clearance, ten healthy subjects were evaluated via simultaneous manometry, pH, and impedance [51]. An esophageal acid bolus was given, both while upright and supine. In those with moderate ineffective esophageal clearance, defined as 30–80% abnormal peristaltic sequences, upright and supine positioning did not have an effect on esophageal

clearance. In patients with severe ineffective esophageal motility, defined as >80% abnormal peristaltic sequences, volume clearance was slightly prolonged in the upright position and significantly prolonged in the supine position. This study showed that only severe ineffective esophageal motility affected esophageal clearance when supine.

Feeding

To date, consequently, there has been a dearth of studies that have examined the efficiency of esophageal clearance over the course of a 24-h period. In 2007, Woodley and Mousa reported the results of a study in which they examined the effects of feeding on the efficiency of volume clearance and chemical clearance in 12 symptomatic infants (aged 1–44 weeks). In their study, they calculated median durations of volume clearance and chemical clearance during feeding, the 1st hour postprandial, the 2nd hour postprandial, and fasting (defined as the period of time beginning 120 min after feeding and extending until the next feeding). Events occurring during sleep were discarded. Their data showed that while volume clearance remained virtually unchanged over the course of the study, chemical clearance became increasingly less efficient the further the patient was from feeding. The median duration of chemical clearance in the fasting state (132 s) was statistically less efficient when compared to the feeding (13 s) and 1st hour postprandial (64 s) states. To test the possibility that decreasing chemical clearance over the course of the feeding cycle was due to coordinate decreases in pH nadir of refluxates, a mixed model was used to test the relationship between pH nadir and chemical clearance. This examination failed to achieve statistical significance. These data suggest that esophageal clearance as a function of time of day is likely to affect chemical clearance but not volume clearance. The authors of this study concluded that increases in hydrogen concentration over time following a feed cannot explain the corresponding chemical clearance inefficiency during later phases of the feeding cycle and that reduced efficiency of acid clearance mechanisms may be due to decreased salivation, peristalsis, and/or intraluminal secretion in the fasting state.

Disease States Impacting Esophageal Clearance

Gastroesophageal Reflux Disease

Given that volume clearance is composed of both primary and secondary peristalsis, clearance can be impaired when there is a disturbance in peristalsis. When comparing primary peristalsis in control patients versus those with GERD, one study found no difference in the amplitude, duration, and velocity of primary peristalsis contractions [52]. However, control patients had more frequent and effective peristalsis, with a greater pH response per swallow. These findings have been confirmed by later studies. In a retrospective review of combined impedance-esophageal

manometry data of GERD, functional heartburn, and control patients, ineffective esophageal contractions and abnormal bolus transit were more frequent in GERD and functional heartburn patients than in controls [53]. Bolus transit was slower in GERD patients and was associated with a longer acid clearance. This further demonstrated that GERD patients have peristaltic dysfunction and incomplete and slower esophageal bolus transit, thereby predisposing them to prolonged acid contact.

In one study aimed at evaluating the integrity of secondary peristalsis, air and water were injected into the mid-esophagus of GERD and control patients [54]. It was found that secondary peristalsis was triggered significantly less frequently in GERD patients as opposed to controls and that the major pattern of failure was a complete absence of secondary peristaltic response. These findings were confirmed by a separate study that showed that triggering of secondary peristalsis was defective in nonerosive reflux disease [55]. Patients with heartburn were also shown to have infrequent and ineffective secondary peristalsis [56]. One study was able to demonstrate that ineffective esophageal motility associated with defective triggering of secondary peristalsis contributed to impaired esophageal clearance. In this study, the following patient groups were studied: (1) controls, (2) ineffective esophageal motility without GERD, and (3) ineffective esophageal motility with GERD. Only the last group showed a larger threshold volume to induce secondary peristalsis and a lower frequency of peristaltic response.

It is not known if GERD results from a primary defect in motility or if inflammation leads to impaired motility. There have been studies that suggest the latter. When comparing patients with GERD, patients with and without esophagitis, and controls, those with esophagitis had lower amplitude of primary contractions, less secondary peristaltic episodes, and lower amplitude of secondary peristaltic episodes [57]. This suggests that esophagitis itself impairs both primary and secondary peristalsis.

Achalasia

Achalasia is a primary motility disorder characterized by absence of esophageal body peristalsis and incomplete relaxation of the lower esophageal sphincter (LES) [58]. This disease results from acquired degeneration of the Auerbach's myenteric plexus, resulting in loss of inhibitory enteric neurons [59]. As a result, there is an imbalance between excitatory and inhibitory input, leading to ineffective esophageal peristalsis and LES relaxation. This results in symptoms of progressive dysphagia, regurgitation of undigested food not mixed with gastric secretions, and chest pain [60]. The diagnosis is confirmed by esophageal manometry. While achalasia can be classified into three subtypes, the absence of esophageal body peristalsis is needed to make the diagnosis.

Given that the esophagus is aperistaltic in achalasia, esophageal clearance is thought to occur passively, as the pressure builds up in the esophagus and opens up the LES [61]. As such, it is not surprising that abnormal bolus transit is noted uniformly on esophageal manometry [62]. On combined multichannel intraluminal impedance

and esophageal manometry (MII-EM), all patients show a low baseline impedance level in the distal esophagus [63, 64], suggesting stasis of fluids, as well as elevated intraesophageal pressure [64]. It has been shown that intrabolus pressure is what drives the bolus through the esophagus and the intrabolus pressure depends on the force generated by esophageal contraction and resistance to bolus movement [65]. In achalasia, resistance to flow may be difficult to pick up at small volumes, given that the esophageal body can become relatively dilated. In these cases, performing multiple repeated swallows can reveal a resistance to flow and the LES, as there will be progressively large volume and progressively larger resistance built up [66].

Systemic Scleroderma

Systemic scleroderma is a complex autoimmune disease characterized by collagen deposition in tissues [67]. The primary event triggering the onset is unknown, but the resulting endothelial damage induces mononuclear cell infiltration of vascular tissue that over time results in deposition of fibrotic tissue, affecting the skin and various internal organs [68]. It is estimated that up to 90% of patients with scleroderma have some degree of gastrointestinal fibrosis, which can include the mouth, esophagus, stomach, small intestine, large intestine, and liver [67]. Esophageal involvement is the most common. Myenteric neural dysfunction and destruction from collagen deposition or autoantibodies, smooth muscle inflammation and atrophy, and fibrosis lead to incoordination or paralysis of muscles [69, 70].

Impaired esophageal clearance has been demonstrated by esophageal transit scintigraphy [71], manometry [72, 73], and impedance testing [74, 75] and is multifactorial in nature. Manometry studies show that scleroderma patients have an incompetent LES and low-amplitude smooth muscle contractions of the esophagus [70]. The impaired peristalsis correlates to delayed clearance of acid and increased exposure time to acid [72]. The retrograde movement of gastric contents, related to the low LES pressure, further exposes the esophagus to acidity, which can further compromise peristalsis. When comparing patients with scleroderma and those with no connective tissue disorders, those with systemic sclerosis had significantly fewer reflux events, though they were of significantly longer duration [74]. From this observation, it is hypothesized that decreased esophageal peristalsis leading to decreased esophageal clearance is the primary contributor to acid exposure as opposed to incompetent LES causing increased reflux events.

As a result of increased acid exposure to the distal esophagus, patients with scleroderma are at increased risk of distal esophagitis, Barrett's esophagus, and esophageal strictures if the acid is not controlled. However, the presence and severity of gastroesophageal symptoms do not always reflect the severity of esophageal involvement, with many patients being asymptomatic despite having esophageal dysmotility [75–77]. One study noted that symptoms of heartburn, dysphagia, and regurgitation were notably absent in the majority of scleroderma patients who had severe esophageal dysmotility, including failed peristalsis >75%, hypotensive LES, and acid reflux >200 times per day [75].

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is an antigen-driven T_H2 inflammatory disorder, whereby esophageal inflammation results from repeated exposure to food and/or aeroallergens in genetically susceptible individuals. This chronic inflammation can lead to structural remodeling, ultimately resulting in esophageal strictures [78], as well as a vast symptom profile. While older children and adults experience symptoms of dysphagia and food impaction, younger children are more likely to experience feeding refusal, symptoms of gastroesophageal reflux disease, failure to thrive, chest pain, emesis, or abdominal pain [79–81]. The clinical symptoms and complications of EoE are largely a consequence of esophageal remodeling. Remodeling changes include epithelial basal zone hyperplasia, lamina propria fibrosis, increased vascularity, and epithelial-mesenchymal transformation, which leads to smaller esophageal diameter, increased smooth muscle mass with smooth muscle dysfunction, decreased esophageal compliance, and increased esophageal stiffness [82].

EoE releases agents that relax the lower esophageal sphincter [83, 84] and have direct cytotoxic effects on the epithelium, making the epithelium more susceptible to injury from refluxed material [85, 86]. Esophageal remodeling secondary to EoE can cause esophageal dysmotility resulting in impaired acid and refluxate clearance and thus increased acid exposure [87–89]. Dysmotility is demonstrated by different diagnostic techniques. Results from stationary esophageal manometry are varied, with primary motility disorders being rare, presence of decreased LES tone occasionally picked up, and the remaining being nonspecific abnormalities in esophageal peristalsis [90, 91]. Up to one third of children with EoE show abnormalities in esophageal peristalsis. In a study using prolonged esophageal manometry and pH metry, children with EoE had an increased number of isolated and high-amplitude contractions and higher percentage of ineffective peristalsis as compared to children with GERD and controls [89]. Abnormal peristaltic events correlated with dysphagia. The most frequent abnormality picked up by high-resolution manometry in one study was pan-esophageal pressurization [92], while in another it was weak and failed peristaltic integrity [87]. Pan-esophageal pressurization is thought to be due to reduced esophageal compliance and is associated with bolus impaction [92]. The use of combined impedance and manometry suggests that motility abnormalities may not effectively represent esophageal function, as almost half of ineffective swallows on manometry have normal bolus transit [62]. In children, 75% of swallows with ineffective peristalsis have effective bolus clearance. Functional luminal impedance shows decreased esophageal compliance and distensibility in EoE patients compared to controls [93], with decrease correlated with the rate and future risk of food impactions [94].

Cystic Fibrosis

Cystic fibrosis (CF) is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene, which results in abnormal chloride transport in multiple organs [95]. This leads to thickened secretions, including mucous, bile, and pancreatic

juices. Gastroesophageal reflux is common in CF and is likely promoted by several factors: airway hyperinflation from obstructive lung disease, frequent cough leading to increased intra-abdominal pressure, increased frequency of transient lower esophageal sphincter relaxations, chest physiotherapy increasing GER, high-fat diet, and delayed gastric emptying [95, 96]. In a recent study [97], the time relation between GER and cough was studied in children, and the cough-reflux sequence was noted to be rare, with cough responsible for 0.01% of esophageal acid and 0.005% of volume exposures. It was determined that GER was a primary process in these children, and not secondary to cough.

When using pH metry, acid exposure and duration can be determined. Compared to controls, CF patient had increased (1) acid GER (AGER) frequency, (2) average duration of acid reflux events, and (3) reflux index. Reflux index is defined as the percentage of total monitored time that the esophageal pH <4 [98]. In order to better assess if the increased acid exposure in CF patients is due to volume clearance, chemical clearance, or both, combined esophageal pH monitoring and multichannel intraluminal impedance (pH-MII) has been utilized. This methodology allows detection of both acid and nonacid GER; detects anterograde versus retrograde flow; determines the height of refluxate; differentiates between liquid, gas, or mixed refluxate; and differentiates between volume and chemical clearance [99, 100]. When reflux and acid exposure was assessed using pH-MII in symptomatic GERD children, both with CF and age-matched controls, it was found that CF children had more effective bolus clearance but delay in acid clearance [27]. It was the delayed acid clearance, not an increase in frequency of acid reflux events or degree of acidity, which led to increased AGER duration.

Clearance of reflux typically occurs in two phases: volume clearance followed by chemical clearance. In chemical clearance, acidified esophageal mucosa is neutralized by saliva. Saliva reaches the distal esophagus via two mechanisms: (1) oral saliva, produced mainly by the submandibular, parotid, and sublingual glands transported via primary and secondary peristalsis [101], and (2) direct secretion into the esophagus by esophageal submucosal glands [20]. In CF, chemical clearance is affected by oral saliva having lower bicarbonate secretion, reduced flow rate, and higher viscosity [102]. In an in vitro model, the cystic fibrosis mutation is shown to impair bicarbonate secretion from the submucosal gland, resulting in lower basal bicarbonate secretion and also decreased bicarbonate production when the gland is stimulated [20]. Chemical clearance may also be affected by gastric hypersecretion and increased acidity, in which more acidic material would take longer to clear [27].

Esophageal Atresia-Tracheoesophageal Fistula

GERD is common in esophageal atresia (EA)-tracheoesophageal fistula (TEF), affecting between 22 and 75% of pediatric patients [103–105] and leading to complications such as recurrent anastomotic strictures, dysphagia, failure to thrive, and recurrent respiratory infections. EA patients are at increased risk for GER due to both intrinsic dysmotility and structural factors. Primary dysmotility is a result of

abnormal development of the esophageal smooth muscle, with distorted smooth muscle tissue, fibrous tissue in between muscle layers [106], degeneration of smooth muscle cells [106], and tracheobronchial remnants in the form of disorganized muscle, abnormal mucous glands and ducts, and cartilage [107]. In addition, abnormal congenital neural innervation of the esophagus contributes to esophageal dysmotility. The Auerbach plexus is hypoplastic, with marked hypoganglionosis and immature ganglion cells [108–110]. The interstitial cells of Cajal (ICC) are absent or decreased in number [111]. Structurally, most EA patients lose some function of the anti-reflux barrier after surgical repair, particularly those with long-gap EA. In long-gap atresia, gastric pull-up causes the lower esophageal sphincter to no longer overlap with the crural diaphragm, weakens the phrenoesophageal ligament, decreases the angle of His, and creates a hiatal hernia [112–114].

While 24-h pH monitoring is a useful tool to determine acid burden, children with EA are more often found to have weakly acid or nonacid GER [115, 116], making pH-MII a more useful tool. In addition, pH-MII can detect both volume and chemical clearance.

GER, compounded by EA patients who almost universally have esophageal dysmotility [115, 117], leads to impaired reflux clearance. Both volume and bolus clearance are significantly delayed in infants and older children with EA as compared to controls [116, 118, 119], and the delay in clearance parameters correlates with patient symptoms [119, 120]. Studies have demonstrated the relationship between poor esophageal clearance and esophageal dysmotility. In one study, while 79% of swallows were accompanied by abnormal motility patterns, approximately 60% of swallows showed abnormal bolus transit and 66% of all GER episodes initiated no clearing mechanism [121]. Furthermore, EA patients have a significantly lower percentage of complete bolus transit for liquid and viscous swallows, and their higher bolus index and reflux indices are significantly related to increased symptom scores [122]. Using ambulatory manometry, one study showed that TEF patients had an ineffective peristaltic pump, with remarkably disorganized propulsive activity and with almost all waves being ineffective [123]. The propulsion of ingested material and clearance of reflux in these patients was primarily being done by gravity. In the recumbent position, the majority of reflux events were detected, and clearance was very prolonged [120, 123].

Barrett's Esophagus

Barrett's esophagus (BE) is a complication of GERD, characterized by metaplasia of the distal esophagus, replacing the stratified squamous epithelium by simple columnar epithelium. It is a premalignant lesion that has the potential to develop into esophageal adenocarcinoma. Risk factors include male gender, genetics, white ethnicity, family history, obesity, hiatal hernia, smoking, and *H. pylori* [124]. Conditions that predispose the distal esophagus to acid promote the development of BE. These include hypotensive lower esophageal sphincter (LES) [125], presence of hiatal hernia [126], and esophageal peristaltic dysfunction [127].

Esophageal clearance is in part activated and regulated by reflexes triggered by esophageal distention [54, 128], and patients with BE have been shown to be hyposensitive to mechanical distention, which affects esophageal clearance [129]. Multiple studies show that patients with BE have increased acid exposure and prolonged acid clearance time [130, 131]. In a study with standardized esophageal acid clearance test and pH-MII testing, BE patients swallowed 60% more often than controls with shorter acid clearance; however, they still had greater acid exposure compared to controls [132]. It was concluded that acid-evoked, protective reflexes facilitated more frequent swallowing. This compensatory mechanism is still inadequate, given the fact that large-volume repeated reflux occurs in BE patients as a result of decreased LES tone and the high prevalence of hiatal hernia.

Hiatal Hernia

In sliding hiatal hernias, there is a weakness of the phrenoesophageal ligament leading to an upward displacement of the LES into the lower mediastinum. As a result, the defense of LES, angle of His, and the diaphragm are compromised [112]. The LES and crural diaphragm no longer overlap, and the LES length and pressure are reduced. This leads to increased frequency and volume of refluxate.

Additionally, hiatal hernia patients have delayed esophageal clearance. This occurs when a hernia sac is created between the LES proximally and the crural diaphragm distally [113]. This sac has increased acid exposure and impaired clearance, since after an episode of reflux, the reflux is cleared by secondary peristalsis, but a small amount of acid can get trapped in this sac. The retained fluid will then reflux back up during subsequent swallow-induced relaxations of the LES [113]. This repeated sequence can significantly prolong esophageal acid clearance.

In a study aimed to prove that hiatal hernias contribute to delayed acid clearance, hiatal hernia and GER patients underwent simultaneous esophageal pH recording and radionuclide scans [133]. Acid clearance was found to be faster at 10 cm above the LES as opposed to 5 cm above the LES across all patients. However, clearance was slower 5 cm above the LES in hiatal hernia patients as compared to GER patients. In GER patients, each swallow resulted in an increase in pH, but in hiatal hernia patients, there was a biphasic pH response, with an initial fall in pH before a rise. This biphasic response corresponded to radionuclide studies showing reflux into the esophagus followed by clearance, with each swallow. This study helped demonstrate that acid trapped in the hiatal hernia sac can reflux during swallows, when the LES relaxes, leading to repeated episodes of acid reflux contributing to delayed acid clearance.

Another mechanism that will contribute to delayed esophageal clearance is impaired esophageal peristalsis, as hiatal hernia patients have lower-amplitude peristalsis in the distal esophagus [134]. By evaluating patients with esophageal manometry and barium swallow, one study was able to correlate delayed clearance in hiatal hernia patients to lower frequency and amplitude of esophageal body peristalsis [135].

Those with large hiatal hernias are at increased risk for prolonged acid exposure, as they have a shorter and weaker LES, greater amount of reflux, and less-efficient

acid clearance [136]. While most studies have shown that hiatal hernia contributes to delayed clearance in the distal esophagus, another study showed that patients with hiatal hernias have decreased esophageal clearance in both the proximal and distal esophagus [137]. This prolonged clearance was independent of body position.

Benefits and Limitations in Measuring Clearance

The 24-h esophageal pH monitoring measures the frequency and duration of esophageal acid reflux, thereby quantifying esophageal acid burden. While the sensitivity of abnormal esophageal pH in predicting erosive esophagitis in adults and children is high, ranging from 83 to 100% [138, 139], there are limitations to standard pH monitoring. It is a poor detector of weakly acid (pH 4–7) reflux [140] and can also overestimate acid exposure by picking up "pH-only" episodes, in which there is no detected retrograde liquid refluxate [141]. In infants and children, weakly acid GER is more prevalent than in adults [141, 142], which can explain why symptoms are not always detected by esophageal pH monitoring [138]. Clearance, particularly of nonacid reflux, cannot be picked up by pH testing alone.

Impedance monitoring has the ability to detect direction of flow; differentiate between liquid, gas, or mixed refluxate; and detect reflux regardless of pH volume [99]. Alone, impedance is able to measure volume clearance. In a study of 73 patients, pH-detected acid clearance time was significantly longer than impedance-detected bolus clearance time, in upright and recumbent positions [143]. The greatest difference was seen in the recumbent position. Measuring volume clearance alone leads to underestimation of acid exposure to the esophagus, given that volume clearance happens quickly as compared to chemical clearance.

With pH-MII, together, both volume and acid clearance can be measured. pH-MII optimizes the yield of GER-symptom association in infants and children [144]. Indications of pH-MII include (1) evaluating the efficacy of anti-reflux therapy, (2) endoscopy-negative patients with symptoms concerning for reflux despite PPI therapy in whom documentation of nonacid reflux will alter clinical management [99, 145], and (3) evaluating tube-fed patients for reflux, as the majority of refluxate during tube feeding is nonacidic [99]. Limitations of pH-impedance testing include limited availability in all medical centers, time consuming to interpret, and when baseline impedance is low, it can be hard to pick up reflux events.

References

1. Vandenplas Y, Hassall E. Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2002;35(2):119–36.
2. Sherman PM, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104(5):1278–95. quiz 1296
3. Martigne L, et al. Prevalence and management of gastroesophageal reflux disease in children and adolescents: a nationwide cross-sectional observational study. Eur J Pediatr. 2012;171(12):1767–73.

4. Nelson SP, et al. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med. 2000;154(2):150–4.
5. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. Gastroenterology. 1997;113(2):399–408.
6. Werlin SL, et al. Mechanisms of gastroesophageal reflux in children. J Pediatr. 1980;97(2): 244–9.
7. Helm JF. Esophageal acid clearance. J Clin Gastroenterol. 1986;8(Suppl 1):5–11.
8. Woodley FW, Fernandez S, Mousa H. Diurnal variation in the chemical clearance of acid gastroesophageal reflux in infants. Clin Gastroenterol Hepatol. 2007;5(1):37–43.
9. Helm JF, et al. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med. 1984;310(5):284–8.
10. Helm JF, et al. Determinants of esophageal acid clearance in normal subjects. Gastroenterology. 1983;85(3):607–12.
11. Richter JE, et al. Relationship of radionuclide liquid bolus transport and esophageal manometry. J Lab Clin Med. 1987;109(2):217–24.
12. Phaosawasdi K, et al. Cholinergic effects on esophageal transit and clearance. Gastroenterology. 1981;81(5):915–20.
13. Kjellen G, Tibbling L. Influence of body position, dry and water swallows, smoking, and alcohol on esophageal acid clearing. Scand J Gastroenterol. 1978;13(3):283–8.
14. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology. 1988;94(1):73–80.
15. Bremner RM, et al. Pharyngeal swallowing. The major factor in clearance of esophageal reflux episodes. Ann Surg. 1993;218(3):364–9. discussion 369-70
16. Yazaki E, Sifrim D. Anatomy and physiology of the esophageal body. Dis Esophagus. 2012;25(4):292–8.
17. Holloway RH. Esophageal body motor response to reflux events: secondary peristalsis. Am J Med. 2000;108(Suppl 4a):20s–6s.
18. Anggiansah A, et al. Primary peristalsis is the major acid clearance mechanism in reflux patients. Gut. 1994;35(11):1536–42.
19. Sarosiek J, et al. Enhancement of salivary esophagoprotection: rationale for a physiological approach to gastroesophageal reflux disease. Gastroenterology. 1996;110(3):675–81.
20. Abdulnour-Nakhoul S, et al. Ion transport mechanisms linked to bicarbonate secretion in the esophageal submucosal glands. Am J Physiol Regul Integr Comp Physiol. 2011;301(1):R83–96.
21. Yandrapu H, et al. Role of saliva in esophageal defense: implications in patients with nonerosive reflux disease. Am J Med Sci. 2015;349(5):385–91.
22. Shay S, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol. 2004;99(6):1037–43.
23. Boyd DD, Carney CN, Powell DW. Neurohumoral control of esophageal epithelial electrolyte transport. Am J Phys. 1980;239(1):G5–11.
24. Meyers RL, Orlando RC. In vivo bicarbonate secretion by human esophagus. Gastroenterology. 1992;103(4):1174–8.
25. Strobel CT, et al. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. J Pediatr. 1979;94(1):81–4.
26. Wenzl TG, et al. Gastroesophageal reflux and respiratory phenomena in infants: status of the intraluminal impedance technique. J Pediatr Gastroenterol Nutr. 1999;28(4):423–8.
27. Woodley FW, et al. Children with cystic fibrosis have prolonged chemical clearance of acid reflux compared to symptomatic children without cystic fibrosis. Dig Dis Sci. 2014;59(3):623–30.
28. Woodley FW, et al. Chemical clearance in infants and children with Acid reflux in the physiologic range. J Pediatr Gastroenterol Nutr. 2015;60(6):783–6.
29. Frazzoni M, et al. Esophageal chemical clearance is impaired in gastro-esophageal reflux disease--a 24-h impedance-pH monitoring assessment. Neurogastroenterol Motil. 2013;25(5): 399–406. e295

30. Tutuian R, et al. Esophageal function testing with combined multichannel intraluminal impedance and manometry: multicenter study in healthy volunteers. Clin Gastroenterol Hepatol. 2003;1(3):174–82.
31. Martinucci I, et al. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. Neurogastroenterol Motil. 2014;26(4):546–55.
32. Cho YK, et al. The relationship of the post-reflux swallow-induced peristaltic wave index and esophageal baseline impedance with gastroesophageal reflux disease symptoms. J Neurogastroenterol Motil. 2017;23:237–44.
33. Sankaran J, et al. Effect of Severity of Esophageal Acidification on Sleep vs Wake Periods in Infants Presenting with Brief Resolved Unexplained Events. J Pediatr. 2016;179:42–48.e1.
34. Orr WC, Johnson LF, Robinson MG. Effect of sleep on swallowing, esophageal peristalsis, and acid clearance. Gastroenterology. 1984;86(5 Pt 1):814–9.
35. Orr WC, Robinson MG, Johnson LF. The effect of esophageal acid volume on arousals from sleep and acid clearance. Chest. 1991;99(2):351–4.
36. Orr WC, Johnson LF. Responses to different levels of esophageal acidification during waking and sleep. Dig Dis Sci. 1998;43(2):241–5.
37. Orr WC, et al. Proximal migration of esophageal acid perfusions during waking and sleep. Am J Gastroenterol. 2000;95(1):37–42.
38. Orr WC, Robinson MG, Johnson LF. Acid clearance during sleep in the pathogenesis of reflux esophagitis. Dig Dis Sci. 1981;26(5):423–7.
39. Sondheimer JM. Clearance of spontaneous gastroesophageal reflux in awake and sleeping infants. Gastroenterology. 1989;97(4):821–6.
40. Lear CS, Flanagan JB Jr, Moorrees CF. The frequency of deglutition in man. Arch Oral Biol. 1965;10:83–100.
41. Pasricha PJ. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. Am J Med. 2003;115(Suppl 3A):114s–8s.
42. Dantas RO, Aben-Athar CG. Aspects of sleep effects on the digestive tract. Arq Gastroenterol. 2002;39(1):55–9.
43. Qureshi A, et al. The role of sleep in the modulation of gastroesophageal reflux and symptoms in NICU neonates. Pediatr Neurol. 2015;53(3):226–32.
44. Khan BA, et al. Effect of bed head elevation during sleep in symptomatic patients of nocturnal gastroesophageal reflux. J Gastroenterol Hepatol. 2012;27(6):1078–82.
45. Khoury RM, et al. Influence of spontaneous sleep positions on nighttime recumbent reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol. 1999;94(8):2069–73.
46. Zhang X, et al. Esophageal motility in the supine and upright positions for liquid and solid swallows through high-resolution manometry. J Neurogastroenterol Motil. 2013;19(4):467–72.
47. Kaye MD, Wexler RM. Alteration of esophageal peristalsis by body position. Dig Dis Sci. 1981;26(10):897–901.
48. Dooley CP, Schlossmacher B, Valenzuela JE. Modulation of esophageal peristalsis by alterations of body position. Effect of bolus viscosity. Dig Dis Sci. 1989;34(11):1662–7.
49. Chang FY, et al. Alteration of distal esophageal motor functions on different body positions. Hepato-Gastroenterology. 1996;43(9):510–4.
50. Sears VW Jr, Castell JA, Castell DO. Comparison of effects of upright versus supine body position and liquid versus solid bolus on esophageal pressures in normal humans. Dig Dis Sci. 1990;35(7):857–64.
51. Simren M, et al. Relevance of ineffective oesophageal motility during oesophageal acid clearance. Gut. 2003;52(6):784–90.
52. Anggiansah A, et al. Oesophageal motor responses to gastro-oesophageal reflux in healthy controls and reflux patients. Gut. 1997;41(5):600–5.
53. Cho YK, et al. Impaired esophageal bolus transit in patients with gastroesophageal reflux disease and abnormal esophageal Acid exposure. Gut Liver. 2012;6(4):440–5.
54. Schoeman MN, Holloway RH. Integrity and characteristics of secondary oesophageal peristalsis in patients with gastro-oesophageal reflux disease. Gut. 1995;36(4):499–504.

55. Iwakiri K, et al. Defective triggering of secondary peristalsis in patients with non-erosive reflux disease. J Gastroenterol Hepatol. 2007;22(12):2208–11.
56. Allen ML, Castell JA, DiMarino AJ Jr. Mechanisms of gastroesophageal acid reflux and esophageal acid clearance in heartburn patients. Am J Gastroenterol. 1996;91(9):1739–44.
57. Aben-Athar CG, Dantas RO. Primary and secondary esophageal contractions in patients with gastroesophageal reflux disease. Braz J Med Biol Res. 2006;39(8):1027–31.
58. Gunasingam N, et al. Update on therapeutic interventions for the management of achalasia. J Gastroenterol Hepatol. 2016;31(8):1422–8.
59. Kraichely RE, Farrugia G. Achalasia: physiology and etiopathogenesis. Dis Esophagus. 2006;19(4):213–23.
60. Pohl D, Tutuian R. Achalasia: an overview of diagnosis and treatment. J Gastrointestin Liver Dis. 2007;16(3):297–303.
61. Tutuian R, et al. Clearance mechanisms of the aperistaltic oesophagus: the "pump gun" hypothesis. Gut. 2006;55(4):584–5.
62. Tutuian R, Castell DO. Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: study in 350 patients. Am J Gastroenterol. 2004;99(6):1011–9.
63. Conchillo JM, et al. Assessment of oesophageal emptying in achalasia patients by intraluminal impedance monitoring. Neurogastroenterol Motil. 2006;18(11):971–7.
64. Agrawal A, et al. Manometry and impedance characteristics of achalasia. Facts and myths. J Clin Gastroenterol. 2008;42(3):266–70.
65. Brasseur JG, Dodds WJ. Interpretation of intraluminal manometric measurements in terms of swallowing mechanics. Dysphagia. 1991;6(2):100–19.
66. Fox M. Multiple rapid swallowing in idiopathic achalasia: from conventional to high resolution manometry. Neurogastroenterol Motil. 2007;19(9):780–1. author reply 782
67. Bharadwaj S, et al. Gastrointestinal manifestations, malnutrition, and role of enteral and parenteral nutrition in patients with scleroderma. J Clin Gastroenterol. 2015;49(7):559–64.
68. Kahaleh B. Vascular disease in scleroderma: mechanisms of vascular injury. Rheum Dis Clin N Am. 2008;34(1):57–71. vi
69. Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum. 1994;37(9):1265–82.
70. Ntoumazios SK, et al. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. Semin Arthritis Rheum. 2006;36(3):173–81.
71. Bestetti A, et al. Esophageal scintigraphy with a semisolid meal to evaluate esophageal dysmotility in systemic sclerosis and Raynaud's phenomenon. J Nucl Med. 1999;40(1):77–84.
72. Basilisco G, et al. Oesophageal acid clearance in patients with systemic sclerosis: effect of body position. Eur J Gastroenterol Hepatol. 1996;8(3):205–9.
73. Luciano L, et al. Esophageal and anorectal involvement in systemic sclerosis: a systematic assessment with high resolution manometry. Clin Exp Rheumatol. 2016;34(Suppl 100(5)):63–9.
74. Murphy JR, et al. Prolonged clearance is the primary abnormal reflux parameter in patients with progressive systemic sclerosis and esophagitis. Dig Dis Sci. 1992;37(6):833–41.
75. Raja J, et al. High-resolution oesophageal manometry and 24-hour impedance-pH study in systemic sclerosis patients: association with clinical features, symptoms and severity. Clin Exp Rheumatol. 2016;34(Suppl 100(5)):115–21.
76. Duraj V, et al. Esophageal damages in systemic scleroderma. Med Arh. 2007;61(1):47–8.
77. Weber P, et al. Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease. J Rheumatol. 2000;27(11):2692–5.
78. Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. Immunol Allergy Clin N Am. 2009;29(1):197–211. xiii-xiv
79. Furuta GT, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2007;133(4):1342–63.

80. Straumann A, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy. 2012;67(4):477–90.
81. Rodrigues M, et al. Clinical manifestations, treatment, and outcomes of children and adolescents with eosinophilic esophagitis. J Pediatr. 2013;89(2):197–203.
82. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterol Clin N Am. 2014;43(2):297–316.
83. Cheng L, et al. Hydrogen peroxide reduces lower esophageal sphincter tone in human esophagitis. Gastroenterology. 2005;129(5):1675–85.
84. Cheng E, Souza RF, Spechler SJ. Eosinophilic esophagitis: interactions with gastroesophageal reflux disease. Gastroenterol Clin N Am. 2014;43(2):243–56.
85. Tobey NA, et al. Dilated intercellular spaces: a morphological feature of acid reflux--damaged human esophageal epithelium. Gastroenterology. 1996;111(5):1200–5.
86. Ravelli A, et al. Dilated intercellular spaces in eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2014;59(5):589–93.
87. van Rhijn BD, et al. Prevalence of esophageal motility abnormalities increases with longer disease duration in adult patients with eosinophilic esophagitis. Neurogastroenterol Motil. 2014;26(9):1349–55.
88. Colizzo JM, Clayton SB, Richter JE. Intrabolus pressure on high-resolution manometry distinguishes fibrostenotic and inflammatory phenotypes of eosinophilic esophagitis. Dis Esophagus. 2016;29(6):551–7.
89. Nurko S, Rosen R, Furuta GT. Esophageal dysmotility in children with eosinophilic esophagitis: a study using prolonged esophageal manometry. Am J Gastroenterol. 2009;104(12):3050–7.
90. Nurko S, Rosen R. Esophageal dysmotility in patients who have eosinophilic esophagitis. Gastrointest Endosc Clin N Am. 2008;18(1):73–89. ix
91. Roman S, et al. Manometric features of eosinophilic esophagitis in esophageal pressure topography. Neurogastroenterol Motil. 2011;23(3):208–14. e111
92. Martin Martin L, et al. Esophageal motor abnormalities in eosinophilic esophagitis identified by high-resolution manometry. J Gastroenterol Hepatol. 2011;26(9):1447–50.
93. Kwiatek MA, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology. 2011;140(1):82–90.
94. Nicodeme F, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2013;11(9):1101–7. e1
95. Robinson NB, DiMango E. Prevalence of gastroesophageal reflux in cystic fibrosis and implications for lung disease. Ann Am Thorac Soc. 2014;11(6):964–8.
96. Mousa HM, Woodley FW. Gastroesophageal reflux in cystic fibrosis: current understandings of mechanisms and management. Curr Gastroenterol Rep. 2012;14(3):226–35.
97. Blondeau K, et al. Characteristics of gastroesophageal reflux and potential risk of gastric content aspiration in children with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;50(2):161–6.
98. Winans CS, Harris LD. Quantitation of lower esophageal sphincter competence. Gastroenterology. 1967;52(5):773–8.
99. Mousa HM, et al. Esophageal impedance monitoring for gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2011;52(2):129–39.
100. Shin MS. Esophageal pH and combined impedance-pH monitoring in children. Pediatr Gastroenterol Hepatol Nutr. 2014;17(1):13–22.
101. Proctor GB. The physiology of salivary secretion. Periodontol 2000. 2016;70(1):11–25.
102. da Silva Modesto KB, et al. Salivary flow rate and biochemical composition analysis in stimulated whole saliva of children with cystic fibrosis. Arch Oral Biol. 2015;60(11):1650–4.
103. Shawyer AC, et al. Quality of reporting of the literature on gastrointestinal reflux after repair of esophageal atresia-tracheoesophageal fistula. J Pediatr Surg. 2015;50(7):1099–103.
104. Little DC, et al. Long-term analysis of children with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2003;38(6):852–6.
105. Engum SA, et al. Analysis of morbidity and mortality in 227 cases of esophageal atresia and/or tracheoesophageal fistula over two decades. Arch Surg. 1995;130(5):502–8. discussion 508-9

106. Al-Shraim MM, et al. Ultrastructural changes of the smooth muscle in esophageal atresia. Ultrastruct Pathol. 2015;39(6):413–8.
107. Dutta HK, Mathur M, Bhatnagar V. A histopathological study of esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2000;35(3):438–41.
108. Boleken M, et al. Reduced neuronal innervation in the distal end of the proximal esophageal atretic segment in cases of esophageal atresia with distal tracheoesophageal fistula. World J Surg. 2007;31(7):1512–7.
109. Zuccarello B, et al. Intramural ganglion structures in esophageal atresia: a morphologic and immunohistochemical study. Int J Pediatr. 2009;2009:695837.
110. Nakazato Y, Landing BH, Wells TR. Abnormal Auerbach plexus in the esophagus and stomach of patients with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 1986;21(10):831–7.
111. Midrio P, et al. Reduction of interstitial cells of Cajal in esophageal atresia. J Pediatr Gastroenterol Nutr. 2010;51(5):610–7.
112. Mikami DJ, Murayama KM. Physiology and pathogenesis of gastroesophageal reflux disease. Surg Clin North Am. 2015;95(3):515–25.
113. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil. 2015;27(9):1202–13.
114. Banjar HH, Al-Nassar SI. Gastroesophageal reflux following repair of esophageal atresia and tracheoesophageal fistula. Saudi Med J. 2005;26(5):781–5.
115. Tong S, Mallitt KA, Krishnan U. Evaluation of gastroesophageal reflux by combined multichannel intraluminal impedance and pH monitoring and esophageal motility patterns in children with esophageal atresia. Eur J Pediatr Surg. 2016;26(4):322–31.
116. Catalano P, et al. Gastroesophageal reflux in young children treated for esophageal atresia: evaluation with pH-multichannel intraluminal impedance. J Pediatr Gastroenterol Nutr. 2011;52(6):686–90.
117. Lemoine C, et al. Characterization of esophageal motility following esophageal atresia repair using high-resolution esophageal manometry. J Pediatr Gastroenterol Nutr. 2013;56(6):609–14.
118. Di Pace MR, et al. Evaluation of esophageal motility and reflux in children treated for esophageal atresia with the use of combined multichannel intraluminal impedance and pH monitoring. J Pediatr Surg. 2011;46(3):443–51.
119. Iwanczak BM, et al. Assessment of clinical symptoms and multichannel intraluminal impedance and pH monitoring in children after thoracoscopic repair of esophageal atresia and distal tracheoesophageal fistula. Adv Clin Exp Med. 2016;25(5):917–22.
120. Soyer T, et al. Results of multichannel intraluminal impedance pH metry in symptomatic children with normal pH metry findings. Eur J Pediatr Surg. 2014;24(6):514–8.
121. van Wijk M, et al. Evaluation of gastroesophageal function and mechanisms underlying gastroesophageal reflux in infants and adults born with esophageal atresia. J Pediatr Surg. 2013;48(12):2496–505.
122. Frohlich T, et al. Combined esophageal multichannel intraluminal impedance and pH monitoring after repair of esophageal atresia. J Pediatr Gastroenterol Nutr. 2008;47(4):443–9.
123. Tovar JA, et al. Ambulatory 24-hour manometric and pH metric evidence of permanent impairment of clearance capacity in patients with esophageal atresia. J Pediatr Surg. 1995;30(8):1224–31.
124. Roman S, Kahrilas PJ. Mechanisms of Barrett's oesophagus (clinical): LOS dysfunction, hiatal hernia, peristaltic defects. Best Pract Res Clin Gastroenterol. 2015;29(1):17–28.
125. Banki F, et al. Barrett's esophagus in females: a comparative analysis of risk factors in females and males. Am J Gastroenterol. 2005;100(3):560–7.
126. Lord RV, et al. Hiatal hernia, lower esophageal sphincter incompetence, and effectiveness of Nissen fundoplication in the spectrum of gastroesophageal reflux disease. J Gastrointest Surg. 2009;13(4):602–10.
127. Savarino E, et al. Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011;34(4):476–86.

128. Namiot Z, et al. Interrelationship between esophageal challenge with mechanical and chemical stimuli and salivary protective mechanisms. Am J Gastroenterol. 1994;89(4):581–7.
129. Krarup AL, et al. Proximal and distal esophageal sensitivity is decreased in patients with Barrett's esophagus. World J Gastroenterol. 2011;17(4):514–21.
130. Gutschow CA, et al. NERD, GERD, and Barrett's esophagus: role of acid and non-acid reflux revisited with combined pH-impedance monitoring. Dig Dis Sci. 2008;53(12):3076–81.
131. Savarino E, et al. Characteristics of gastro-esophageal reflux episodes in Barrett's esophagus, erosive esophagitis and healthy volunteers. Neurogastroenterol Motil. 2010;22(10):1061–e280.
132. Lottrup C, et al. Esophageal acid clearance during random swallowing is faster in patients with Barrett's esophagus than in healthy controls. J Neurogastroenterol Motil. 2016;22(4):630–42.
133. Mittal RK, Lange RC, McCallum RW. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. Gastroenterology. 1987;92(1):130–5.
134. Kasapidis P, et al. Effect of hiatal hernia on esophageal manometry and pH-metry in gastroesophageal reflux disease. Dig Dis Sci. 1995;40(12):2724–30.
135. Ye P, et al. Esophageal motility in patients with sliding hiatal hernia with reflux esophagitis. Chin Med J. 2008;121(10):898–903.
136. Patti MG, et al. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. Am J Surg. 1996;171(1):182–6.
137. Emerenziani S, et al. Effect of hiatal hernia on proximal oesophageal acid clearance in gastroesophageal reflux disease patients. Aliment Pharmacol Ther. 2006;23(6):751–7.
138. Salvatore S, et al. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr. 2005;40(2):210–5.
139. Cucchiara S, et al. Value of the 24 hour intraoesophageal pH monitoring in children. Gut. 1990;31(2):129–33.
140. Rosen R, Lord C, Nurko S. The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. Clin Gastroenterol Hepatol. 2006;4(2):167–72.
141. Woodley FW, Mousa H. Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements. Dig Dis Sci. 2006;51(11):1910–6.
142. Wenzl TG, et al. Association of apnea and nonacid gastroesophageal reflux in infants: Investigations with the intraluminal impedance technique. Pediatr Pulmonol. 2001;31(2):144–9.
143. Vikneswaran N, Murray JA. Discounting the duration of bolus exposure in impedance testing underestimates acid reflux. BMC Gastroenterol. 2016;16(1):60.
144. Loots CM, et al. Addition of pH-impedance monitoring to standard pH monitoring increases the yield of symptom association analysis in infants and children with gastroesophageal reflux. J Pediatr. 2009;154(2):248–52.
145. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol. 2007;102(3):668–85.

Symptoms

4

Paolo Quitadamo and Annamaria Staiano

Abstract

Gastroesophageal reflux (GER) is defined as 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, such as cough, wheezing, and hoarseness, may also be associated with GERD, being sometimes the only "atypical" presentation of the disease.

P. Quitadamo
Department of Translational Medical Science, Section of Pediatrics, "Federico II", University of Naples, Naples, Italy

Department of Pediatrics, AORN Santobono-Pausilipon, Naples, Italy

A. Staiano (✉)
Department of Translational Medical Science, Section of Pediatrics, "Federico II", University of Naples, Naples, Italy
e-mail: annamaria.staiano@unina.it

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_4

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 defined as 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 [1]. In contrast, according to the latest clinical practice guidelines for the diagnosis and management of reflux in the pediatric population, jointly published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), gastroesophageal reflux disease (GERD) is present when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications [2]. Reflux symptoms may vary widely according to age and distinguishing physiologic GER from GERD may often be tricky, especially in infants. Thus, a proper diagnosis of these two conditions, besides other possible conditions mimicking reflux, is crucial in order to target the treatment, avoiding the overuse of antacid drugs which currently represents a major source of concern. The clinical picture alone is frequently nonspecific and does not allow, except than in older children and adolescents, to detect the actual need for acid-suppressive medications. Therefore, instrumental diagnostic testing, such as combined esophageal multiple intraluminal impedance and pH monitoring and upper gastrointestinal endoscopy, is 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 (ALTEs). 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

Regurgitation, vomiting, and irritability are very common in healthy infants, especially during the first 6 months of life. About 70% of healthy infants physiologically regurgitate 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]. 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.

Irritability and excessive crying are also very frequent in infants and may present along with regurgitation and vomiting. Nevertheless, as well as regurgitation, they affect a large proportion of healthy subjects and spontaneously decrease with time [6]. The concept that infant irritability and sleep disturbances are manifestations of GER is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy [7–10]. Although one study in infants showed a correlation between infant grimacing and episodes of reflux [11], multiple other studies have shown no relation between crying and GERD determined by esophageal pH testing [12–15] or the presence of esophagitis [13, 16]. 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. 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 [17]. The questionnaire has undergone several revisions [18]. 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 [19]. 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 [20]. In another study, the questionnaire was unable to identify a group of infants responsive to proton pump inhibitor (PPI) therapy [2].

Thus, 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 (especially vomiting) and to identify possible complications of GERD. 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 on feeding composition. Overfeeding exacerbates recurrent regurgitation [5]. Thickened or anti-regurgitation formulas decrease overt regurgitation [21].

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. Therefore, a small proportion of symptomatic infants may deserve an instrumental diagnostic assessment for GERD or other GERD-mimicking diseases. To help identifying this subgroup of infants, the latest international GER guidelines drafted a list of warning signals requiring investigations in infants with regurgitation or vomiting (Table 4.1).

Table 4.1 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

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 opinion, although the verbal child can communicate pain, the description of quality, intensity, location, and severity generally is 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 diagnose (Table 4.2).

Table 4.2 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

Clinical Picture of GERD in Older Children and Adolescents

In older children and adolescents heartburn, chest pain and regurgitation are the characteristic symptoms of GERD. According to expert opinion, the description and localization of these symptoms are a reliable indicator for 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 from 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].

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 careful approach upper GI symptoms, being aware that the current 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, sometimes 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, as for 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 allow 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 fundamental scientific basis for diagnostic and therapeutic choices.

References

1. Sherman P, Hassall E, Fagundes-Neto U, et al. A global evidence-based consensus on the definition of gastroesophageal reflux disease in children. Am J Gastroenterol. 2009;104:1278–95.
2. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
3. Hegar B, Dewanti NR, Kadim M, et al. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009;98:1189–93.
4. Orenstein SR. Curr Gastroenterol Rep. 2013;15:353.
5. Moore DJ, Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr. 2003;143:219–37.
6. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20.
7. Singh S, Richter JE, Bradley LA, et al. The symptom index. Differential usefulness in suspected acid-related complaints of heartburn and chest pain. Dig Dis Sci. 1993;38:1402–8.
8. Richter JE. A critical review of current medical therapy for gastroesophageal reflux disease. J Clin Gastroenterol. 1986;8(Suppl 1):S72–80.
9. Vakil N. Proton pump inhibitors for dyspepsia. Dig Dis. 2008;26:215–7.
10. Feranchak AP, Orenstein SR, Cohn JF. Behaviors associated with onset of gastroesophageal reflux episodes in infants. Prospective study using split-screen video and pH probe. Clin Pediatr (Philadelphia). 1994;33:654–62.
11. Heine RG, Jordan B, Lubitz L, et al. Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health. 2006;42:134–9.
12. Vandenplas Y, Badriul H, Verghote M, et al. Oesophageal pH monitoring and reflux oesophagitis in irritable infants. Eur J Pediatr. 2004;163:300–4.
13. Heine RG, Cameron DJ, Chow CW, et al. Esophagitis in distressed infants: poor diagnostic agreement between esophageal pH monitoring and histopathologic findings. J Pediatr. 2002;140:14–9.
14. Heine RG, Jaquiery A, Lubitz L, et al. Role of gastro-oesophageal reflux in infant irritability. Arch Dis Child. 1995;73:121–5.
15. Chadwick LM, Kurinczuk JJ, Hallam LA, et al. Clinical and endoscopic predictors of histological oesophagitis in infants. J Paediatr Child Health. 1997;33:388–93.
16. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain. 2007;127:140–50.
17. Kleinman L, Rothman M, Strauss R, et al. The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument. Clin Gastroenterol Hepatol. 2006;4:588–96.
18. Aggarwal S, Mittal SK, Kalra KK, et al. Infant gastroesophageal reflux disease score: reproducibility and validity in a developing country. Trop Gastroenterol. 2004;25:96–8.
19. Salvatore S, Hauser B, Vandemaele K, et al. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr. 2005;40:210–5.
20. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing efficacy & safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154:514–20.
21. Tolia V, Vandenplas Y. Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. Aliment Pharmacol Ther. 2009;29:258–72.
22. Stordal K, Johannesdottir GB, Bentsen BS, et al. Gastroesophageal reflux disease in children: association between symptoms and pH monitoring. Scand J Gastroenterol. 2005;40:636–40.

23. Deal L, Gold BD, Gremse DA, et al. Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: development and initial validation. J Pediatr Gastroenterol Nutr. 2005;41:178–85.
24. Tolia V, Bishop PR, Tsou VM, et al. Multicenter, randomized, double-blind study comparing 10, 20 and 40mg pantoprazole in children (5–11 years) with symptomatic gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2006;42:384–91.
25. Stanford EA, Chambers CT, Craig KD. The role of developmental factors in predicting young children's use of a self-report scale for pain. Pain. 2006;120:16–23.
26. Stanford EA, Chambers CT, Craig KD. A normative analysis of the development of pain-related vocabulary in children. Pain. 2005;114:278–84.
27. Beyer JE, McGrath PJ, Berde CB. Discordance between selfreport and behavioral pain measures in children aged 3–7 years after surgery. J Pain Symptom Manag. 1990;5:350–6.
28. Shields BJ, Palermo TM, Powers JD, et al. Predictors of a child's ability to use a visual analogue scale. Child Care Health Dev. 2003;29:281–90.
29. Shi G, Bruley des Varannes S, Scarpignato C, et al. Reflux related symptoms in patients with normal oesophageal exposure to acid. Gut. 1995;37:457–64.
30. Vakil N. Review article: the role of surgery in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;25:1365–72.
31. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management—the Genval workshop report. Gut. 1999;44(Suppl 2):S1–6.
32. Chirila I, Morariu ID, Barboi OB, Drug VL. The role of diet in the overlap between gastroesophageal reflux disease and functional dyspepsia. Turk J Gastroenterol. 2016;27(1):73–8.
33. Lee SW, Lee TY, Lien HC, Yeh HZ, Chang CS, Ko CW. The risk factors and quality of life in patients with overlapping functional dyspepsia or peptic ulcer disease with gastroesophageal reflux disease. Gut Liver. 2014;8(2):160–4.
34. Rasquin-Weber A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla PJ, et al. Childhood functional gastrointestinal disorders. Gut. 1999;45:II60–8.
35. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology. 1998;115:1346–52.
36. Peter CS, Sprodowski N, Bohnhorst B, et al. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. Pediatrics. 2002;109:8–11.
37. Wenzl TG, Schenke S, Peschgens T, et al. Association of apnea and nonacid gastroesophageal reflux in infants: investigations with the intraluminal impedance technique. Pediatr Pulmonol. 2001;31:144–9.
38. Mousa H, Woodley FW, Metheney M, et al. Testing the association between gastroesophageal reflux and apnea in infants. J Pediatr Gastroenterol Nutr. 2005;41:169–77.
39. Menon AP, Schefft GL, Thach BT. Apnea associated with regurgitation in infants. J Pediatr. 1985;106:625–9.
40. Cote A, Hum C, Brouillette RT, et al. Frequency and timing of recurrent events in infants using home cardiorespiratory monitors. J Pediatr. 1998;132:783–9.
41. Kahn A, Rebuffat E, Sottiaux M, et al. Lack of temporal relation between acid reflux in the proximal oesophagus and cardiorespiratory events in sleeping infants. Eur J Pediatr. 1992;151:208–12.
42. Sahewalla R, Gupta D, Kamat D. Apparent life-threatening events: an overview. Clin Pediatr (Philadelphia). 2015;55:5–9.
43. Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope. 2002;112:1019–24.
44. McMurray JS, Gerber M, Stern Y, et al. Role of laryngoscopy, dual pH probe monitoring, and laryngeal mucosal biopsy in the diagnosis of pharyngoesophageal reflux. Ann Otol Rhinol Laryngol. 2001;110:299–304.
45. Yellon RF, Coticchia J, Dixit S. Esophageal biopsy for the diagnosis of gastroesophageal reflux-associated otolaryngologic problems in children. Am J Med. 2000;108:131S–8S.

46. Halstead LA. Gastroesophageal reflux: a critical factor in pediatric subglottic stenosis. Otolaryngol Head Neck Surg. 1999;120:683–8.
47. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. Am J Gastroenterol. 1999;94:3131–8.
48. Fortunato JE, Troy AL, Cuffari C, et al. Outcome after percutaneous endoscopic gastrostomy in children and young adults. J Pediatr Gastroenterol Nutr. 2010;50:390–3.
49. Field SK. A critical review of the studies of the effects of simulated or real gastroesophageal reflux on pulmonary function in asthmatic adults. Chest. 1999;115:848–56.
50. Herve P, Denjean A, Jian R, et al. Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. Am Rev Respir Dis. 1986;134:986–9.

Diagnosis of Gastroesophageal Reflux Disease

5

Yvan Vandenplas

Abstract

The diagnosis of gastroesophageal reflux disease (GERD) remains a challenge. The symptoms and manifestations caused by GERD vary from nonerosive reflux disease over Barrett's esophagus to chronic respiratory disease. As a consequence, it is clear that not one investigation technique will provide an answer in all situations. Although many diagnostic techniques are available, most of them are not needed to diagnose GERD. Upper gastrointestinal tract endoscopy with biopsies is indicated to exclude differential diagnoses, but not to diagnose GERD. Multiple intraluminal impedance (MII) has been extensively evaluated in recent years, but will be discussed more in detail in a different chapter.

Keywords

Acid reflux • Barium meal • (Upper) endoscopy • Extra-esophageal symptoms • Gastroesophageal reflux (disease) • (Multiple intraluminal) Impedance • pH meter • pH monitoring • Scintiscanning • Symptom association • Ultrasound • Vomiting • Weakly acid reflux

Y. Vandenplas
Department of Pediatrics, UZ Brussel, Free University of Brussels,
Laarbeeklaan 101, 1090 Brussels, Belgium
e-mail: yvan.vandenplas@uzbrussel.be

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_5

Diagnostic Tests

Although many tests have been developed to diagnose GERD, few studies compare their utility. It is not known whether tests can predict an individual patient's response to therapy. Tests may be useful to document the presence of pathologic reflux or its complications, to establish a causal relationship between reflux and symptoms, to evaluate the effect of therapy, and to exclude other conditions [1]. Since no single test can address all these questions, tests must be carefully selected according to the information sought, and the limitations of each test must be recognized.

History and Physical Examination

The major role of history and physical examination in the evaluation of GERD is to recognize other disorders that present with vomiting and to identify complications of GERD. Presenting symptoms of GERD in childhood vary with age. Symptoms and signs associated with reflux are nonspecific. The severity of reflux or esophagitis found on diagnostic testing does not directly correlate with the severity of symptoms [1].

In adults, GERD is often diagnosed clinically, based on a history of heartburn defined as retrosternal, burning chest pain, with or without regurgitation. Recent adult and pediatric consensus guidelines have applied the terms "typical reflux syndrome" or "reflux chest pain syndrome" to this presentation [1, 2]. However, a clinical diagnosis based on a history of heartburn cannot be used in infants, children, or nonverbal adolescents (e.g., those with neurologic impairment) as these individuals cannot reliably communicate the quality and quantity of their symptoms [3, 4]. 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 [1].

Because individual symptoms do not consistently correlate with objective findings or response to medical treatment, parent or patient-reported questionnaires based on clusters of symptoms have been developed (Table 5.1). Orenstein et al. developed a diagnostic questionnaire for GERD in infants [5]. A score of >7 (of 25 possible) on the initial instrument demonstrated a sensitivity of 0.74 and specificity of 0.94 during primary validation. The questionnaire has undergone revisions [6]. The questionnaire has been shown to be reliable for documentation and monitoring of reported symptoms. However, when applied to a population in India, sensitivity and specificity were only 43% and 79%, respectively, compared to pH monitoring results [7]. In another study in infants referred for symptoms of reflux disease and controls, the questionnaire had a sensitivity and specificity of 47 and 81% for a reflux index (% of the investigation time with a pH <4.0; RI) >10% and 65 and 63% for a RI >5% [8]. 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 [8]. In another study, the questionnaire was unable to identify a group of infants responsive to therapy with PPIs [9]. However,

Table 5.1 Symptoms and signs that may be associated with gastroesophageal reflux

Symptoms	Recurrent regurgitation with/without vomiting Failure to thrive or weight loss Irritability in infants Ruminative behavior Heartburn or chest pain, pyrosis Hematemesis Dysphagia, odynophagia Wheezing Cough, hoarseness
Signs	Esophagitis Esophageal stricture Barrett's esophagus Laryngeal/pharyngeal inflammation Recurrent respiratory infections Anemia Dental erosion Feeding refusal Dystonic neck posturing (Sandifer syndrome) In infants: apnea spells, apparent life-threatening events (ALTE)

GER is in some patients associated with these "symptoms and signs"; it does not mean that these "symptoms and signs" are specific for GER; these "symptoms and signs" are associated with many different etiologies

recent data showed that PPIs were not effective in infants (<12 months of age) and children with esophagitis [10].

A five-item questionnaire developed for children 7–16 years of age had a sensitivity of 75% and specificity of 96% compared to pH monitoring during primary validation [11]. No subsequent independent confirmatory validation has been performed. Other diagnostic questionnaires such as the "GERD symptom questionnaire" have not been compared to objective standards like endoscopy, pH monitoring, or esophageal MII monitoring.

Esophageal pH Monitoring

Intraluminal esophageal pH monitoring measures the frequency and duration of episodes of acidity in the esophagus. By convention, a drop in esophageal pH below 4.0 is considered as an acid episode. This cutoff was initially chosen because heartburn induced by acid perfusion in the esophagus in adults generally occurs at pH <4.0 [1]. The Bernstein test is a test during which acid is perfused in the esophagus in order to relate the presence of acid to the development of stridor. The test did not become popular and was abandoned [12].

Antimony electrodes are nowadays the most popular electrodes although they are less accurate than glass or ion-sensitive field effect transistor (ISFET) pH electrodes. Hygienic recommendations to use the electrodes only once resulted in the disappearance of glass electrodes because of their high cost. Slow electrode response

times (antimony being the slowest) do not substantially alter the assessment of total reflux time but may affect the accuracy of correlation between symptoms and reflux episodes [1]. Data obtained with a glass, ion-sensitive field effect transistor (ISFET), and antimony electrodes correlate poorly. Glass electrodes measure about twice as much acid reflux than antimony electrodes [13, 14]. As a consequence, normal ranges obtained with glass electrodes as those published by Vandenplas et al. cannot be used for recordings with antimony electrodes.

The reflux index (% time with esophageal pH <4.0, RI) is the most commonly used summary score. Several scoring systems for pH monitoring studies have been developed, such as the DeMeester or Boix-Ochoa scores, but no system is clearly superior to the RI. In pH studies performed with antimony electrodes, a RI >7% is considered abnormal, a RI <3% is considered normal, and a RI between 3% and 7% is indeterminate. Normal data depend on the definition of a "normal population." In the first study by Vandenplas, showing a low RI in young infants, the definition of a "normal infant" was an infant that did not regurgitate or vomit [15]. In the second study, a "normal population" was defined as an infant that had not been or was not treated for reflux [16]. While the definition of the first study was biased toward "normal" population, the second study included all untreated infants, thus possibly some infants with GERD. For these reasons, specific "cut-off" values that discriminate between physiologic GER and pathologic GERD are suspect; rather, it is likely that a continuum exists such that normal ranges should be regarded as guidelines for interpretation rather than absolutes. Esophageal pH monitoring results may help to correlate symptoms with acid reflux by applying various analytic methods, including the symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP). Esophageal pH monitoring is useful for evaluating the efficacy of antisecretory therapy. An "oscillatory index" was developed to measure the time that the pH oscillates around pH 4.0 and thus provides information on the possibility of erroneous interpretation of the pH meter [17]. The "area under pH 4.0" correlates well with the risk of finding histologic esophagitis [18].

Wireless sensors that can be clipped to the esophageal mucosa during endoscopy have allowed pH monitoring, without a nasal passage or presence, for up to 48 h. The size of current wireless electrodes precludes their use in small infants. Benefits, risks, and indications for wireless electrode monitoring have not been fully defined in children. Recently, a new technique was developed to measure oropharyngeal acid reflux (Restech®). However, compared to impedance, the technique seems not reliable [19, 20]. Nevertheless, more recent uncontrolled data in adults suggest that the test results are specific and "reasonably sensitive" [21], suggesting that more data are needed regarding the reliability of this technique (Table 5.2).

Continuous monitoring of bilirubin in the esophagus has been suggested as a means of detecting esophageal reflux of duodenal juice or duodenogastroesophageal reflux (DGER). Duodenal juice components appear to damage the esophagus in a pH-dependent manner. The development of multiple intraluminal impedance (MII) recording did result in the disappearance of this technique.

Table 5.2 Definition of gastroesophageal reflux detected by multichannel intraluminal impedance

Liquid GER: drop in impedance to less than 50% of baseline values
Acid GER: pH falls below 4 for at least 4 s or, if pH was already below 4, decreases by at least 1 pH unit sustained for more than 4 s
Nonacid reflux: weakly acidic and weakly alkaline GOR
Weakly acidic reflux: pH drop of at least 1 pH unit sustained for more than 4 seconds with basal pH remaining between 7 and 4
Weakly alkaline: pH does not drop below 7
Gas reflux: rapid and pronounced rise in impedance

Based on expert opinion, in places were pH-MII is not available, the WG suggests to use pH meter only:

- *To correlate persistent troublesome symptoms with acid GER events*
- *To clarify the role of acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD*
- *To determine the efficacy of acid suppression therapy*

Combined Multiple Intraluminal Impedance and pH Monitoring

Multiple intraluminal impedance (MII) is a procedure for measuring the movement of fluids, solids, and air in the esophagus. MII measures changes in the electrical impedance (i.e., resistance) between multiple electrodes located along an esophageal catheter. This technique is discussed more in detail in a different chapter.

Motility Studies

Manometric studies are important in confirming a diagnosis of motor disorders such as achalasia which may mimic GERD. Esophageal manometry does not measure GER, but it can be abnormal in patients with GERD. It will not predict response to medical or surgical therapy [1]. Esophageal manometry is severely abnormal in children with esophageal atresia and psychomotor retardation. There is no indication for motility studies in the routine diagnosis or management of GERD.

Manometry

Based on expert opinion, the working group suggests not to use manometry for the diagnosis of GERD in infants and children.

Based on expert opinion, the working group considers to use manometry when a motility disorder is suspected.

Endoscopy and Biopsy

Upper GI endoscopy allows direct visual examination of the esophageal mucosa. If a patient with reflux symptoms has a normal endoscopy but suffers GERD, "nonerosive reflux disease (NERD)" is used. NERD is by far more frequent than erosive reflux disease, when esophagitis is present. Recent global consensus guidelines define reflux esophagitis as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the GE junction [1]. Evidence from adult studies indicates that visible breaks in the esophageal mucosa are the endoscopic sign of greatest interobserver reliability. Operator experience is an important component of interobserver reliability [1]. Mucosal erythema and an irregular Z-line are not reliable signs of reflux esophagitis. Grading the severity of esophagitis, using a recognized endoscopic classification system, is useful for evaluation of the severity of esophagitis and response to treatment. The Hetzel-Dent classification has been used in several pediatric studies, while the Los Angeles classification is also suitable for children. The presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of nonerosive reflux disease or esophagitis of other etiologies [1].

The diagnostic yield of endoscopy is generally greater if multiple samples of good size and orientation are obtained from biopsy sites that are identified relative to major esophageal landmarks. Histologic findings of eosinophilia, elongation of papillae (rete pegs), basal hyperplasia, and dilated intercellular spaces (spongiosis) are neither sensitive nor specific for reflux esophagitis. Recent studies have shown considerable overlap between the histology of reflux esophagitis and eosinophilic esophagitis [22]. GERD is likely one of the most common causes of esophagitis in children, but other disorders such as eosinophilic esophagitis (in some parts of the world equally frequent as GERD as cause of esophagitis, while almost nonexisting in other parts of the world), Crohn's disease, and infections also cause esophagitis. In infants, eosinophilic esophagitis and GERD have very similar symptoms and signs and can be best distinguished by endoscopy with biopsy. Solid food dysphagia heightens concern about eosinophilic esophagitis as the underlying diagnosis [22]. The primary role for esophageal histology is to rule out other conditions in the differential diagnosis, such as eosinophilic esophagitis, Crohn's disease, Barrett's esophagus, infection, and others. When biopsies show columnar epithelium, the term Barrett's esophagus (BE) should be applied and the presence or absence of intestinal metaplasia specified. Thus, BE may be diagnosed in the presence of only cardia-type mucosa BE which occurs with greatest frequency in children with underlying conditions putting them at high risk of GERD. Children with conditions such as cerebral palsy, with repaired esophageal atresia, and cystic fibrosis are at increased risk for severe GERD and thus BE.

The WG suggests not to use EGD for diagnosing GERD in infants and children.

Based on expert opinion, the working group suggests to use EGD with biopsies to assess complications of GERD, in case an underlying mucosal disease is suspected and prior to escalation of therapy.

Barium Contrast Radiography

Upper gastrointestinal (GI) series are neither sensitive nor specific for diagnosing GERD. The brief duration of the upper GI series produces false-negative results, while the frequent occurrence of non-pathological reflux during the examination produces false-positive results. Using the pH/MII tests as the reference for GER, UGI had a sensitivity of 42.8% and a negative predictive value of 24% [30]. There was no significant correlation ($P > 0.05$) between the reflux index and the number of reflux episodes in the pH/impedance tests and height of reflux in the UGI study. There were low incidences of malrotation (0.9%), hiatus hernia (1%), and delayed gastric emptying (0.4%) [23]. However, upper GI series is useful to detect anatomic abnormalities such as esophageal stricture, hiatal hernia, achalasia, tracheoesophageal fistula, intestinal malrotation, or pyloric stenosis which may be considered in the differential diagnosis of infants and children with symptoms suggesting GERD.

*The WG suggests **not** to use barium contrast studies for the diagnosis of GERD in infants and children.*

Based on expert opinion, the WG suggests to use barium contrast studies for excluding anatomical abnormalities.

Nuclear Scintigraphy

In gastroesophageal scintigraphy, food or formula labeled with ^{99}technetium is introduced into the stomach, and areas of interest—stomach, esophagus, and lungs—are scanned for evidence of reflux and aspiration. The nuclear scan evaluates only postprandial reflux and demonstrates reflux independent of the gastric pH. Scintigraphy can provide information about gastric emptying, which may or may not be delayed in children with GERD [24]. A lack of standardized techniques and the absence of age-specific norms limit the value of this test. Sensitivity and specificity of a 1 h scintigraphy for the diagnosis of GERD are 15–59% and 83–100%, respectively, when compared to 24-hour esophageal pH monitoring [1].

Gastroesophageal scintigraphy scanning can detect reflux episodes and aspiration occurring during or shortly after meals [25], but its reported sensitivity for microaspiration is relatively low. Evidence of pulmonary aspiration may be detected

during a 1-hour scintigraphic study or on images obtained up to 24 h after administration of the radionuclide. A negative test does not exclude the possibility of infrequently occurring aspiration. One study of children with refractory respiratory symptoms found that half had scintigraphic evidence of pulmonary aspiration. However, aspiration of both gastric contents and saliva also occurs in healthy adults during deep sleep.

The working group recommends not to use scintigraphy for the diagnosis of GERD in infants and children.

Esophageal and Gastric Ultrasonography

Ultrasonography of the GE junction can detect fluid movements over short periods of time regardless of their acidity. It can also detect hiatus hernia, length and position of the LES relative to the diaphragm, and magnitude of the gastroesophageal angle of His. Barium upper gastrointestinal series can provide the same information. When compared to the results of 24 h esophageal pH testing as a diagnostic test for GERD, the sensitivity of color Doppler ultrasound performed for 15 min postprandial is about 95%, however, with a specificity of only 11%, and there is no correlation between reflux frequency detected by ultrasound and reflux index detected by pH monitoring [26]. Ultrasound allows exclusion of several non-GER causes of symptoms and that it provides morphological and functional data with high sensitivity and positive predictive value for the diagnosis of GER [27]. Sonographic assessment of findings such as abdominal esophageal length, esophageal diameter, esophageal wall thickness, and gastroesophageal angle provides important diagnostic indicators of reflux and related to the degree of GER [28]. There is a need for standardization of the procedure and for defining diagnostic criteria.

Based on expert opinion, the WG suggests NOT to use ultrasonography for the diagnosis of GERD in infants and children.

Based on expert opinion, the WG suggests to use ultrasonography for excluding anatomical abnormalities.

Gastric Emptying Studies

Although the deduction that “delayed gastric emptying” is likely to be related to an increased incidence of GER, data from literature are contradictory. At best, gastric emptying is an indirect indicator of a “GER risk.” Electrogastrography is

a technique developed to measure gastric motility. The relation between abnormal or decreased gastric contraction and GER has not been clearly shown, and because of technical limitations, electrogastrography is only performed in research conditions.

Tests on Ear, Lung, and Esophageal Fluids

Recent studies have suggested that finding pepsin, a gastric enzyme, in middle ear effusions of children with chronic otitis media indicates that reflux is playing an etiologic role. However, there are also studies showing no relationship between the presence of pepsin in the middle ear and symptoms of GERD. Anyway, this relationship has not been validated in controlled treatment trials. Similarly, the presence of lactose, glucose, pepsin, or lipid-filled macrophages in bronchoalveolar lavage fluids has been proposed to implicate aspiration secondary to reflux as a cause of some chronic pulmonary conditions. Of these, lipid-filled macrophages have been the best studied and shown to be nonspecific and thus not usable to diagnose GERD. No controlled studies have proven that reflux is the only reason these compounds appear in bronchoalveolar lavage fluids or that reflux is the cause of pulmonary disease when they are present. Research using appropriate and innovative methodologies to investigate potential inflammatory agents such as pepsinogen, pepsin, bile salts, or other components of reflux materials in patients with GERD is required to determine the underlying factors associated with pulmonary disorders in these patients [1, 29].

A positive salivary pepsin test may obviate the need for more expensive and invasive diagnostic testing [30]. In preterm infants, pepsin detection in saliva correlates with clinical symptoms of GER [30]. The same has been reported before for simple pH measurement [31]. However, one could question what the added value is of having a "diagnostic test" when the symptoms are clinically visible. Of course, the fact that these tests are "positive" when reflux is clinically visible provides no information on these tests in clinically nonvisible reflux. A positive test does not provide information on the severity of GERD, and a negative test does not exclude the presence of GERD.

The WG suggests not to use currently available tests for the assessment of salivary pepsin for the diagnosis of GERD in infants and children.

Based on expert opinion, the WG suggests not to use currently available tests for the assessment of ear/tracheal/lung/esophageal fluids for the diagnosis of GERD in infants and children.

Empiric Trial of Acid Suppression as a Diagnostic Test

In adults, empiric treatment with acid suppression, i.e., without diagnostic testing, has been used for complaints of heartburn, chronic cough, noncardiac chest pain, and dyspepsia. However, empiric therapy has only modest sensitivity and specificity as a diagnostic test for GERD depending upon the comparative reference standard used (endoscopy, pH monitoring, symptom questionnaires). A meta-analysis evaluating pooled data from three large treatment trials among adults with nonerosive reflux disease showed that 85% of patients who had symptom resolution after 1 week of PPI treatment remained well for the entire 4 weeks of PPI treatment, thus "confirming" the diagnosis of GERD [27]. However, 22% of patients who had no improvement after 1 week of treatment did improve by the fourth week of treatment. An uncontrolled trial of esomeprazole therapy in adolescents with heartburn, epigastric pain, and acid regurgitation showed complete resolution of symptoms in 30–43% by 1 week, but the responders increased to 65% following 8 weeks of treatment [32]. Another uncontrolled treatment trial of pantoprazole in children aged 5–11 years reported greater symptom improvement at 1 week with a 40 mg dose compared to a 10 or 20 mg dose [33]. After 8 weeks, all treatment groups improved. Similar improvement in symptoms over time has been observed in adults with erosive esophagitis [34, 35]. One study of infants with symptoms suggestive of GERD who were treated empirically with a PPI showed no efficacy over placebo [10].

The treatment period required to achieve uniform therapeutic responses with PPI therapy probably varies with disease severity, treatment dose, and specific symptoms or complications. In an older child or adolescent with symptoms suggesting GERD, an empiric PPI trial is justified for up to 4 weeks. Improvement following treatment does not confirm a diagnosis of GERD since symptoms may improve spontaneously or respond by a placebo effect. There is no evidence to support an empiric trial of pharmacologic treatment in infants and young children as a diagnostic test of GERD. However, depending on the circumstances (availability of diagnostic testing regarding distance, waiting time, cost, etc.), a therapeutic trial may be the only option.

Based on expert opinion, the WG suggests a trial up to 8 weeks of PPIs for typical symptoms (heartburn, retrosternal or epigastric pain) in children as a diagnostic test for GERD.

Based on expert opinion, the WG suggests not to use a trial of PPIs as a diagnostic test for GERD in patients presenting with extraintestinal symptoms.

Based on expert opinion, the WG suggests not to use a trial of PPIs as a diagnostic test for GERD in infants.

References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
2. Lightdale JR, Gremse DA, Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013;131:e1684–95.
3. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain. 2007;127:140–50.
4. Stanford EA, Chambers CT, Craig KD. The role of developmental factors in predicting young children's use of a self-report scale for pain. Pain. 2006;120:16–23.
5. Orenstein SR, Shalaby TM, Cohn JF. Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire. Clin Pediatr (Philadelphia). 1996;35:607–14.
6. Kleinman L, Rothman M, Strauss R, Orenstein SR, Nelson S, Vandenplas Y, Cucchiara S, Revicki DA. The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument. Clin Gastroenterol Hepatol. 2006;4:588–96.
7. Aggarwal S, Mittal SK, Kalra KK, et al. Infant gastroesophageal reflux disease score: reproducibility and validity in a developing country. Trop Gastroenterol. 2004;25:96–8.
8. Salvatore S, Hauser B, Vandemaele K, et al. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr. 2005;40:210–5.
9. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing efficacy & safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154:514.e4–20.e4.
10. Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the treatment of GERD in infants ages 1-11 months. J Pediatr Gastroenterol Nutr. 2012;55:14–20.
11. Deal L, Gold BD, Gremse DA, et al. Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: development and initial validation. J Pediatr Gastroenterol Nutr. 2005;41:178–85.
12. Orenstein SR, Kocoshis SA, Orenstein DM, Proujansky R. Stridor and gastroesophageal reflux: diagnostic use of intraluminal esophageal acid perfusion (Bernstein test). Pediatr Pulmonol. 1987;3:420–4.
13. Vandenplas Y, Badriul H, Verghote M, et al. Glass and antimony electrodes for oesophageal pH monitoring in distressed infants: how different are they? Eur J Gastroenterol Hepatol. 2004;16:1325–30.
14. Hemmink GJ, Weusten BL, Oors J, et al. Ambulatory oesophageal pH monitoring: a comparison between antimony, ISFET, and glass pH electrodes. Eur J Gastroenterol Hepatol. 2010;22:572–6.
15. Vandenplas Y, Sacre-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0–15 months old. J Pediatr Gastroenterol Nutr. 1987;6:220–4.
16. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics. 1991;88:834–40.
17. Vandenplas Y, Lepoudre R, Helven R. Dependability of esophageal pH-monitoring data in infants on cutoff limits: the oscillatory index. J Pediatr Gastroenterol Nutr. 1990;11:304–9.
18. Vandenplas Y, Franckx-Goossens A, Pipeleers-Marichal M, Derde MP, Sacré-Smits L. Area under pH 4: advantages of a new parameter in the interpretation of esophageal pH monitoring data in infants. J Pediatr Gastroenterol Nutr. 1989;9:34–9.

19. Ummarino D, Vandermeulen L, Roosens B, et al. Gastroesophageal reflux evaluation in patients affected by chronic cough: Restech versus multichannel intraluminal impedance/pH metry. Laryngoscope. 2013;123:980–4.
20. Chiou E, Rosen R, Nurko S. Effect of different pH criteria on dual-sensor pH monitoring in the evaluation of supraesophageal gastric reflux in children. J Pediatr Gastroenterol Nutr. 2011;52:399–403.
21. Vailati C, Mazzoleni G, Bondi S, Bussi M, Testoni PA, Passaretti S. Oropharyngeal pH monitoring for laryngopharyngeal reflux: is it a reliable test before therapy? J Voice. 2013;27:84–9.
22. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:3–20.
23. Macharia EW. Comparison of upper gastrointestinal contrast studies and pH/impedance tests for the diagnosis of childhood gastro-oesophageal reflux. Pediatr Radiol. 2012;42:946–51.
24. Sager S, Halac M, Selcuk N, Dogan I, Kabasakal L, Onsel C, Uslu I. Temporal relationship between gastroesophageal reflux and rate of gastric emptying in children. Nucl Med Commun. 2010;31:1059–62.
25. Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. Chest. 2006;130:1520–6.
26. Jang HS, Lee JS, Lim GY, Choi BG, Choi GH, Park SH. Correlation of color Doppler sonographic findings with pH measurements in gastroesophageal reflux in children. J Clin Ultrasound. 2001;29(4):212–7.
27. Talley NJ, Armstrong D, Junghard O, Wiklund I. Predictors of treatment response in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2006;24:371–6.
28. Savino A, Cecamore C, Matronola MF, Verrotti A, Mohn A, Chiarelli F, Pelliccia P. US in the diagnosis of gastroesophageal reflux in children. Pediatr Radiol. 2012;42:515–24.
29. Saber H, Ghanei M. Extra-esophageal manifestations of gastroesophageal reflux disease: controversies between epidemiology and clinic. Open Respir Med J. 2012;6:121–6.
30. Farhath S, He Z, Saslow J, Soundar S, Amendolia B, Bhat V, Pyon K, Stahl G, Mehta D, Aghai ZH. Detection of pepsin in mouth swab: correlation with clinical gastroesophageal reflux in preterm infants. J Matern Fetal Neonatal Med. 2013;26:819–24.
31. James ME, Ewer AK. Acid oro-pharyngeal secretions can predict gastro-oesophageal reflux in preterm infants. Eur J Pediatr. 1999;158:371–4.
32. Gold BD, Gunasekaran T, Tolia V, Wetzler G, Conter H, Traxler B, Illueca M. Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2007;45:520–9.
33. Tolia V, Bishop PR, Tsou VM, Gremse D, Soffer EF, Comer GM. Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5–11 years) with symptomatic gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2006;42:384–91.
34. Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, D'Amico D, Hamelin B, Joelsson B. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther. 2000;14:1249–58.
35. Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, Marino V, Hamelin B, Levine JG. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol. 2001;96:656–65.

Manometry

6

Taher Omari

Abstract

Esophageal manometry has been in use for physiological measurement and diagnostics for many years. Solid-state high-resolution manometry (HRM) offers the ability to record pressures from the upper esophageal sphincter to the stomach with fidelity and high spatial resolution, and this has led to the definition of new objective biomechanical measures that may guide clinical decision-making in relation to paediatric patients with typical gastroesophageal reflux (GER) disease symptoms. The most important application of HRM is for the preoperative investigation of children undergoing work-up for anti-reflux surgery. Whilst the performance of HRM can be challenging in younger children, HRM can be used to exclude achalasia as a cause of typical symptoms and can provide a range of information on esophageal biomechanics that may be informative for determining disease severity. This includes characterisation of esophageal peristalsis and esophagogastric junction (EGJ) barrier function, based upon EGJ hiatus hernia subtype morphology and EGJ contractility. HRM may potentially have a role for investigation of recurrent transit hold-up symptoms following anti-reflux surgery. Finally, HRM may differentiate GER disease from rumination syndrome.

Keywords

Gastroesophageal reflux • Esophageal motility • High-resolution manometry • Diagnosis • Dysphagia

T. Omari
Human Physiology, Medical Science and Technology, School of Medicine,
Flinders University, Adelaide, South Australia
e-mail: taher.omari@flinders.edu.au

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_6

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) with/without impedance measurement is a significant enhancement of measurement technique. HRM essentially supersedes and renders obsolete the previous standard (i.e. eight-channel manometry with LES sleeve sensor). The ability to record pressure and bolus flow with high fidelity and spatial resolution has led to the definition of new objective biomechanical measures that describe anatomical features, flow resistance, and muscle contractility. It is hoped that the characterisation of these phenomena can enable assessment of pathophysiology and guide clinical decision-making in relation to patients with symptoms of GER disease and other upper gastrointestinal motility disorders.

This chapter will discuss the potential role of HRM for the assessment of children with GER disease. It will focus predominantly on the evaluation of children with typical signs and symptoms of primary GER disease drawing on evidence that, at the present time, is mostly only available in the adult reflux literature. The role of HRM for the assessment of GER that may be secondary to other pathologies (e.g. esophageal atresia) and in relation to the atypical symptoms (e.g. supra-esophageal reflux) will not be discussed.

The Practicalities of Performing Esophageal HRM Studies in Children

The standardisation of HRM procedures allows the measurements made to be compared against reference ranges for diagnostic purposes. In paediatric patients, standardisation is a significant challenge due to differences in patient size and ability to swallow boluses of the same volume and consistency. This impacts HRM recordings and changes optimal reference range thresholds [1].

The 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 HRM. Catheter size can have a significant impact on tolerance; a catheter size of 8Fr or less is optimal for children. Local anaesthetic-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 are able to understand the need for the procedure and are able to follow instructions will usually tolerate the procedure very well. Local

anaesthetic spray can be used to reduce nasal discomfort. Essentially the procedure can be performed as for an adult patient.

Supine body positioning, the standard for adult HRM investigations, is often impractical particularly for young children of toddler age.

When optimally positioned, the catheter pressure sensor array should straddle the region from the stomach to upper esophageal sphincter (UES). Swallowing of a bolus typically reveals manometric features such as the UES relaxation, proximal esophageal and distal esophageal propagated contraction and the esophagogastric junction.

A typical full swallow protocol used in this author's centre consists of five to ten repeat bolus swallows of liquid (water or saline), semi-solid (e.g. 'pudding') and solid (e.g. bread). In this author's experience, a full and meaningful swallow protocol, including all bolus consistencies, can be achieved in most children of 7 years and older.

Typically, liquid and semi-solid boluses should be administered to the mouth via a syringe and then the patient asked to swallow on command; hence, the delivery method is standardised, and only volitional swallowing is tested. Boluses should ideally be administered no more than every 20–30 s.

In older adolescent patients, provocative manoeuvres, such as *multiple rapid swallowing* (MRS), can also be performed. However, in many paediatric patients, the protocol may be too demanding and will need to be reduced in terms of 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 characterise motor patterns clinically relevant to the severity of GER and to exclude a primary motor disorder (i.e. achalasia) based on the current Chicago Classification for diagnosis of swallowing disorders [2]. However, when dysphagia symptoms are being investigated, the semi-solid and solid consistency bolus is more likely to provoke symptoms during the test which can be correlated with the motor patterns seen.

Why Do Esophageal HRM?

A HRM study may provide a range of information on esophageal biomechanics that may be informative for further confirming disease severity in a paediatric patient with GER disease symptoms, particularly when pH impedance probe and endoscopy evidence of gastroesophageal reflux disease may be equivocal. The most important reason for the extra step of performing HRM in a GER disease patient is for the preoperative work-up 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 [3] 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

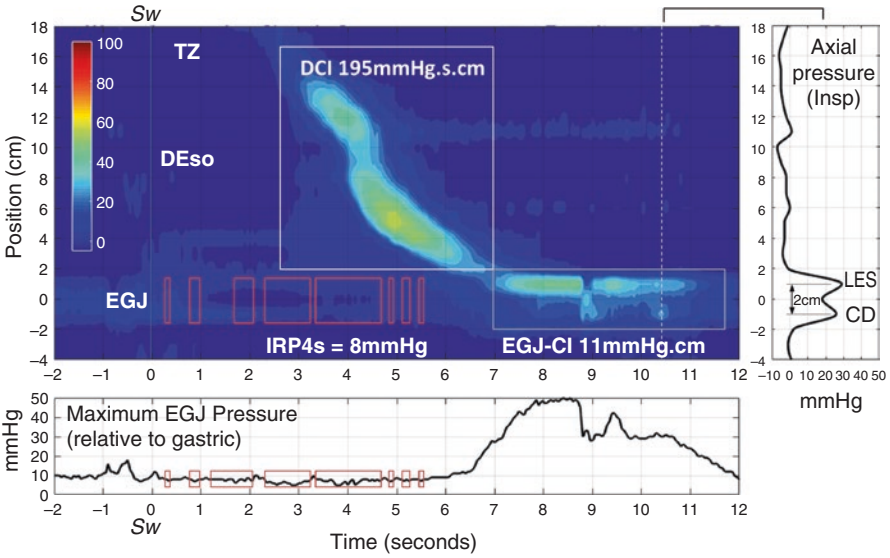


Fig. 6.1 Manometric features consistent with GER disease. An esophageal pressure topography plot of a 5 ml liquid swallow from a 14-year-old boy with a primary indication of typical symptoms of heartburn and regurgitation and significant esophageal acid exposure on 24 h pH probe (reflux index > 10%). This patient reported minor bolus hold-up symptoms prior to surgery, and these symptoms resolved following 360° Nissen fundoplication. HRM investigation was performed as part of the preoperative work-up. Anatomical locations of transition zone (TZ), distal esophagus (DEso) and esophagogastric junction (EGJ) are shown. A swallow (Sw) initiates peristaltic contraction of the esophageal body and relaxation of the EGJ. Esophageal body contractility is measured using the *distal contractile integral* (DCI), EGJ relaxation pressure is measured using the *4 s integrated relaxation pressure* (IRP4s; red boxes show the lowest EGJ pressures over 4 seconds), and post-relaxation EGJ contractility is measured using the *EGJ contractile integral* (EGJ-CI). In this case, manometry reveals several features consistent with GER disease. There are: (**1**) Weak basal EGJ tone prior to swallow with sufficient EGJ relaxation during the swallow (line plot below). (**2**) Weak esophageal body contractility consistent with a diagnosis of ineffective esophageal motility (DCI<450 mmHg s cm, [2]). (**3**) Weak EGJ contractility (EGJ-CI < 13 mmHg cm, [39]) consistent with barrier dysfunction. (**4**) Axial pressures during inspiration (line plot right) which reveal an intermittent, double-peaked, EGJ pressure zone with the inter-peak nadir pressure greater than gastric pressure and a range of LES-CD separation up to 2 cm in length, fulfilling the criteria for hiatus hernia with a 'type II' EGJ morphology [2]

catheter for this purpose without also capturing bolus swallows to at least characterise the dominant esophageal motor pattern and to exclude a primary motor disorder which may alternatively explain symptoms of regurgitation, heartburn, chest pain or dysphagia. Furthermore, HRM offers the opportunity to assess features of peristalsis and to characterise the gastroesophageal barrier function. As peristalsis is often weak and the EGJ function known to be disrupted in GER disease patients, HRM may provide additional information that may inform and support a diagnosis of GER disease.

Figure 6.1 illustrates, in a single patient swallow, many of the manometric hallmarks of GER disease and is illustrative of the commentary that follows for the remainder of this chapter.

What Can Esophageal HRM Measure That Is Relevant to GER Disease?

Most GER disease patients undergoing HRM will have either *normal* motility or evidence of a hypo-contractile esophagus, and usually *ineffective esophageal motility* (IEM) is 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 [2]. However, amongst reflux patients, the degree of IEM may be a marker of disease severity [4]. HRM also allows dynamic characterisation of the anti-reflux function of the esophagogastric junction (EGJ), comprising the lower esophageal sphincter (LES) and crural diaphragm (CD). This is by determining high-pressure zone length, respiratory pressure augmentation of CD squeeze pressure, hiatus hernia subtype morphology based on CD-LES separation, and post-relaxation contractility of the EGJ. Finally, HRM may potentially have a role for 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 work-up for anti-reflux surgery is 1% [5]; equivalent data for children is currently unavailable. HRM is now considered the optimal method for diagnosis and subtyping of achalasia [2, 6]. 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 preoperative work-up [5, 7–10]. Typical symptoms, such as heartburn that is refractory to PPI therapy, have been documented in up to one-third of adult patients with achalasia [11]. In patients with refractory GER disease without esophagitis, other diseases, such as achalasia, need to be considered [10, 12], and there is at least one recently published case study of a child (9 years), with troublesome symptoms, consistent GER disease and significant non-acid reflux on MII-pH monitoring, receiving anti-reflux surgery only to be discovered subsequently to have achalasia [13].

In this author's experience, manometry to exclude achalasia can be achieved in almost every child undergoing HRM; however, meaningful manometry to diagnose other primary esophageal motor disorders, IEM and/or EGJ features requires a very cooperative patient who is able to swallow boluses on command. In all circumstances, 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 Body Motility

The diagnosis of IEM indicates that the esophageal body is poorly propulsive leading to failure of bolus transport and delayed reflux volume clearance. The definition of IEM has changed in line with the evolution of manometry [14]. Currently, IEM is defined by the Chicago Classification based on a distal

contractile integral (DCI) of <450 mmHg cm s during ≥50% peristaltic sequences [2]. In GER disease patients, IEM is associated with increased acid exposure and delayed bolus clearance [15] and more likely to be associated with typical symptoms of heartburn and regurgitation, than dysphagia [16]. The prevalence of IEM, or other evidence of hypomotility, in patients undergoing anti-reflux surgery work-up ranges from 24 to 50% [5, 14, 15, 17, 18]. The prevalence of IEM in paediatric GER disease is not well characterised. However, the incidence of IEM increases in relation to patient age [18, 19]. In this author's experience, IEM may be less common in children than in adults. An example swallow from a GER disease patient with IEM is shown in Fig. 6.1.

The incidence of IEM overall does not significantly change post-operatively [18]; however, amongst individual patients, IEM may persist, or new IEM may emerge despite an improvement in GER disease symptoms [18]. It is suggested that the presence of IEM or other evidence of diminished esophageal contractile force could inform surgical approach (i.e. partial fundoplication approaches rather than full). However, whilst intuitive, objective evidence underpinning 'tailoring' the degree of fundoplication based on preoperative esophageal motility seems to be lacking [9, 14]. A recent study by Andolfi and colleagues [17] employed a strategy of partial fundoplication when IEM patients complained preoperatively of dysphagia; however, outcomes showing the advantage of this specific choice were unclear.

Additive Value Multiple Rapid Swallows

Multiple rapid swallowing (MRS) is a provocative test performed during an HRM procedure which, during preoperative work-up, is designed to reveal dysfunction of the enteric nervous system, specifically a subtle imbalance 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 attenuation of post-MRS augmentation together suggest failure of descending inhibition due to inadequate release of endogenous nitric oxide by inhibitory postsynaptic neurones.

In the context of GER disease and fundoplication, the ability to assess peristaltic reserve preoperatively may predict whether the esophageal body contractility is sufficient to overcome the surgically induced outflow obstruction. Mello et al. (2016) [18] used MRS to predict post-operative IEM phenotypes during preoperative 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 for the post-operative assessment of patients reporting post-operative dysphagia, where an elevated intra-bolus pressure during multiple water swallows may identify the presence of and EGJ outflow obstruction [20]. In the case of the patient with IEM at preoperative work-up, 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 in both health and disease in both adults [21] and children [22]. The main factor differentiating GER disease patients from healthy controls is a higher prevalence of liquid refluxate *during* transient LES relaxation, rather than the frequency of relaxations overall [23].

The EGJ is a main gatekeeper that prevents 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, allowing gastric contents to pass into the esophageal body [24]. The proximal spread of refluxate depends on its consistency (gas, mixed, liquid) and the magnitude of the gastroesophageal pressure gradient which can be augmented by more positive abdominal pressures (e.g. in association with obesity [25]) or more negative thoracic pressures (e.g. in association with COPD [26]).

Transient LES relaxation episodes can now be reliably identified and quantified by HRM criteria [27]. 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.

Esophagogastric Junction Morphology

Morphometric analysis utilises 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 ultrahigh-resolution circumferential pressure measurement throughout the EGJ [28, 29]. However, when measured using 1 cm-spaced pressure sensors, HRM recording can still readily identify the different EGJ components and quantify LES pressure, CD pressure augmentation and the presence and extent of LES-CD separation which defines hiatus hernia (HH) size (see Fig. 6.1).

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 [30]. Functional failure of the CD has also been characterised in patients with esophagitis [31]. HRM criteria can detect HH and measure HH size with equivalent accuracy to endoscopy and radiology [32]. HRM allows determination of three HH subtypes based on the degree of LES-CD separation [2]. 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 [30, 33].

Figure 6.1 shows an example of 'type II' EGJ morphology. Patient series characterising EGJ morphology in paediatric GER disease are yet to be published.

Esophagogastric Junction Contractility

Barrier function of the EGJ can also be assessed based on 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 [34], and, conversely, anti-reflux surgery is associated with increased length and higher pressures [34, 35]. A mechanically defective LES is common in medically refractory patients undergoing diagnostic work-up for anti-reflux surgery [5].

Several groups have more recently investigated the diagnostic potential of a new HRM-based *EGJ contractile integral* (EGJ-CI) which defines contractility by measuring pressure over the length of the EGJ and over time. EGJ-CI is lower in GERD patients and, in relation to HH, negatively associated with acid exposure, and the number of reflux episodes [33, 36, 37] is augmented by anti-reflux surgery (full fundoplication > partial fundoplication), and post-operative EGJ-CI is higher in patients with post-operative dysphagia [18, 38]. There is a suggestion that EGJ-CI may be higher in PPI nonresponders [39].

The relevance of these observations to paediatric GER disease requires further investigation.

Preoperative HRM to Select Patients at Risk of Post-operative Dysphagia: Is There Reason to Hope?

Dysphagia symptoms are not uncommon in GER disease patients undergoing anti-reflux surgery. In this author's experience, most carefully surveyed children undergoing preoperative work-up will report bolus hold-up to some food consistencies at the time of HRM study (unpublished). In published adult and paediatric series, 'early' post-operative dysphagia, which resolves in the short term, can occur in ~20–40% of patients [3, 40, 41]. The acute effects of surgery probably result in a degree of post-operative EGJ outflow obstruction which can be recorded manometrically as an elevated EGJ relaxation pressure [42].

When symptoms of dysphagia to solids are carefully assessed both pre- and post-operatively, allowing sufficient time for early symptoms to resolve, three groups of patients typically emerge: (1) those with no dysphagia, (2) those with preoperative dysphagia which usually persists post-operatively and (3) those who develop 'new' dysphagia following the surgery. In adults, Myers et al. (2012) [43] reported proportions of 21, 42 and 37% for these subgroups, respectively. A recent paediatric study observed new-onset dysphagia in 12% of patients receiving fundoplication [3], and another showed an incidence of 40% amongst paediatric patients who were already preselected for surgery based on the appearance of normal motility [45]. However, in 4–11% of patients overall, dysphagia can become troublesome [3, 41, 43]. These symptoms may mar an otherwise successful anti-reflux procedure; a patient may be reduced to swallowing only liquids and may require intervention. In such circumstances, the data from a preoperative HRM study can be very helpful for objectively quantifying the impact that surgery has had on EGJ barrier. Postsurgical HRM evaluation would typically show elevated EGJ pressures, which is consistent with the desired effect of the surgery. However, marked distal compartmentalised pressurisation during individual swallows or high intra-bolus 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 [20].

If no evidence of outflow obstruction is apparent and/or dilation of the EGJ fails to relieve the symptoms of dysphagia, then the value of the anti-reflux procedure in the first place comes into question. Ideally one would wish to be able to identify such patients early and counsel against surgery due to high post-operative risk; this has been a significant challenge. The adult literature shows that, with the exception of the rare case of unrecognised achalasia, the presence of any other primary esophageal motor disorders does not in itself predict post-operative dysphagia symptoms. Symptom outcomes of patients with disordered or normal motility are reported to be similar [40]. Finally, the data is very clear that *normal* HRM findings reported many GER disease patients receiving anti-reflux surgery [17]; this is almost certainly the case in paediatric GER disease patients who have a lower incidence of IEM and are less likely to have a disrupted HH morphology. Overall, the HRM diagnosis of IEM is not *sensitive* for predicting post-operative dysphagia, neither is a normal HRM *specific* for a low risk of post-operative dysphagia.

There is, however, some cause for hope that methods to predict unwanted side effects of anti-reflux surgery will be discovered. In a landmark study, Stoikes and colleagues (2012) [45] found that late post-operative dysphagia was more prevalent in individuals who show poor peristaltic reserve on MRS. As previously discussed, IEM phenotypes, revealed by HRM with MRS protocols, are thought to be useful for tailoring operative approach; however, this has not been rigorously tested. Indeed Mello et al. (2016) [18] found that IEM augmentation by MRS did not differentiate dysphagia. However, EGJ-CI trended higher in those who had post-operative dysphagia. Finally, there are two reports by this author, suggesting that novel pressure-impedance measures and derivation of a 'dysplasia risk index' may allow the detection of subtle esophageal abnormalities before surgery that are not

detectable with the use of conventional methods [43, 44]. Work is ongoing to confirm and implement these early findings using HRM with impedance.

Together, these different observations are suggestive of a subtle excitatory-inhibitory imbalance in the enteric nervous system that may impair mechanisms of bolus propulsion or conversely increase bolus flow resistance during bolus transport. Whilst sub-clinical or causal of symptoms that are incorrectly attributed to GER disease, this unrecognised dysfunction may become clinically relevant when the EGJ is surgically reconfigured.

Use of Manometry with Impedance to Diagnose Rumination Syndrome

Rumination syndrome is an abnormal straining behaviour that causes recurrent regurgitation of gastric contents into the mouth, usually soon after a meal. Whilst rare, rumination syndrome is considered a functional gastrointestinal disorder, rather than a motility disorder (such as GER disease, functional vomiting or gastroparesis), and behavioural therapy or diaphragmatic breathing may be effective.

Recent studies have demonstrated the value of manometry, combined with impedance monitoring, to detect and characterise rumination episodes. The goal of investigation in this case is to observe regurgitation episodes (retrograde bolus flow from the stomach to the proximal esophagus on impedance) that are preceded by a transient rise in intra-gastric pressure due to abdominal wall contraction.

Studies utilising manometry with impedance in children referred for clinical suspicion of rumination have recently been published [46, 47]. Whilst different technologies and methods were used, namely, ambulatory assessment based on 24 h study using pH impedance and manometry probe [47] or stationary short postprandial assessment (for 30 min) using HRIM [46], the diagnosis of patterns consistent with rumination syndrome was achieved in both studies. Four rumination patterns were characterised between these studies: (1) primary rumination, when abdominal pressure increase precedes retrograde flow; (2) secondary rumination, when abdominal pressure increase follows the onset of a reflux event (usually a transient LES relaxation) and (3) when abdominal pressure increase follows a supra-gastric belch; and (4) rumination through a closed LES.

The characterisation of rumination pattern may allow better targeting of interventions. Whilst several rumination patterns can be identified, secondary rumination is by far the dominant pattern, indicating that patients may sense gastric refluxate in the distal esophagus which in turn causes an abdominal strain response which propels refluxed material into the pharynx and oral cavity. Overall, these findings suggest that impedance manometry methods do have a role in the investigation of rumination syndrome and may differentiate rumination syndrome from GER disease. Clearly, if a patient undergoing HRM (with impedance) during work-up for anti-reflux surgery demonstrates patterns consistent with rumination syndrome, then a change of management approach needs to be considered.

Conclusion

Technology to perform esophageal HRM is now widely available, and there is the opportunity to take advantage of this technique for the evaluation of children with symptoms of GER disease. Currently, there is a paucity of evidence available from paediatric studies, and further research is clearly needed to link HRM measures to GER disease severity and clinical outcomes in children. Nevertheless the existing evidence from the adult literature shows that HRM can define import features of esophageal dysmotility and EGJ barrier dysfunction that can support a diagnosis of GER disease. The consensus amongst adult experts is that HRM is an important test that needs to be considered when performing diagnostic work-up for anti-reflux surgery. The interpretation of HRM findings should focus on detecting a primary motor disorder, which may alternatively explain symptoms (achalasia) or guide operative technique (IEM), and/or identifying abnormalities consistent with disruption of the anti-reflux barrier which may be surgically correctable. HRM findings of normal motility and normal barrier function are potentially inconsistent with GER disease and should not be considered reliable predictors of a good post-operative outcome.

References

1. Singendonk MMJ, Kritas S, Cock C, Ferris L, McCall L, Rommel N, et al. Applying the Chicago classification criteria of esophageal motility to a pediatric cohort: effects of patient age and size. Neurogastroenterol Motil. 2014;26(9):1333–41.
2. Kahrilas PJ, Bredenoord a J, Fox M, Gyawali CP, Roman S, Smout a JPM, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27:160–74.
3. Mauritz FA, Conchillo JM, LWE VH, Siersema PD, CEJ S, RHJ H, et al. Effect and efficacy of laparoscopic fundoplication in children with GERD: The Dutch prospective, multicenter study. Surg Endosc Other Interv Tech. 2016;30:S49. Springer US
4. Martinucci I, de Bortoli N, Giacchino M, Bodini G, Marabotto E, Marchi S, et al. Esophageal motility abnormalities in gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther. 2014;5(2):86–96.
5. Chan WW, Haroian LR, Gyawali CP. Value of preoperative esophageal function studies before laparoscopic antireflux surgery. Surg Endosc Other Interv Tech. 2011;25:2943–9.
6. Pandolfino JE, M a K, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology. 2008;135(5):1526–33.
7. Patti MG. An evidence-based approach to the treatment of gastroesophageal reflux disease. JAMA Surg. 2015;151(1):1–6.
8. Singhal V, Khaitan L. Preoperative evaluation of gastroesophageal reflux disease. Surg Clin North Am. 2015;95(3):615–27. Elsevier Inc;
9. Jobe BA, Richter JE, Hoppo T, Peters JH, Bell R, Dengler WC, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the esophageal diagnostic advisory panel. J Am Coll Surg. 2013;217(4):586–97. Elsevier Inc;
10. Karamanolis GP, Sifrim D. Patients with refractory gastroesophageal reflux disease: diagnostic tools. Ann Gastroenterol Q Publ Hell Soc Gastroenterol. 2013;26:6–10.
11. Andolfi C, Bonavina L, Kavitt RT, Konda VJ, Asti E, Patti MG. Su1151 importance of esophageal manometry and pH monitoring in the evaluation of patients with "Refractory GERD". A multicenter study. Gastroenterology. 2016;150(4):S1205.

12. Richter JE. How to manage refractory GERD. Nat Clin Pract Gastroenterol Hepatol. 2007;4(12):658–64.
13. Pyun J, Choi D, Lee L, Yoo K, Shim J. Achalasia previously diagnosed as gastroesophageal reflux. Pediatr Gastroenterol Hepatol Nutr. 2015;18(1):55–9.
14. Abdel Jalil AA, Castell DO. Ineffective Esophageal Motility (IEM): the old-new frontier in esophagology. Curr Gastroenterol Rep. 2015;18:1–7.
15. Ribolsi M, Balestrieri P, Emerenziani S, Guarino MPL, Cicala M. Weak peristalsis with large breaks is associated with higher acid exposure and delayed reflux clearance in the supine position in GERD patients. Am J Gastroenterol. 2014;109(1):46–51. Nature Publishing Group
16. Simic AP, Skrobic OM, Gurski RR, Sljukic VM, Ivanovic NR, Pesko PM. Can different subsets of ineffective esophageal motility influence the outcome of nissen fundoplication? J Gastrointest Surg. 2014;18:1723–9.
17. Andolfi C, Vigneswaran Y, Kavitt RT, Herbella FA, Patti MG. Laparoscopic antireflux surgery: importance of patient's selection and preoperative workup. J Laparoendosc Adv Surg Tech. 2016;27(2):101–5. doi:10.1089/lap.2016.0322.
18. Mello MD, Shriver a R, Li Y, Patel a, Gyawali CP. Ineffective esophageal motility phenotypes following fundoplication in gastroesophageal reflux disease. Neurogastroenterol Motil. 2016;28:292–8.
19. Cock C, Besanko L, Kritas S, Burgstad CM, Thompson A, Heddle R, et al. Impaired bolus clearance in asymptomatic older adults during high-resolution impedance manometry. Neurogastroenterol Motil. 2016;28:1890–901.
20. Wang YT, Tai LF, Yazaki E, Jafari J, Sweis R, Tucker E, et al. Investigation of dysphagia after antireflux surgery by high-resolution manometry: impact of multiple water swallows and a solid test meal on diagnosis, management, and clinical outcome. Clin Gastroenterol Hepatol. 2015;13(9):1575–83. Elsevier, Inc
21. Mittal R, Holloway R, Penagini R, Blackshaw L, Dent J. Transient lower esophageal sphincter relaxation. Gastroenterology. 1995;109(2):601–10.
22. Omari T, Benninga M, Sansom L, Butler R, Dent J, Davidson G. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal disease. J Pediatr. 2006;149:468–74.
23. Sifrim D, Holloway R, Silny J, Tack J, Lerut A, Janssens J. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96(3):647–55.
24. Pandolfino JE, Zhang QG, Ghosh SK, Han A, Boniquit C, Kahrilas PJ. Transient lower esophageal sphincter relaxations and reflux: mechanistic analysis using concurrent fluoroscopy and high-resolution manometry. Gastroenterology. 2006;131:1725–33.
25. Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology. 2006 Mar;130(3):639–49.
26. Del Grande LM, Herbella F a M, Bigatao AM, Abrao H, Jardim JR, Patti MG. Pathophysiology of gastroesophageal reflux in patients with chronic pulmonary obstructive disease is linked to an increased transdiaphragmatic pressure gradient and not to a defective esophagogastric barrier. J Gastrointest Surg. 2016;20:104–10.
27. Roman S, Zerbib F, Belhocine K, Bruley Des Varannes S, Mion F. High resolution manometry to detect transient lower oesophageal sphincter relaxations: Diagnostic accuracy compared with perfused-sleeve manometry, and the definition of new detection criteria. Aliment Pharmacol Ther. 2011;34:384–93.
28. Kwiatek MA, Pandolfino JE, Kahrilas PJ. 3D-high resolution manometry of the esophagogastric junction. Neurogastroenterol Motil. 2011 Nov;23(11):e461–9.
29. Nicodème F, Pandolfino JE, Lin Z, Xiao Y, Escobar G, Kahrilas PJ. Adding a radial dimension to the assessment of esophagogastric junction relaxation: validation studies of the 3D-eSleeve. Am J Physiol Gastrointest Liver Physiol. 2012;303(3):G275–80.
30. Pandolfino JE, Kim H, Ghosh SK, Clarke JO, Zhang Q, Kahrilas PJ. High-resolution manometry of the EGJ: An analysis of crural diaphragm function in GERD. Am J Gastroenterol. 2007;102:1056–63.

31. E Souza MÂ, Nobre RA, Bezerra PC, Dos Santos AA, Sifrim D. Anatomical and functional deficiencies of the crural diaphragm in patients with esophagitis. Neurogastroenterol Motil. 2016;29:e12899.
32. Weijenborg PW, van Hoeij FB, Smout a JPM, Bredenoord a J. Accuracy of hiatal hernia detection with esophageal high-resolution manometry. Neurogastroenterol Motil. 2015;27: 293–9.
33. Tolone S, De Bortoli N, Marabotto E, de Cassan C, Bodini G, Roman S, et al. Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value? Neurogastroenterol Motil. 2015;27:1423–31.
34. Hoshino M, Srinivasan A, Mittal SK. High-resolution manometry patterns of lower esophageal sphincter complex in symptomatic post-fundoplication patients. J Gastrointest Surg. 2012;16:705–14.
35. Yamamoto SR, Akimoto S, Hoshino M, Mittal SK. High-resolution manometry findings in symptomatic post-Nissen fundoplication patients with normal endoscopic configuration. Dis Esophagus. 2015;29:967–70.
36. Jasper D, Freitas-Queiroz N, Hollenstein M, Misselwitz B, Layer P, Navarro-Rodriguez T, et al. Prolonged measurement improves the assessment of the barrier function of the esophagogastric junction by high-resolution manometry. Neurogastroenterol Motil. 2016;29:e12925.
37. Gor P, Li Y, Munigala S, Patel a B a, Gyawali CP. Interrogation of esophagogastric junction barrier function using the esophagogastric junction contractile integral: an observational cohort study. Dis Esophagus. 2015;29:820–8.
38. Wang D, Patel a, Mello M, Shriver a, Gyawali CP. Esophagogastric junction contractile integral (EGJ-CI) quantifies changes in EGJ barrier function with surgical intervention. Neurogastroenterol Motil. 2016;28:639–46.
39. Nicodeme F, Pipa-Muniz M, Khanna K, Kahrilas PJ, Pandolfino JE. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: Normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil. 2014;26(3):353–60.
40. Dell'Acqua-Cassao B, Mardiros-Herbella FA, Farah JF, Bonadiman A, Silva LC, Patti MG. Outcomes of laparoscopic Nissen fundoplication in patients with manometric patterns of esophageal motility disorders. Am Surg. 2013;79:361–5.
41. Ribeiro M, Tercioti-júnior V, Souza-neto JC, Lopes LR, Morais DJ, Andreollo NA. Identification of preoperative risk factors for persistent postoperative dysphagia after laparoscopic antireflux surgery. Arq Bras Cir Dig. 2013;26(3):165–9.
42. Marjoux S, Roman S, Juget-Pietu F, Robert M, Poncet G, Boulez J, et al. Impaired postoperative EGJ relaxation as a determinant of post laparoscopic fundoplication dysphagia: a study with high-resolution manometry before and after surgery. Surg Endosc Other Interv Tech. 2012;26:3642–9.
43. Myers JC, Nguyen NQ, Jamieson GG, Van't Hek JE, Ching K, Holloway RH, et al. Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis. Neurogastroenterol Motil. 2012;24:812–e393.
44. Loots C, van Herwaarden MY, Benninga MA, VanderZee DC, van Wijk MP, Omari TI. Gastroesophageal reflux, esophageal function, gastric emptying, and the relationship to dysphagia before and after antireflux surgery in children. J Pediatr. 2013;162(3):566–73.e2. Mosby, Inc.
45. Stoikes N, Drapekin J, Kushnir V, Shaker A, Brunt LM, Gyawali CP. The value of multiple rapid swallows during preoperative esophageal manometry before laparoscopic antireflux surgery. Surg Endosc. 2012;26(12):3401–7.
46. Rosen R, Rodriguez L, Nurko S. Pediatric rumination subtypes: a study using high-resolution esophageal manometry with impedance. Neurogastroenterol Motil. 2016;29:e12998.
47. Singendonk MMJ, Oors JM, Bredenoord AJ, Omari TI, van der Pol RJ, Smits MJ, et al. Objectively diagnosing rumination syndrome in children using esophageal pH-impedance and manometry. Neurogastroenterol Motil. 2017;29:e12996.

Multichannel Intraluminal Impedance and pH Monitoring (pH-MII) in Infants and Children

7

Maartje M.J. Singendonk, F. Jaime, S. Salvatore, M.M. Tabbers, M.A. Benninga, and Y. Vandenplas

Abstract

The application of combined pH and multichannel intraluminal impedance (pH-MII) monitoring has enhanced the recognition and characterization of gastro-oesophageal reflux disease (GORD). Its main advantages over traditional pH monitoring lie in the additional ability to detect non-acid gastro-oesophageal reflux (GOR), to discern between liquid and gas GOR and to determine the proximal extent of a GOR episode. When conducted in combination with manometry, it reveals information on the relationship between oesophageal pressures and oesophageal bolus flow, enhancing the evaluation of oesophageal function testing in terms of assessment of mechanisms of oesophageal bolus clearance. The measurement of mean impedance baseline has also provided novel insights into oesophageal mucosal integrity changes as an indicator of oesophageal inflammation. However, a few clinical and technical shortcomings, of which some are specific to the paediatric population, must be considered when interpreting study results and limit the diagnostic value of pH-MII monitoring in children. In this

M.M.J. Singendonk • M.M. Tabbers • M.A. Benninga
Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, The Netherlands

F. Jaime
Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, The Netherlands

Department of Paediatric Gastroenterology and Nutrition, Pontificia Universidad Católica de Chile, Santiago, Chile

S. Salvatore
Paediatrics, Clinical Pediatrica di Varese, Universita dell'Insubria, Varese, Italy

Y. Vandenplas (✉)
Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussels, Brussels, Belgium
e-mail: Yvan.Vandenplas@uzbrussel.be

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_7

chapter, the technical aspects of pH-MII monitoring will therefore first be addressed, and, second, the current clinical benefits and limitations of oesophageal pH-MII in children will be highlighted.

Keywords
pH • Impedance • pH-MII • Monitoring • Children • Reflux • Acid reflux • Weakly acid reflux • Non-acid reflux • Catheter • Reflux index

Introduction

The effect of oesophageal acid exposure on heartburn in patients with suspected gastro-oesophageal reflux disease (GORD) started to be studied in the early twentieth century [1]. Oesophageal pH metre does not measure GOR: it (only) objectifies acidic changes in oesophageal pH and lacks the ability to detect weakly acidic or superimposed GOR (i.e. a new GOR episode during a previous acid GOR episode not yet cleared). With advancing technical possibilities, it became possible to measure reflux by using also multiple intraluminal impedance (MII) recording. The combined monitoring of pH and impedance allows to recognize the existence of other types of GOR [2], currently defined as weakly acid and alkaline GOR and also known as non-acid reflux.

Since its introduction, oesophageal pH-MII has been used in several areas: (1) as a new diagnostic tool for GORD, specifically to assess symptoms that might be related to GORD; (2) to evaluate the efficacy of treatment, especially if response to treatment is not as expected; (3) and, in combination with manometry, to enable determination of the relationship between oesophageal pressures and oesophageal bolus flow. Indications, methodology and interpretation have been reported by an ESPGHAN working group in 2012 [3].

Basic Principles and Technical Aspects of Intraluminal pH and Impedance (pH-MII) Monitoring

The MII technique is based on changes in resistance to electrical current flow between two electrodes when a (liquid and/or gas) bolus moves between them [4]. Hence, as impedance shows the inverse of conductivity, liquids that have high conductance provoke a drop of impedance, while gas that has a low conductance provokes a rapid rise in impedance [4, 5]. The impedance signal depends on the environment surrounding the electrodes, including the luminal content (food, reflux, gas, etc.), the characteristics of the mucosa, the wall thickness, the oesophageal contraction and the cross-sectional area [4]. The value of impedance present in the oesophagus in absence of a bolus (swallowing or reflux) is called the impedance baseline [6]. Simultaneous video-fluoroscopic and impedance measurements of oesophageal function during swallowing have validated typical changes observed with bolus entry, presence and clearing in the impedance-measuring segment [7]. Combined pH-MII measurement allows to classify GOR episodes as acid, weakly acidic and weakly alkaline [3, 4, 8] (Table 7.1, Fig. 7.1).

Table 7.1 Reflux parameters

GOR	Sequential change in impedance, starting distally and propagating orally to at least three adjacent recording segments (two channels). The episode ends when the impedance value returns to at least 50% of the initial (baseline) value
Liquid GOR	Drop in impedance to less than 50% of baseline value
• Acid GOR	pH falls below 4 for at least 4 s or, if pH was already below 4, decreases by at least 1 pH unit sustained for more than 4 s
• Weakly acid GOR	pH drop of at least 1 pH unit sustained for > 4 s with basal pH remaining between ≥4.0 and <7.0
• Weakly alkaline GOR	pH does not drop below 7 or increases to above 7
Gas GOR	Sharp increase of impedance to >3000 ohm in any two consecutive impedance channels with one site having an absolute value >7000 ohms
Reflux index/total acid exposure index	Percentage of time with pH <4
• Normal	<3%
• Indeterminate	3–7%
• Abnormal	>7% (infants >10%)
Number of episodes of GOR events	
• Abnormal	Age < 1 year: >100 episodes
	Age ≥ 1 year: >70 episodes
Total bolus clearance time	Time needed for a bolus to be cleared from the oesophagus
Total bolus exposure index	Percentage of time that a bolus is present in the oesophagus

GOR gastro-oesophageal reflux

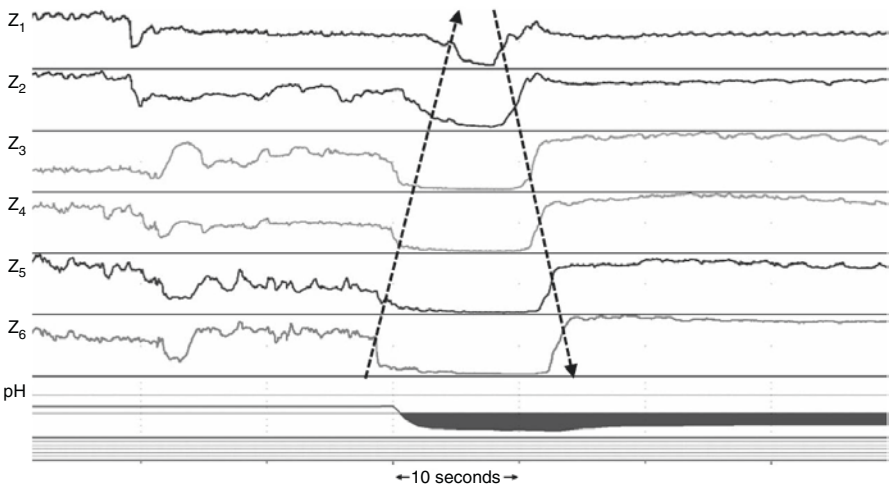


Fig. 7.1 Acid gastro-oesophageal reflux. Drop in the impedance signal starting in the most distal channel, indicating liquid bolus reflux. Drop in the pH to below 4. Impedance signal returns to baseline, starting in the most proximal channel. Z_1—Z_6 indicate the six impedance channels. pH indicates the pH channel. *Arrows* indicate the direction of flow through the oesophagus

By using multiple impedance channels in the oesophageal catheter, the direction of flow as well as the proximal extent and duration of a GOR episode can also be determined. The height of a reflux event is defined by the most proximal impedance-measuring segment reached by the liquid component of the reflux episode. A reflux is commonly considered as 'proximal' if the most proximal extent of the bolus reflux reaches the first impedance channel. Gas reflux events are not assigned a proximal extent since they travel nearly simultaneously over the full length of the oesophagus.

Hardware

The pH-MII equipment consists of a portable case (data logger) for ambulatory data recording and a catheter. The data logger is designed small and light enough to be carried by a child during a 24-h measurement, either in a small backpack or shoulder-bag. Its interface is purpose designed to be friendly enough to allow parents or older children to indicate positioning, meals and symptoms easily but not to erase documented events or to stop the study unexpectedly. At the end of the study, the device is connected to a computer to analyse the results with purpose-designed software programmes (see under 'Analysis').

The pH and Impedance Catheters

The pH-impedance catheter has two types of built-in sensors, one to monitor the pH and another to monitor the impedance signal. pH-MII catheters can contain one or two pH electrodes (for oesophageal, oesophageal and gastric or laryngopharyngeal and gastric monitoring).

pH electrodes exist in different forms, including glass, antimony and ion-sensitive field effect transistors (ISFET), each with their own advantages and disadvantages. Glass electrodes have shown to detect higher acid exposure times versus ISFET and antimony electrodes both in vivo and in vitro [9]. It is important to notice that data obtained with a glass electrode poorly correlates with data obtained with an antimony electrode [9, 10]. This implies that every type of electrode should have, and should be used with, its own normal values (also see under 'pH-MII parameters and normative values'). Glass electrodes have a longer lifetime than ISFET electrodes, but they are more expensive and their larger diameter (2.5–3.0 mm) [11] limits the number of sensors that can be installed on one catheter to measure distal and proximal pH. Additionally, passage of such larger diameter catheter through the nostril of an infant can be challenging. Although nowadays glass microelectrodes (1.2 mm) exist, their insertion can however also be difficult because of their flexibility, and a rolling up is possible during the passage through the nostrils, pharynx and oesophagus. Despite these limitations, the use of these microelectrodes, together with small diameter antimony (2.1 and 1.5 mm) electrodes, is preferred in infants.

pH-MII catheters are available in different lengths, tailored to the size of the patient ('infant' for children smaller than 75 cm, 'paediatric' for children between 75 and 150 cm and 'adult' for patients taller than 150 cm). They usually contain seven impedance rings, separated by 1.5 (in the case of infant catheters) or 2 cm, thereby forming six impedance channels.

Performing a pH-MII Measurement in Clinical Practice

Performing an oesophageal pH-MII measurement involves several steps, which are outlined below:

1. Calibration
   Prior to each study, an in vitro two-point calibration of the pH electrode must be carried out, according to instructions of each manufacturer. For this purpose, the electrode is placed in two buffer solutions (usually pH 4.0 and 7.0) at either room or body temperature until stabilization is reached.
2. Installation of the Catheter
   The catheter is placed via one of the nostrils, after lubrication with a water-soluble gel, with or without topical anaesthesia. The exact oesophageal location of the pH electrode is of critical importance for adequate registration of the number and duration of acid reflux episodes. Shortenings of oesophageal length that may happen during deglutition can eventually displace the pH electrode and may therefore being wrongly sensed as reflux episodes [12]. In adults, by consensus, the pH electrode is placed 5 cm above the proximal border of the lower oesophageal sphincter (LOS), and correct placement is determined by means of a standard stationary oesophageal manometry study. This approach is also generally accepted in older children and adolescents [3, 5, 11, 13] but considered less ideal in younger children, because of difficulty in performing manometry and also because it locates the electrode at a fixed distance to the LOS, while the length of the oesophagus increases from less than 10 cm in a newborn to over 25 cm in an adult [14, 15]. Therefore, in younger children, several other (combinations of) techniques have been proposed, including fluoroscopy, chest X-ray, calculation of the oesophageal length (most commonly according to Strobel's distance from the nose to the cardia = 5 + 0.252 [length in cm]) [13, 16, 17] and endoscopy. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group recommends to confirm or adjust position of the catheter by fluoroscopy or X-ray [3]. As the tip of the electrode moves with and during respiration, the tip should be positioned in such a way that it overlies the third vertebral body above the diaphragm throughout the respiration cycle [18, 19].
3. Patient Preparation
   Patients are required to fast for at least 4 h prior to the study, as positioning of the catheter might elicit vomiting. Depending on the indication of the study, pH-MII

might be undertaken on or off acid-suppressive medication. If the primary aim of the study is to confirm an unclear diagnosis of GORD, especially in children presenting with extra-oesophageal symptoms or before anti-reflux surgery, patients should undergo testing *off* acid-suppressive medication. The main indication to perform a test *on* acid-suppressive medication is the evaluation of treatment efficacy on the frequency and duration of (acid) GOR in patients with persisting symptoms despite therapy [5, 12]. If a pH-MII is performed off medication, proton pump inhibitors (PPIs) should be stopped at least 7 days before and H_2 receptor antagonists (H2RAs), 3–7 days before the study [20]. Prokinetic use should be ceased at least 2 days before a diagnostic pH-MII [8].

4. During the Investigation
   Patients (and/or their parents or caregivers) are asked to record a symptom diary on both the data logger and on a special diary form. Meal and sleep times are asked to be marked, and, additionally, in older children, alcohol intake and smoking should be documented. Patients are advised to keep their routines as usual as they can, as a too restricted diet or lifestyle might alter the patient's normal habits in such a way that the investigation is no longer performed under physiologic conditions. However, some recommendations regarding dietary intake are given in order not to interfere with the performance of the test. As the pH electrodes are temperature sensitive, very hot and cold meals should be avoided. Gum chewing should also be avoided, as this increases saliva production and thereby lowers the number of reflux episodes [3, 8]. Generally, no restrictions are given regarding the intake of foods and beverages with a low pH (e.g. soft drinks, fruit juice, etc.), as duration of ingestion is limited to a few minutes only, and with combined impedance monitoring, bolus movement can also be determined (e.g. from proximal to distal as in a swallow).

   Patients or their parents are also asked to provide information on positioning (i.e. recumbent sleeping or standing) as body positioning is known to influence the number of reflux episodes. In older children [21] and healthy adults [22], more reflux episodes (acid and non-acid) are seen in supine position when comparing to recumbent position. Studies in (preterm) infants have shown that left lateral position and prone position reduce the number of liquid reflux episodes, albeit not reflux symptoms, when compared to right lateral position [23–25]. This has been attributed to more transient lower sphincter relaxations in right lateral position [26]. However, in infants, supine sleeping position is recommended to reduce the risk of sudden infant death syndrome (SIDS) [27].

5. Duration of Monitoring
   The duration of the pH-MII recording should be as close as possible to 24 h and at least 18 h, including a day and a night period [3, 19]. Studies in adults [28] and children [29, 30] have shown higher variabilities of reflux index with shorter studies (e.g. 4, 6, 12 h or day versus night). On the other hand, whether 24 h should be regarded as optimal duration for pH-MII monitoring has yet to be determined. One study in children showed good intra-individual correlation for

reflux index (Pearson correlation coefficient between 0.87 and 0.98) [31] and impedance results [56] when comparing 24-h results of 1 day to another, while other authors failed to replicate these results with both pH monitoring [32, 33] and impedance monitoring [34].

Analysis of Paediatric pH-MII Recordings

MII monitoring data can be read manually or analysed automatically using commercially available software. The additional information that MII provides has added new parameters to the classic pH monitoring parameters (being DeMeester composite score and Boix-Ochoa scoring systems the most used) (Table 7.1).

Interpreting pH-MII Results

There is still controversy on how GOR episodes should be defined (Table 7.1). Despite guidelines on the interpretation being available, many readers consider pattern recognition more important than adhering to strict criteria [3]. In an analysis study performed with experts from throughout the world, it was hard to reach consensus on several types of episodes that were considered difficult to analyse manually [35]. Conventionally, most analysts start the process with automatic analysis and then manually go through the tracing by confirming, adding and/or deleting reflux events [3]. However, using this approach there is still considerable diversity in performance and interpretation of pH-MII recordings between users with diverging results of inter- and intra-observer reproducibility [3, 36–38].

A specifically difficult issue regards the presence of pH drops below 4 without any impedance signal accompanying them [39]. It is still largely unclear what these 'pH-only' events represent. It is hypothesized that these events are related to altered oesophageal peristalsis, reflux oesophagitis, slow pH drift, insufficient bolus extension or volume to be MII detected, 'backwash' acid caused by the swallowing-related opening of the LOS or by reflux from acid pocket [40]. One study found that 'pH-only' events may reflect the presence of a hiatal hernia when patients have more episodes of reflux detected by the pH electrode than those detected by impedance [41]. Another study in premature infants found that those with bronchopulmonary dysplasia had more pH-only events when compared to infants without dysplasia, and these events were also more frequently related to symptoms [40]. Although it is still debated, our opinion is that these events should be included in the pH-MII analysis; considering that in some paediatric pH-MII tracings, these 'pH-only' episodes contribute to more than a quarter of reflux events and consequently to a significant part of the total oesophageal acid exposure [42, 43].

In general, 'pH reflux' does last (much) longer than 'impedance reflux', or in other words, acid exposure lasts longer than bolus exposure. This observation is likely to be related to a difference in clearance time between chemical and bolus clearance [44]. Therefore, if the diet does not include acid beverages, as in infants,

considering the total time with acid exposure (and not just bolus acid reflux classically detected by MII) may be important for possible correlation with oesophageal damage, hypersensitivity or symptomatic association.

The minimal decrease of impedance corresponding to a bolus reflux still needs to be studied, especially in infants. According to adult-based MII definition of GOR, the reflux, or 'drop in impedance', should reach two distal MII channels on the MII catheter that correspond to a distance at least 2.25 cm above the pH sensor, thus to a minimum of 4.25 cm above the LOS, if the pH sensor is positioned 2 cm from the LOS, to be detected as an 'impedance reflux'. This means nearly half of the oesophageal length in infants and ±30% in older children.

As a result of the issues outlined above, validation of automated analysis is hard. Full manual analysis is time-consuming requiring from 30 min to 4 h [45], depending directly on the number of reflux events present as well as on the level of experience of the analyst. In addition, manual analysis not necessarily leads to a study result that better reflects the truth, and outcome studies comparing manual and automated analysis are not available. Different studies have found large discrepancies between automated analysis and manual reading [46–48]. Nowadays, available software is tuned to high sensitivity and includes additional options to improve manual recognition of GOR but still needs improvement in terms of specificity.

pH-MII Parameters and Reference Values

The automated MII-pH analysis system provides the number, duration, percentage and content of all reflux episodes. One of the major issues of paediatric pH-MII is the lack of normal parameters for the different age groups. This is a direct result of the invasive nature of the test, making it ethically unacceptable to be performed in healthy infants and children. Several attempts were made to establish reference values that come as close to normal values. The normal values are depicted in Fig. 7.2 but should be used with caution.

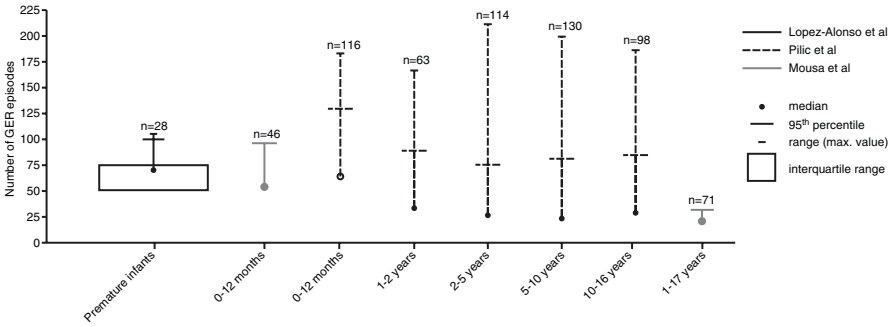


Fig. 7.2 Available reference values for number of GOR episodes per 24 h in children, according to age. Reproduced from: Singendonk M, et al. Reflux monitoring in children. 2016;28(10):1452–1459

One of these studies was conducted in preterm otherwise healthy infants, who were unable to feed orally [49]. Although helpful for the interpretation of pH-MII studies in young infants, the values obtained from this study have several drawbacks that limit their clinical application. First, all infants received tube feeding, which indicates that in fact they cannot be considered completely healthy as they were unable to tolerate full oral feeding. Second, it has been shown that a tube straddling the lower oesophageal sphincter affects the number of GOR episodes [50].

All other studies were performed in symptomatic children, using different inclusion criteria and different study protocols in different age and patient groups. The German Paediatric Impedance Group (G-PIG) published the largest series of 700 paediatric pH-MII tracings from children 3 weeks to 16 years of age presenting with symptoms of GOR disease. They defined a study to be abnormal if the following criteria were fulfilled: (1) symptom index (SI) ≥50% (also see under 'symptom association') or a high number of reflux episodes (arbitrarily defined as >70 episodes in 24 h in patients ages 1 year or older and >100 episodes in those younger than 1 year) [18]. The authors concluded pH-MII to be superior to pH monitoring alone because 45% of patients with abnormal GOR would not have been recognized by sole 24-h pH measurement. Additionally, Mousa et al. aimed to identify a normal range of non-acid GOR impedance values for infants and children referred for the evaluation of GOR, without pathological acid exposure based on pH results and no positive temporal associations of GOR with symptoms. For infants (age ≤12 months), they found a median non-acid GOR index of 2.2% (range 0.0–5.9%), while for children (age >12 months), they found a median non-acid GOR index of 1.1% (range 0.0–3.0%). Furthermore, in 46 infants they reported a median GOR frequency of 54 over 24 h (95th percentile of 93), while in 71 children, a GOR frequency of 21 (95th percentile of 71). This series of references values and their 95th percentile may be of clinical importance in the identification of patients who are at risk of developing complications associated with abnormal GOR [21]. Recently, Woodley et al. reported reference values for chemical clearance of acid GOR in children with cystic fibrosis and acid GOR in the physiologic range. P95 was 148.5 s per episode in infants and 114.4 s per episode in children [51]. However, as this study did not include children with acid GOR outside the physiologic range, these values cannot yet be used as 'cut-off' values.

Applications of pH-MII in Children

Currently, one of the main purposes of pH-MII in children is to associate reflux events with symptoms. Also, increasing evidence is appearing regarding the usefulness of pH-MII to predict the natural course of GORD and response to treatment. Table 7.2 outlines the indications for the performance of a pH-MII based on the most recently published clinical guidelines [52–54].

Table 7.2 Indications to perform a pH-MII

1. Evaluation of extra-oesophageal GOR symptoms or signs [52–54] • Respiratory symptoms ◦ Unexplained apnoeas/ALTE [47, 49] ◦ Reactive airways disease not responding to therapy [47, 49] ◦ Suspected recurrent aspiration pneumonia [49] • Other extra-oesophageal symptoms ◦ Frequent otitis media [54] ◦ Unexplained non-epileptic seizure-like events/Sandifer's syndrome [54] ◦ Unexplained crying or distressed behaviour [52] ◦ Dental enamel erosion associated with neurodisability [54] ◦ Unexplained laryngeal inflammation
2. Evaluation of therapy-resistant GORD [3]
3. Evaluation in the work-up prior to fundoplication [54]
4. (*Research purposes* [3]) • To evaluate diagnostic value of pH-MII for GORD • To evaluate effectiveness of treatments for GORD [69] • To evaluate prognostic factors for GORD

pH-MII pH-impedance monitoring, *GOR* gastro-oesophageal reflux, *GORD* GOR disease, *ALTE* apparent life-threatening event

Symptom Association

As pH-MII allows the detection of all types of GOR, it has the potential of diagnosing an association between GOR episodes and GOR symptoms. Current guidelines suggest using pH-MII instead of pH monitoring only for symptom association studies [52]. Three measures have been described to measure a temporal association of GOR symptoms and pH-MII-detected GOR events: symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP).

SI reflects the percentage of symptoms related to GOR episodes. The optimal threshold is estimated to be 50%, but a bimodal distribution of SI has been seen in adults [55]. The SSI reflects the percentage of GOR episodes associated with symptoms, and values of 10% or higher are considered positive. The SI does not take into account the total number of GOR episodes and can thus be false positive due to frequent reflux episodes that once in a while coincide with randomly occurring symptoms. On the other hand, the SSI does not take the total number of symptoms into account and thus causes false negative results when the total number of GOR events exceeds ten times the number of symptoms. Computational models have shown the SI overestimating the true presence of GOR-related symptoms [56].

The SAP is a parameter that statistically evaluates the probability of a given symptom to be related to a GOR episode. For its calculation, the pH-MII data is divided into 2-min segments. For each segment it is determined whether reflux happened or not and whether there was a symptom or not. In that way, a 2 × 2 contingency table is constructed (S^+R^+, S^+R^-, S^-R^+ and S^-R^-) and analysed with Fisher's exact test. SAP is calculated from $(1-p) \times 100\%$, and $\geq 95\%$ is considered positive.

The SAP is considered to be superior to the SI and SSI because it takes both the number of GOR symptoms and number of GOR episodes and will only increase when GOR symptom association is increased [57]. There are, however, no published criteria with respect to the minimum number of symptoms that should be recorded to consider a SAP calculation reliable, given that its statistical relevance improves with the number of symptoms occurring during the investigation. According to one study in infants, a minimum of five symptom episodes are suggested to support a positive SAP [56]. It should still be noted that these three measures remain association and not causality indexes.

Apart from the issues outlined above, several other limitations apply to the analysis of the relationship between GOR and GOR-associated symptoms. Studies have shown that symptom reported during a pH-MII measurement on itself is not reliable [58–60]. For example, using chronic cough as a model, between 50 and 90% of the actual episodes were not reported in adults and children, and the use of manometry-based cough detection leads to an increase of SAP+ patients of 66% [60]. This issue is particularly critical in young children, who may not be able to self-report symptoms given their age, as well as for the evaluation of symptoms that appear more often during sleeping.

Another issue regards the optimal timeframe to determine whether a given symptom is related to GOR. Current evidence shows that 2 min could be an adequate frame for cough but could well be different for other GOR symptoms [55, 61]. Additionally, symptom association scores will not be helpful for symptoms not occurring daily or caused by chronic GOR exposure, such as poor appetite, wheezing and bronchial hyperreactivity [61].

Paediatric Studies on Symptom Association

Multiple studies have assessed a possible temporal relationship between GOR events and GOR-associated symptoms. However, all studies present high heterogeneity in terms of population recruited, means of association and time intervals, hampering a direct comparison between studies. The symptom most commonly studied is apnoea in premature infants. Even while this symptom can be objectively registered, the association varies widely in the different studies (Table 7.3). This is not only due to the imperfect measures of association but also to largely varying inclusion criteria, different definitions of apnoea and low numbers of patients. Most studies fail to show a temporal link between apnoea and GOR, and when an association is found, apnoea more frequently precedes GOR and then follows GOR. Other symptoms commonly thought to be GOR related are predominantly studied with subjective measures (e.g. reported by parents). These studies show that non-acidic reflux is often detected and frequently related to positive symptom association in children with intractable respiratory symptoms [43] and recurrent respiratory infections [62]. Additionally, acid reflux has found to be related to GOR symptoms even more frequently than weakly acid reflux [63–65].

Table 7.3 Studies evaluating association between GOR and symptoms

Condition	Reference	Inclusion criteria	Window frame for symptoms	Age	N	Symptom	GOR-related symptoms			SI+	SSI+	SAP+
							AR	NAR	All			
Chronic cough	Rosen et al. [43]	Intractable respiratory symptoms	2 min	0.25–18 years	28	Cough			38%	33%	25%	
	Condino et al. [64]	Difficult to treat CC	5 min	0.4–5.6 years	24	Cough	17%	9%	26%	37%		
	Thilmany et al. [99]	CC of unclear aetiology	2 min	0.5–15 years	25	Desaturations	39%	2%	41%			
	Blondeau et al. [60]	CC of unclear aetiology	2 min	1–10.5 years	26	Cough	4%	6%	10%			38%
	Borrelli et al. [100]	CC of unclear aetiology	2 min	1–16 years	45	Cough	33%	17%	50%			38%
	Tolín Hernani et al. [101]	Asthma, CC or recurrent laryngitis	5 min	3–16 years	49	Cough	19%	13%	32%	28%	62%	
						Pain	12%	12%	24%	27%	63%	
	Ghezzi et al. [102]	CC	2 min	2.8–8.2 years	106	GOR-cough			48%[a]			
				(IQR)		Cough-GOR			2%			
	Rosen et al. [59]	CC and wheezing		1.1–16.7 years	112	Cough			33%	20%	90%	40%
	Pavic I et al. [103]	CC	2 min	0.3–18 years	150	Cough*	9%	60%	88%			

Apnoea/ALTE	Wenzl et al. [104]	Recurrent regurgitation or respiratory symptoms	30 s	0.1–0.3	22	Apnoea	7%	23%	30%			
	Mousa et al. [65]	ALTE	5 min		25	Apnoea	7%	8%	15%			8%
	Magistà et al. [105]	AOP	20 s	27–36 WAG	6	Apnoea	13%	29%	42%	17%	67%	
	Corvaglia et al. [106]	Preterm infants with recurrent apnoea	30 s	35 ± 2 WGA	54	GOR-apnoea			8%			
						Apnoea-GOR			4%			
	Nobile et al. [40]	Preterm infants with and without BPD	2 min	33–36 WAG	46	Any			25%			
						Apnoea + desaturations			11%			
Sleep disturbances	Machado et al. [107]	Infants derived for PSG + pH-MII	2 min	0.1–0.8 year	24	Arousal						29%
						Awakenings						38%
	Machado et al. [108]	Obese patients derived for PSG + pH-MII	5 min	10.8–16.4 years	13	Arousal						31%
						Awakenings						39%
						Desaturations						15%
						Cough						8%

(continued)

Table 7.3 (continued)

Condition	Reference	Inclusion criteria	Window frame for symptoms	Age	N	Symptom	GOR-related symptoms			SI+	SSI+	SAP+
							AR	NAR	All			
Other	Mattioli et al. [63]	Children derived for pH-MII	5 min	0.1–14 years	50	Any				22%		
	Loots et al. [57]	Children derived for pH-MII	2 min	0.2–9.8 years	50	Any				30%	48%	60%
	Salvatore et al. [109]	Children derived for pH-MII	2 min		155	Crying	20%	25%	45%	57%		26%
						Vomiting	35%	51%	86%	96%		42%
						Cough	25%	27%	52%	60%		30%
						Pain				64%		18%
	Lüthold et al. [110]	Infants derived for pH-MII	5 min	0.04–0.9 years	23	Irritability			39%	35%	22%	13%
						Cough			47%	57%	9%	4%
	Greifer et al. [111]	Extra-oesophageal symptoms	5 min	0.3–17 years	63	Any				15%		

AR acid reflux, *NAR* non-acid reflux, *CC* chronic cough, *ALTE* apparent life-threatening event, *AOP* apnoea of prematurity, *WAG* weeks of gestational age, *PSG* polysomnography

[a]Reported as means by the author

pH-MII as Prognostic Measure and as Outcome Measure for Intervention Studies

Evidence is still controversial as to which reflux parameters can be helpful in predicting the natural outcome of GORD. In adults with GORD without treatment, acid exposure time and SAP were the pH-MII parameters that predicted symptomatic response to proton pump inhibitors on follow-up [66]. Literature on follow-up data is currently limited in children. According to a study in infants, the impedance bolus exposure index and the proximal weakly acidic reflux frequency have shown a high prognostic value for persistence of symptoms [67]. Another study in infants found a high reflux index to be associated with persistence of symptoms at 3 and 12 months [68].

In their 'guideline on the evaluation of drugs for treatment of gastro-oesophageal reflux' [69], the European Medicines Agency states that pH-MII should be used in clinical trials, and it has been used as an objective outcome measure in several intervention studies since then [70].

Paediatric guidelines suggest the use of thickeners as a non-pharmacological management in formula-fed infants with GOR and marked distress [54]. Results on the effect of feed thickeners on pH-MII-detected GOR are however conflicting [71]. One crossover study in full-term infants fed with formula with and without bean gum found a small, albeit significant, reduction in the number of weakly acid GOR episodes and the proximal GOR episodes [71, 72]. However, another crossover study in preterm infants fed with human milk with and without precooked starch could not identify a difference in the number of acidic and buffered reflux episodes [72]. The same authors reproduced these results in a small pilot cohort study using a new preterm formula thickened with amylopectin [73].

Recently, the first randomized controlled trials evaluating the effect of PPIs on GOR based on pH-MII data in infants and children have been published. Consecutive studies from the same group have shown that omeprazole and esomeprazole do not decrease the total number of reflux episodes but merely change acid GOR events into non-acid events [74, 75]. In one study, a reduction of acid episodes after the use of PPIs was found to result in the occurrence of fewer potentially GOR-related symptoms, such as crying [76].

In patients with refractory GORD who underwent fundoplication, pH-MII has demonstrated an important decrease of acid [77] and non-acid reflux events [78, 79]. Studies aiming to determine predictors of fundoplication outcome show conflicting results; some authors found no predictive value of pH-MII [80, 81], while others have found a more pronounced GOR reduction in children with a higher number of GOR episodes on preoperative pH-MII [82].

Future Applications of pH-MII

Several studies have investigated the possible correlation between reflux oesophagitis proven by endoscopy and reflux patterns on pH-MII monitoring, with diverging results. Different endoscopic grading systems [83, 84] applied in different age

groups in combination with large heterogeneity between study in- and exclusion criteria may explain the inconsistency between study results. Most studies have found that traditional parameters assessed by pH-MII do not correlate with oesophagitis [85–88]. However, recent paediatric studies have found that the DeMeester score, occurrence of acid reflux for more than 5 min, duration of longest acid reflux ≥17 min [89] and total number of reflux and its subtypes (acid and non-acid events) [90] were related to erosive oesophagitis.

Baseline impedance is considered a marker for mucosal integrity and was found to be lower in adult patients with oesophagitis when compared with patients with non-erosive reflux disease [91]. In a paediatric study, baseline impedance was found to correlate with the reflux index [85]. Other studies in children with GORD found significantly lower baseline impedance levels in the children that had erosive GORD [92–94]. Additionally, low baseline impedance levels have shown to increase after PPI therapy, as well as after fundoplication [77, 78, 95]. These findings support the idea of this parameter as being a marker of damage of the oesophageal mucosa [57]. However, both young age [96] and oesophageal atresia [97] may result in a low impedance baseline. The value of baseline impedance in clinical practice has thus to be further investigated.

pH-MII and Manometry

The addition of impedance to manometry has elucidated some aspects of oesophageal motility, as it reveals information on the relationship between oesophageal pressures and oesophageal bolus flow. This test may therefore be particularly useful in patients with ineffective oesophageal motility, dysphagia and also chronic belching, rumination and aerophagia [5]. One report described the application of a novel technique integrating the analysis of impedance and manometry to determine characteristics of oesophageal pressure and flow in children with dysphagia [98], potentially enhancing the characterization of primary oesophageal motor disorders in this age group.

Conclusion

The addition of impedance to classic pH monitoring has resulted in better understanding of the physiopathology of GORD, by allowing the assessment of both acid and non-acid GOR events. Given the lack of normative data in paediatrics as a result of ethical considerations, pH-MII cannot be considered a true gold standard for GORD. Challenges that the clinician has to face regarding the interpretation of pH-MII in children include its high inter- and intra-observer variability and the uncertainty of the impact of the relationship between symptoms and clinical outcome. Costs of pH-MII catheters also limit its widespread use. Future studies to determine whether pH-MII will be able to provide data to determine disease severity, prognosis and response to therapy in paediatric patients are needed. Considering its outlined potential advantages, especially in subsets of paediatric patients with specific symptoms or treatment-resistant GORD, it is likely a matter of time before pH-MII will become part of standard clinical care for paediatric GORD.

References

1. Bernstein LM, Fruin RD, Pacini R. Differentiation of esophageal pain from angina pectoris: role of the esophageal acid perfusion test. Medicine (Baltimore). 1962;41:143–62.
2. Francavilla R, Magista AM, Bucci N, Villirillo A, Boscarelli G, Mappa L, et al. Comparison of esophageal pH and multichannel intraluminal impedance testing in pediatric patients with suspected gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2010;50(2):154–60.
3. Wenzl TG, Benninga MA, Loots CM, Salvatore S, Vandenplas Y, Group EE-PW. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. J Pediatr Gastroenterol Nutr. 2012;55(2):230–4.
4. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut. 2004;53(7):1024–31.
5. Asge Technology Committee, Wang A, Pleskow DK, Banerjee S, Barth BA, Bhat YM, et al. Esophageal function testing. Gastrointest Endosc. 2012;76(2):231–43.
6. Ummarino D, Salvatore S, Hauser B, Staiano A, Vandenplas Y. Esophageal impedance baseline according to different time intervals. Eur J Med Res. 2012;17(1):18.
7. Silny J, Knigge KP, Fass J, Rau G, Matern S, Schumpelick V. Verification of the intraluminal multiple electrical impedance measurement for the recording of gastrointestinal motility. Neurogastroenterol Motil. 1993;5(2):107–22.
8. Mousa HM, Rosen R, Woodley FW, Orsi M, Armas D, Faure C, et al. Esophageal impedance monitoring for gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2011;52(2):129–39.
9. Hemmink GJ, Weusten BL, Oors J, Bredenoord AJ, Timmer R, Smout AJ. Ambulatory oesophageal pH monitoring: a comparison between antimony, ISFET, and glass pH electrodes. Eur J Gastroenterol Hepatol. 2010;22(5):572–7.
10. Vandenplas Y, Badriul H, Verghote M, Hauser B, Kaufman L. Glass and antimony electrodes for oesophageal pH monitoring in distressed infants: how different are they? Eur J Gastroenterol Hepatol. 2004;16(12):1325–30.
11. Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology. 1996;110(6):1982–96.
12. Hirano I, Richter JE. Practice Parameters Committee of the American College of Gastroenterology. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol. 2007;102(3):668–85.
13. Moreau B, Kambites S, Levesque D. Esophageal length: esophageal manometry remains superior to mathematical equations. J Pediatr Gastroenterol Nutr. 2013;57(2):236–9.
14. Badriul H, Vandenplas Y. Gastro-oesophageal reflux in infancy. J Gastroenterol Hepatol. 1999;14(1):13–9.
15. Singendonk MM, Kritas S, Cock C, Ferris L, McCall L, Rommel N, et al. Applying the Chicago Classification criteria of esophageal motility to a pediatric cohort: effects of patient age and size. Neurogastroenterol Motil. 2014;26(9):1333–41.
16. Staiano A, Clouse RE. Value of subject height in predicting lower esophageal sphincter location. Am J Dis Child. 1991;145(12):1424–7.
17. Mutalib M, Sintusek P, Punpanich D, Thapar N, Lindley K. A new method to estimate catheter length for esophageal multichannel intraluminal impedance monitoring in children. Neurogastroenterol Motil. 2015;27(5):728–33.
18. Pilic D, Frohlich T, Noh F, Pappas A, Schmidt-Choudhury A, Kohler H, et al. Detection of gastroesophageal reflux in children using combined multichannel intraluminal impedance and pH measurement: data from the German Pediatric Impedance Group. J Pediatr. 2011;158(4):650–4.e1.
19. Vandenplas Y, Belli D, Boige N, Bouquet J, Cadranel S, Cezard JP, Chapoy P, Cucchiara S, Dupont C, Gottrand F, Heymans HSA, Kneepkens CMF, Katsiayannikis L, Milla P, Navarro J, Newell SJ, Sandhu BK, Tolboom J. A standardized protocol for the methodology of esophageal pH monitoring and interpretation of the data for the diagnosis of gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1992;14(4):467–71.

20. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–28. quiz 29
21. Mousa H, Machado R, Orsi M, Chao CS, Alhajj T, Alhajj M, et al. Combined multichannel intraluminal impedance-pH (MII-pH): multicenter report of normal values from 117 children. Curr Gastroenterol Rep. 2014;16(8):400.
22. Zerbib F, des Varannes SB, Roman S, Pouderoux P, Artigue F, Chaput U, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther. 2005;22(10):1011–21.
23. Corvaglia L, Rotatori R, Ferlini M, Aceti A, Ancora G, Faldella G. The effect of body positioning on gastroesophageal reflux in premature infants: evaluation by combined impedance and pH monitoring. J Pediatr. 2007;151(6):591–6.e1.
24. van Wijk MP, Benninga MA, Dent J, Lontis R, Goodchild L, McCall LM, et al. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr. 2007;151(6):585–90.e2.
25. Loots C, Kritas S, van Wijk M, McCall L, Peeters L, Lewindon P, et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. J Pediatr Gastroenterol Nutr. 2014;59(2):237–43.
26. Omari TI, Rommel N, Staunton E, Lontis R, Goodchild L, Haslam RR, et al. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr. 2004;145(2):194–200.
27. Moon RY, Fu L. Sudden infant death syndrome: an update. Pediatr Rev. 2012;33(7):314–20.
28. Johnsson F, Joelsson B. Reproducibility of ambulatory oesophageal pH monitoring. Gut. 1988;29(7):886–9.
29. Vandenplas Y, Casteels A, Naert M, Derde MP, Blecker U. Abbreviated oesophageal pH monitoring in infants. Eur J Pediatr. 1994;153(2):80–3.
30. Friesen CA, Hodge C, Roberts CC. Accuracy and reproducibility of 12-h esophageal pH monitoring. J Pediatr Gastroenterol Nutr. 1991;12(2):166–8.
31. Vandenplas Y, Helven R, Goyvaerts H, Sacre L. Reproducibility of continuous 24 hour oesophageal pH monitoring in infants and children. Gut. 1990;31(4):374–7.
32. Hampton FJ, MacFadyen UM, Simpson H. Reproducibility of 24 hour oesophageal pH studies in infants. Arch Dis Child. 1990;65(11):1249–54.
33. Mahajan L, Wyllie R, Oliva L, Balsells F, Steffen R, Kay M. Reproducibility of 24-hour intraesophageal pH monitoring in pediatric patients. Pediatrics. 1998;101(2):260–3.
34. Dalby K, Nielsen RG, Markoew S, Kruse-Andersen S, Husby S. Reproducibility of 24-hour combined multiple intraluminal impedance (MII) and pH measurements in infants and children. Evaluation of a diagnostic procedure for gastroesophageal reflux disease. Dig Dis Sci. 2007;52(9):2159–65.
35. Smits MJ, Loots CM, van Wijk MP, Bredenoord AJ, Benninga MA, Smout AJ. An expert panel-based study on recognition of gastro-esophageal reflux in difficult esophageal pH-impedance tracings. Neurogastroenterol Motil. 2015;27(5):637–45.
36. Loots CM, van Wijk MP, Blondeau K, Dalby K, Peeters L, Rosen R, et al. Interobserver and intraobserver variability in pH-impedance analysis between 10 experts and automated analysis. J Pediatr. 2012;160(3):441–6.e1.
37. Ravi K, DeVault K, Murray J, Bouras EP, Francis D. Inter-observer agreement for multichannel intraluminal impedance–pH testing. Dis Esophagus. 2010;23(7):540–4.
38. Pilic D, Hofs C, Weitmann S, Noh F, Frohlich T, Skopnik H, et al. Inter- and intraobserver agreement in 24-hour combined multiple intraluminal impedance and pH measurement in children. J Pediatr Gastroenterol Nutr. 2011;53(3):255–9.
39. Wenzl TG, Moroder C, Trachterna M, Thomson M, Silny J, Heimann G, et al. Esophageal pH monitoring and impedance measurement: a comparison of two diagnostic tests for gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2002;34(5):519–23.
40. Nobile S, Noviello C, Cobellis G, Carnielli VP. Are Infants with bronchopulmonary dysplasia prone to gastroesophageal reflux? A prospective observational study with esophageal pH-impedance monitoring. J Pediatr. 2015;167(2):279–85.e1.

41. Wu JF, Hsu WC, Tseng PH, Wang HP, Hsu HY, Chang MH, et al. Combined multichannel intraluminal impedance and pH monitoring assists the diagnosis of sliding hiatal hernia in children with gastroesophageal reflux disease. J Gastroenterol. 2013;48(11):1242–8.
42. Rosen R, Lord C, Nurko S. The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. Clin Gastroenterol Hepatol. 2006;4(2):167–72.
43. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol. 2004;99(12): 2452–8.
44. Vikneswaran N, Murray JA. Discounting the duration of bolus exposure in impedance testing underestimates acid reflux. BMC Gastroenterol. 2016;16(1):60.
45. van Wijk MP, Benninga MA, Omari TI. Role of the multichannel intraluminal impedance technique in infants and children. J Pediatr Gastroenterol Nutr. 2009;48(1):2–12.
46. Roman S, des Varannes SB, Pouderoux P, Chaput U, Mion F, Galmiche J, et al. Ambulatory 24-h oesophageal impedance–pH recordings: reliability of automatic analysis for gastro-oesophageal reflux assessment. Neurogastroenterol Motil. 2006;18(11):978–86.
47. Hemmink GJ, Bredenoord AJ, Aanen MC, Weusten BL, Timmer R, Smout AJ. Computer analysis of 24-h esophageal impedance signals. Scand J Gastroenterol. 2011;46(3):271–6.
48. Salvatore S, Hauser B, Luini C, Arrigo S, Salvatoni A, Vandenplas Y. MII-pH: what we can get from the autoscan and manual readings? J Pediatr Gastroenterol Nutr. 2006;42(5):E50.
49. Lopez-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macias M, Silny J, et al. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. Pediatrics. 2006;118(2):e299–308.
50. Peter CS, Wiechers C, Bohnhorst B, Silny J, Poets CF. Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: a multiple intraluminal impedance study. J Pediatr. 2002;141(2):277–9.
51. Woodley FW, Machado R, Di Lorenzo C, Mousa H. Chemical clearance in infants and children with Acid reflux in the physiologic range. J Pediatr Gastroenterol Nutr. 2015;60(6):783–6.
52. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–597.
53. Lightdale JR, Gremse DA. Section on Gastroenterology H, Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013;131(5):e1684–95.
54. Davies I, Burman-Roy S, Murphy MS, Guideline Development G. Gastro-oesophageal reflux disease in children: NICE guidance. BMJ. 2015;350:g7703.
55. Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut. 2005;54(12):1810–7.
56. Barriga-Rivera A, Elena M, Moya M, Lopez-Alonso M. Monte Carlo method for the evaluation of symptom association. Dis Esophagus. 2014;27(6):518–23.
57. Loots CM, Benninga MA, Davidson GP, Omari TI. Addition of pH-impedance monitoring to standard pH monitoring increases the yield of symptom association analysis in infants and children with gastroesophageal reflux. J Pediatr. 2009;154(2):248–52.
58. Kavitt RT, Higginbotham T, Slaughter JC, Patel D, Yuksel ES, Lominadze Z, et al. Symptom reports are not reliable during ambulatory reflux monitoring. Am J Gastroenterol. 2012;107(12):1826–32.
59. Rosen R, Amirault J, Heinz N, Litman H, Khatwa U. The sensitivity of acoustic cough recording relative to intraesophageal pressure recording and patient report during reflux testing. Neurogastroenterol Motil. 2014;26(11):1635–41.

60. Blondeau K, Mertens V, Dupont L, Pauwels A, Farre R, Malfroot A, et al. The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings. Pediatr Pulmonol. 2011;46(3):286–94.
61. Omari TI, Schwarzer A, van Wijk MP, Benninga MA, McCall L, Kritas S, et al. Optimisation of the reflux-symptom association statistics for use in infants being investigated by 24-hour pH impedance. J Pediatr Gastroenterol Nutr. 2011;52(4):408–13.
62. Ghezzi M, Silvestri M, Guida E, Pistorio A, Sacco O, Mattioli G, et al. Acid and weakly acid gastroesophageal refluxes and type of respiratory symptoms in children. Respir Med. 2011;105(7):972–8.
63. Mattioli G, Pini-Prato A, Gentilino V, Caponcelli E, Avanzini S, Parodi S, et al. Esophageal impedance/pH monitoring in pediatric patients: preliminary experience with 50 cases. Dig Dis Sci. 2006;51(12):2341–7.
64. Condino AA, Sondheimer J, Pan Z, Gralla J, Perry D, O'Connor JA. Evaluation of gastroesophageal reflux in pediatric patients with asthma using impedance-pH monitoring. J Pediatr. 2006;149(2):216–9.
65. Mousa H, Woodley FW, Metheney M, Hayes J. Testing the association between gastroesophageal reflux and apnea in infants. J Pediatr Gastroenterol Nutr. 2005;41(2):169–77.
66. Patel A, Sayuk GS, Gyawali CP. Acid-based parameters on pH-impedance testing predict symptom improvement with medical management better than impedance parameters. Am J Gastroenterol. 2014;109(6):836–44.
67. Cresi F, Locatelli E, Marinaccio C, Grasso G, Coscia A, Bertino E. Prognostic values of multichannel intraluminal impedance and pH monitoring in newborns with symptoms of gastroesophageal reflux disease. J Pediatr. 2013;162(4):770–5.
68. van der Pol RJ, van den Ouweland M, Loots CM, Vandenplas Y, Benninga MA, van Wijk MP. Follow-up after pH-metry and pH impedance in pediatric gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2015;60(2):224–9.
69. Committee for Medicinal Products for Human Use. Guideline on the evaluation of drugs for the treatment of Gastro-oesophageal reflux disease. 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/03/WC500103307.pdf.
70. Grabowski M, Seys S, Decraene A, Kasran A, Dilissen E, Barg W, et al. Airway inflammation in patients with chronic non-asthmatic cough. Thorax. 2013;68(2):125–30.
71. Wenzl TG, Schneider S, Scheele F, Silny J, Heimann G, Skopnik H. Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance. Pediatrics. 2003;111(4 Pt 1):e355–9.
72. Corvaglia L, Ferlini M, Rotatori R, Paoletti V, Alessandroni R, Cocchi G, et al. Starch thickening of human milk is ineffective in reducing the gastroesophageal reflux in preterm infants: a crossover study using intraluminal impedance. J Pediatr. 2006;148(2):265–8.
73. Corvaglia L, Spizzichino M, Aceti A, Legnani E, Mariani E, Martini S, et al. A thickened formula does not reduce apneas related to gastroesophageal reflux in preterm infants. Neonatology. 2013;103(2):98–102.
74. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. J Pediatr. 2013;163(3):692–8 e1-2.
75. Turk H, Hauser B, Brecelj J, Vandenplas Y, Orel R. Effect of proton pump inhibition on acid, weakly acid and weakly alkaline gastro-esophageal reflux in children. World J Pediatr. 2013;9(1):36–41.
76. Castellani C, Huber-Zeyringer A, Bachmaier G, Saxena AK, Hollwarth ME. Proton pump inhibitors for reflux therapy in infants: effectiveness determined by impedance pH monitoring. Pediatr Surg Int. 2014;30(4):381–5.
77. Loots CM, Wijnakker R, van Wijk MP, Davidson G, Benninga MA, Omari TI. Esophageal impedance baselines in infants before and after placebo and proton pump inhibitor therapy. Neurogastroenterol Motil. 2012;24(8):758–e352.
78. Fukahori S, Yagi M, Ishii S, Asagiri K, Saikusa N, Hashizume N, et al. Laparoscopic Nissen fundoplication mainly reduces the volume of acid reflux and potentially improves mucosal

integrity up to the middle esophagus in neurologically impaired children detected by esophageal combined pH-multichannel intraluminal impedance measurements. J Pediatr Surg. 2016;51(8):1283–7.
79. Tanaka A, Shimono R, Kubo H, Fujii T, Miyatake N. Evaluation of antireflux surgery using multichannel intraluminal impedance-pH measurement in neurologically impaired patients. Pediatr Surg Int. 2015;31(10):911–6.
80. Rosen R, Levine P, Lewis J, Mitchell P, Nurko S. Reflux events detected by pH-MII do not determine fundoplication outcome. J Pediatr Gastroenterol Nutr. 2010;50(3):251–5.
81. Fike FB, Pettiford JN, St Peter SD, Cocjin J, Laituri CA, Ostlie DJ. Utility of pH/multichannel intraluminal impedance probe in identifying operative patients in infants with gastroesophageal reflux disease. J Laparoendosc Adv Surg Tech A. 2012;22(5):518–20.
82. Mauritz FA, Conchillo JM, van Heurn LW, Siersema PD, Sloots CE, Houwen RH, et al. Effects and efficacy of laparoscopic fundoplication in children with GERD: a prospective, multicenter study. Surg Endosc. 2016;31(3):1101–10.
83. Tutar E, Kutluk G, Bayrak NA, Çelıkel C, Pehlıvanoğlu E, Ertem D. What is the diagnostic utility of endoscopic scoring systems in children? Turkish J Gastroenterol Off J Turkish Soc Gastroenterol. 2012;24(1):22–9.
84. Genta R, Spechler S, Kielhorn A. The Los Angeles and Savary–Miller systems for grading esophagitis: utilization and correlation with histology. Dis Esophagus. 2011;24(1):10–7.
85. van der Pol RJ, Loots CM, Peeters L, Vandenplas Y, Hauser B, Devreker T, et al. Outcomes of endoscopy and novel pH-impedance parameters in children: is there a correlation? J Pediatr Gastroenterol Nutr. 2013;56(2):196–200.
86. Pilic D, Hankel S, Koerner-Rettberg C, Hamelmann E, Schmidt-Choudhury A. The role of baseline impedance as a marker of mucosal integrity in children with gastro esophageal reflux disease. Scand J Gastroenterol. 2013;48(7):785–93.
87. Salvatore S, Hauser B, Devreker T, Arrigo S, Marino P, Citro C, et al. Esophageal impedance and esophagitis in children: any correlation? J Pediatr Gastroenterol Nutr. 2009;49(5):566–70.
88. Dalby K, Nielsen RG, Kruse-Andersen S, Fenger C, Durup J, Husby S. Gastroesophageal reflux disease and eosinophilic esophagitis in infants and children. A study of esophageal pH, multiple intraluminal impedance and endoscopic ultrasound. Scand J Gastroenterol. 2010;45(9):1029–35.
89. Liu YW, Wu JF, Chen HL, Hsu HY, Chang MH, Hsu WC, et al. The correlation between endoscopic reflux esophagitis and combined multichannel intraluminal impedance-pH monitoring in children. Pediatr Neonatol. 2015;57(5):385–9.
90. Hojsak I, Ivkovic L, Trbojevic T, Pavic I, Jadresin O, Misak Z, et al. The role of combined 24-h multichannel intraluminal impedance-pH monitoring in the evaluation of children with gastrointestinal symptoms suggesting gastro-esophageal reflux disease. Neurogastroenterol Motil. 2016;28(10):1488–93.
91. Farre R, Blondeau K, Clement D, Vicario M, Cardozo L, Vieth M, et al. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. Gut. 2011;60(7):885–92.
92. Borrelli O, Salvatore S, Mancini V, Ribolsi M, Gentile M, Bizzarri B, et al. Relationship between baseline impedance levels and esophageal mucosal integrity in children with erosive and non-erosive reflux disease. Neurogastroenterol Motil. 2012;24(9):828–e394.
93. Salvatore S, Salvatoni A, Ummarino D, Ghanma A, Van der Pol R, Rongen A, et al. Low mean impedance in 24-hour tracings and esophagitis in children: a strong connection. Dis Esophagus. 2016;29(1):10–4.
94. Salvatore S, Salvatoni A, Van Steen K, Ummarino D, Hauser B, Vandenplas Y. Behind the (impedance) baseline in children. Dis Esophagus. 2014;27(8):726–31.
95. Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJ, Loots CM, Smout AJ. Esophageal acid exposure decreases intraluminal baseline impedance levels. Am J Gastroenterol. 2011;106(12):2093–7.
96. Salvatore S, Salvatoni A, Van Berkel M, Van Steen K, Unmarino D, Ghanma A, et al. Esophageal impedance baseline is age dependent. J Pediatr Gastroenterol Nutr. 2013;57(4):506–13.

97. Tambucci R, Thapar N, Saliakellis E, Pescarin M, Quitadamo P, Cristofori F, et al. Clinical relevance of esophageal baseline impedance measurement: just an innocent bystander. J Pediatr Gastroenterol Nutr. 2015;60(6):776–82.
98. Singendonk MM, Kritas S, Cock C, Ferris LF, McCall L, Rommel N, et al. Pressure-flow characteristics of normal and disordered esophageal motor patterns. J Pediatr. 2015;166(3): 690–6.e1.
99. Thilmany C, Beck-Ripp J, Griese M. Acid and non-acid gastro-esophageal refluxes in children with chronic pulmonary diseases. Respir Med. 2007;101(5):969–76.
100. Borrelli O, Marabotto C, Mancini V, Aloi M, Macri F, Falconieri P, et al. Role of gastro-esophageal reflux in children with unexplained chronic cough. J Pediatr Gastroenterol Nutr. 2011;53(3):287–92.
101. Tolin Hernani M, Crespo Medina M, Luengo Herrero V, Martinez Lopez C, Salcedo Posadas A, Alvarez Calatayud G, et al. Comparison between conventional ph measurement and multichannel intraluminal esophageal impedance in children with respiratory disorders. An Pediatr (Barc.). 2012;77(2):103–10.
102. Ghezzi M, Guida E, Ullmann N, Sacco O, Mattioli G, Jasonni V, et al. Weakly acidic gastroesophageal refluxes are frequently triggers in young children with chronic cough. Pediatr Pulmonol. 2013;48(3):295–302.
103. Pavic I, Cepin-Bogovic J, Hojsak I. The relationship between gastroesophageal reflux and chronic unexplained cough in children. Clin Pediatr (Philadelphia). 2016;55(7):639–44.
104. Wenzl TGSJ, Schenke S, Peschgens T, Heimann G, Skopnik H. Gastroesophageal reflux and respiratory phenomena in infants: status of the intraluminal impedance technique. J Pediatr Gastroenterol Nutr. 1999;28(4):423–8.
105. Magista AM, Indrio F, Baldassarre M, Bucci N, Menolascina A, Mautone A, et al. Multichannel intraluminal impedance to detect relationship between gastroesophageal reflux and apnoea of prematurity. Dig Liver Dis. 2007;39(3):216–21.
106. Corvaglia L, Zama D, Spizzichino M, Aceti A, Mariani E, Capretti MG, et al. The frequency of apneas in very preterm infants is increased after non-acid gastro-esophageal reflux. Neurogastroenterol Motil. 2011;23(4):303–e152.
107. Machado R, Woodley FW, Skaggs B, Di Lorenzo C, Splaingard M, Mousa H. Gastroesophageal reflux causing sleep interruptions in infants. J Pediatr Gastroenterol Nutr. 2013;56(4):431–5.
108. Machado RS, Woodley FW, Skaggs B, Di Lorenzo C, Eneli I, Splaingard M, et al. Gastroesophageal reflux affects sleep quality in snoring obese children. Pediatr Gastroenterol Hepatol Nutr. 2016;19(1):12–9.
109. Salvatore S, Arrigo S, Luini C, Vandenplas Y. Esophageal impedance in children: symptom-based results. J Pediatr. 2010;157(6):949–54 e1-2.
110. Lüthold SC. Disagreement between symptom-reflux association analysis parameters in pediatric gastroesophageal reflux disease investigation. World J Gastroenterol. 2010;16(19):2401.
111. Greifer M, Ng K, Levine J. Impedance and extraesophageal manifestations of reflux in pediatrics. Laryngoscope. 2012;122(6):1397–400.

Gastroesophageal Reflux (GER) in the Preterm Baby

8

Christophe Dupont

Abstract

Gastroesophageal reflux (GER) is very common among preterm infants, but its real frequency is not well established. GER may be obvious, manifesting with regurgitations or emesis or more difficult to detect when associated with general symptoms such as apnea, bradycardia, pallor, oxygen desaturation, severe malaise, feeding difficulties with weight loss or poor growth (failure to thrive), crying, hematemesis, and melena. The origin probably resides in motor problems in some and in cow's milk allergy in others. Diagnosis is difficult to make, in the absence of reference values. Impedancemetry coupled to a pH probe is interesting since reflux is frequently nonacid. The treatment should always be conservative and stepwise. None of the drugs used are licensed in this age range and some have severe adverse effect.

Keywords

Preterm • Gastroesophageal reflux • Apnea • pH meter • Cow's milk allergy • Thickener • Proton pump inhibitor • Extensively hydrolyzed formulas • Necrotizing enterocolitis

Gastroesophageal reflux (GER) is very common among preterm infants, due to several physiological and pathophysiological mechanisms. However, its real frequency in preterms and very low birth weight (VLBW) infants is not well established: a study estimated a 22% incidence in babies born before 34 weeks of gestation [1]. GER may be obvious, manifesting with regurgitations or emesis, when the gastric

C. Dupont
Necker Hospital, Paris, France
e-mail: christophe.dupont@aphp.fr

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_8

content overwhelms the reservoir capacity of the esophagus. More difficult in the preterm, the responsibility of GER is suspected but always difficult to prove in the genesis of apnea, bradycardia, pallor, cyanosis with or without oxygen desaturation, severe malaise, feeding difficulties with weight loss or poor growth (failure to thrive), crying, hematemesis, melena, and, finally, sudden infant deaths (SIDs). Importantly, in a preterm infant, recurrent vomiting may herald underlying anatomic, metabolic, infectious, or central nervous disorder, but the review of these underlying conditions is not the scope of this chapter.

The Particular Conditions of Preterm Feeding: Progressive Increment of Oral Feeding in Premature Infants

GER in preterms cannot be considered separately from issues regarding feeding and the need to provide them with considerable amounts of food. Premature infants of gestational age (GA) >34 weeks are usually able to coordinate sucking, swallowing, and breathing and so to establish breast- or bottle-feeding. In less mature infants, oral feeding may be neither possible nor safe, because of neurological immaturity or respiratory compromise. These infants must be given continuous infusion or an intermittent bolus of milk through a fine feeding catheter passed via the nose or the mouth to the stomach [2]. In older babies, around 34 weeks of GA, the infant begins to suckle, and the bottle progressively replaces the tube feeding. It is thus clear that the volume delivered at each feeding, the number of feedings, and the speed of each feeding may largely impact the occurrence of GER: a modification of the mode of feeding must always be considered as a first move in the presence of GER in the preterm.

Several Cochrane reviews [3–6] confirm that the introduction of enteral feeding for very preterm infants, i.e., less than 32 weeks of GA or VLBW (<1500 g) infants, is often delayed due to the bad clinical tolerance of early enteral introduction and to the potential risk of developing necrotizing enterocolitis (NEC). However, the available trial data suggest that introducing progressive enteral feeding before 4 days after birth and advancing the rate of feed quantities at more than 24 ml/kg/day does not increase the risk of NEC in very preterm and VLBW infants [3–6]. In contrast, prolonged enteral fasting may diminish the functional adaptation of the immature GI tract and extend the need for parenteral nutrition with its attendant infectious and metabolic risks [6]. Also, delayed introduction or slow advancement of enteral feeding results in several days of delay in the time taken to regain birth weight and establish full enteral feeds [6]. Trophic feeding, giving preterm infants very small quantities of adapted preterm milk formulas to promote intestinal maturation, may enhance feeding tolerance and decrease the time taken to reach full enteral feeding independently of parenteral nutrition [3–6]. It is well agreed that oral feeding should be initiated slowly first by the help of nasogastric tube, and then progressively followed by oral feeding,

the way feeding in started in preterm infants and progressively increased varies widely. The use of dilute formula in preterms or VLBW infants might lead to an important reduction in the time taken for those infants to achieve an adequate daily energy intake [7]. Uncertainty also exists about the risk-benefit balance of different enteral feeding strategies in human milk-fed versus formula-fed very preterm or VLBW infants as the trials and reviews did not contain sufficient data for subgroup analyses [6].

Feeding tolerance is monitored with the help of the orogastric feeding tube. Before any feeding, the gastric residuals are measured following aspiration from the stomach. The volume of feeding extracted from the preterm infant's stomach, the gastric residual volume, indicates the amount of undigested volume before administering the next feeding. The gastric residual volume is largely considered a clinical manifestation of feeding intolerance [8, 9], with a mandatory restriction of the next feeding if it is greater than 50% of prior feed volume.

The Causes of GER in Preterm Babies

Primary GER

Whatever the difficulties and controversies relating to oral feeding of preterm babies, the mandatory large quantities of milk infused or swallowed everyday may overwhelm the ability of the stomach to empty its content, hence a constant monitoring of gastric residuals. GER in preterms thus has always to be discussed in relation with the frequency of the feeds, the volume delivered, and the duration of each feeding period.

It is likely that in infants, such as in adults, reflux occurs when the lower esophageal sphincter (LES) relaxes. An infant, especially a premature baby, is lying supine most of the time, and the gastroesophageal sphincter is underwater: transient lower esophageal sphincter relaxations (TLESRs) result in the esophagus being inundated by the gastric content. At full regimen, the feeding volume of a preterm is considerable compared to adult feeding, explaining why GER may be considered "normality."

With a micromanometric transducer device, a pH catheter, and a feeding tube, Omari et al. [10] analyzed 36 preterm infants, of whom 14 had symptomatic GER, i.e., GER disease (GERD). In both symptomatic and asymptomatic infants, more than 90% of reflux episodes were associated with TLESR. A higher proportion of acid GER (16.5% vs. 5.9%) was seen in symptomatic infants. Thus, despite a similar level of TLESR, the likelihood for liquid and/or acid to reflux was higher during TLESR in infants with GERD. Interestingly, triggers were gastric distension (e.g., feeding) and abdomino-thoracic straining (e.g., during motion), whereas low-volume feeds and shorter feeding intervals reduced acid GER. This further supports the role of feeding volume in the genesis of GER. Also the tube passing through the lower esophageal sphincter might play a role. Using the multiple intraluminal

impedance technique, the frequency of GER almost doubled when the tube ended inside the stomach instead of the esophagus [11]. In contrast, the potential role of delayed gastric emptying after a meal, which allows more time for reflux to occur, remains debated [10, 12].

In addition to the proportionally abundant milk intakes, the supine posture promotes the passage of liquid gastric content into the esophagus, the immature esophageal motility, and the refluxate is poorly cleaned owing to a poor esophageal clearance [10].

Secondary GER

The major symptoms of GERD, vomiting, feeding problems, failure to thrive, and irritability, are those which also characterize cow's milk allergy (CMA), a disorder affecting up to 7.5% of term infants and beginning very early in life, usually, before age 4 months of life [13].

CMA also exists in preterm infants, with the same symptoms such as eosinophilic inflammation of the digestive mucosa [14–19]. The incidence of CMA at this age is unknown, but the diseases reported in relation with CMA suggest a role in recurrent vomiting and irritability of preterm infants with. A recent study suggests that intolerance to milk protein might be responsible for a large part of GER [20] and of other feeding problems in the preterm baby [21]. Confirmation of CMA is given by a trial of cow milk protein-free formula. Some of those infants are also allergic to hydrolysate, and only an amino acid-based formula may cure the disease. More data on the relevance of this potential underlying diagnosis in preterm infants with recurrent vomiting are required.

Atopy patch test may help early diagnosis of cow's milk allergy in preterm infants. In the retrospective analysis of five girls and nine boys, born at 31 ± 2 (mean ± SD) weeks of gestation and presenting digestive symptoms at age 42 ± 18 days, ten had a complete recovery following the shift to an exclusive feeding with an amino acid-based formula. Cow-milk-skin prick tests and specific immunoglobulin E were always negative, whereas the atopy patch test was positive in seven of the ten infants with complete recovery [22].

The Clinical Manifestations of GER

GERD in infants is a complex disorder due to the range of clinical presentations, and the causal relationship between significant acid exposure and clinical symptoms is often difficult to prove. This is even truer in preterms. The only proof could be provided by the ability to demonstrate a temporal association between individual reflux events and the onset of symptomatic episodes. Irritability, generalized behavioral discomfort, vomiting, posturing, grimacing, worsening of lung disease, failure to achieve full feeds, failure to thrive, longer hospitalization, apnea, bradycardia, and desaturation attacks are mostly accepted to be related to GER.

Digestive Manifestations

The occurrence of emesis may indicate gastroesophageal reflux (GER) in a preterm infant. If it is not per se considered a sign of feeding intolerance, it is still taken into account in most of the studies' operational definition of feeding intolerance. Regurgitations may occur, demonstrating the ability of the feeding volume to overcome the reservoir capacity of the esophagus which is extremely low. Weight loss or poor growth (failure to thrive), crying, hematemesis, and melena are more likely to be related to esophagitis.

Apnea and Bradycardia

General belief is for apnea becoming a symptom or consequence of GER. However, studies on this relationship have reported conflicting results, and data on this discussion are currently not enough to come to a definitive conclusion. Actually, the relationship between apnea, bradycardia, and GER is extremely controversial. When GER occurs, owing to a relaxed esophageal sphincter, a common phenomenon in preterm infants, the gastric content enters into the esophagus [23]. GER would then lead to the closure of the glottis as apnea events caused by GER are obstructive in nature. However, relationship between GER episodes and the occurrence of apnea and bradycardia episodes is largely challenged event [24, 25]. A study with esophageal manometry allowing to place a pH-impedance probe at 87% of the nares-LES distance, with a recording performed for about 24 h at cribside, showed that 33% of acid reflux episodes were associated with symptoms (respiratory, sensory, and movement, documented by nurses) and that association of symptoms with acid reflux episodes depended on their most proximal extent and on the acid clearance time [26].

Diagnosis Means for GER in Preterm Babies

GER could be diagnosed for extra-digestive manifestations by 24-h pH meter monitoring and for digestive manifestations by upper GI endoscopy with specific neonatal endoscopes [27].

Rather than relying on measurement of acid exposure based on arbitrary reflux index criteria of intraluminal pH, impedance monitoring allows detection of all reflux independently of pH and, as already demonstrated in adults on and off PPI therapy, improves the accuracy of reflux-symptom associations [28, 29]. Studies in preterms with this technique are still rare, but the importance of nonacid bolus reflux in preterms receiving frequent milk/formula feeding, pH-impedance monitoring will improve the diagnostic yield over and above pH monitoring alone.

In neonates [30], relatively few gastroesophageal reflux episodes cause esophageal acidification to pH <4. Premature infants receive frequent feeds, which can induce a weaker acid secretory response than that observed in older infants and adults. As a consequence, gastric pH may be >4 for prolonged periods, and reflux of

gastric contents might be less acidic or even alkaline. An extensive analysis of 26 preterm babies using 24-h impedance-pH recordings in asymptomatic premature neonates showed that healthy premature neonates had approximately 70 reflux events in 24 h, 25% of which were acid, 73% were weakly acidic, and 2% were weakly alkaline. The number of reflux events per hour (2–3 h^{-1}) was slightly lower than that described in premature neonates with cardiorespiratory events (4 h^{-1}) [30].

In 28 preterm (male 20, female 8) infants with symptoms suggestive of gastroesophageal reflux (GER) (frequent regurgitations, apnea, or transcutaneous oxygen saturation decreased), the 24-h esophageal impedance-pH monitoring technique was safe and tolerated; detected more weakly acidic refluxes, liquid bolus refluxes, and mixed bolus refluxes; and provided some evidence for explaining the relationship between GER and clinical manifestation [31].

As synthetized by Indrio et al. [32], although gastroesophageal reflux disease GERD is thought to cause feeding problems, apnea, desaturation, bradycardia, and stridor, it can be difficult to diagnose in infants, especially mainly because frequent feeds neutralize stomach contents. This may explain the lack of agreement as to the diagnostic cutoff level of the reflux index for preterm babies [1], which in various studies ranges between 5 and 10% [33]. Of notice, using the intraluminal impedance technique indicated that in more than 50% of healthy preterm infants, the esophagus can be exposed to acid 5% of the time [30] so that a generally accepted 5% cutoff level might lack specificity for GERD diagnosis in preterms. The gestational age of preterms might also be taken into consideration [32] underlying the need to establish an age-related diagnostic reflux index to identify infants affected by GERD.

Treatment of GER in Preterm Babies

The therapeutic management of GER still represents a controversial issue among neonatologists. Overtreatment, often unuseful and potentially harmful, is increasingly widespread. Hence, a stepwise approach, firstly promoting conservative strategies such as body positioning (the best position is the ventral decubitus associated with a 30° of orthostatism position under continuous monitoring in the NICU) or changes of feeding modalities, should be considered the most advisable choice in preterm infants with GER [34]. It must be kept in mind that whatever the choices made, there are approved drugs for the treatment of GER in this age range.

Non-pharmacological management of GER might represent a useful tool for neonatologists to reduce the use of anti-reflux medications, i.e., prokinetics and anti-H2 blockers or PPI, which should be limited, due to their side effects, to selected cases of severe symptomatic infants [35, 36].

Positioning

Non-pharmacological management of GER includes positioning. A decrease of GER was noted in prone neonates in 1982, when a [37] and several trials tested the efficacy of different body positions on GER in preterm babies. In combining

esophageal manometry and MII, Omari et al. [38] investigate the efficacy of left versus right lateral position on GER features in healthy preterm infants: left-side positioning resulted in a significant decrease of TLESRs, whereas right lateral position was associated with a higher number of TLESRs and liquid refluxes [39]. However, in asymptomatic, convalescent, prematurely born infants, no statistically significant correlations between the amount of acid GER and the number of either obstructive or total apnea episodes in either the supine or prone position was seen. Supine compared with prone sleeping neither increased clinically important acid GER nor obstructive apnea episodes associated with acid GER [40].

Frequency and Volume of Feeding

Feeding modalities and frequency influence GER. Neonatologists experience daily the effect on GER of changing the feeding method, i.e., reducing the duration of continuous feeding, starting bolus feeding in a child with continuous feeding, or increasing or reducing the percentage of the initial bolus volume in a child with continuous feeding [41]. In that respect it is known that bolus feeding can trigger a gastric distension and thus a transient relaxation of the lower esophageal sphincter, as demonstrated in healthy volunteers [42]. Also, the passage of a tube through the lower esophageal sphincter is likely to increase the occurrence of GER [11]. In order to overcome this negative effect, a strategy might be the withdrawal of the feeding tube after bolus administration [11]. However, this might lead to esophageal irritation so that the benefits need to be confirmed by clinical trials before a recommendation is made on that topic.

The frequency of feeding also matters: a positive correlation between the frequency of feedings and the occurrence of nonacid GER episodes, with a concomitant decrease in the number of acid GER, has been observed [10].

Since acid reflux is known to be determinant for the development of GERD, the hypothesis is that preterm feeding, when frequent with small volume, may reduce GER in case of prolonged esophageal acid exposure but with no benefit in symptomatic babies when predominant GER is nonacid.

Thickening

Thickening feedings in premature babies might be useless or even dangerous. The efficacy of fortified human milk thickened with precooked starch was tested in a small cohort of preterm symptomatic infants, and no improvement in the rates of both acid and nonacid GERs was seen, whereas the total number of GER episodes tended to increase [43, 44].

Furthermore, a possible association between milk thickening and the occurrence of necrotizing enterocolitis was recently documented [45, 46]. For both reasons, and until further data become available on that matter, feed thickening in premature babies should not be done.

Extensively Hydrolyzed Formulas (eHFs)

Hydrolyzed protein formulas (eHFs) have bend extensively tested in different clinical trials and were reported to reduce gastrointestinal transit time, to increase stool frequency, and to improve feeding tolerance, therefore leading to an earlier achievement of full enteral feeding. Several mechanisms have been suggested, such as a higher motilin release than standard preterm formulas (SPFs) and a decreased activity of milk protein-derived opioid receptor agonists (see review in [20]).

Actually, the increasing recognition of the role of CMPA in the feeding problems of the preterm babies [18, 21] and more specifically in GER [35] might shed some light on the efficacy of eHFs. Owing to the relationship demonstrated in older children between GER and CMA, eHFs in premature babies might simply address the original intolerance to milk proteins that constitute the basis of infant formulas. The point is that eHFs are designed for the feeding of older babies and do not address the important issue of increased energy and protein requirements in preterm babies.

Human Milk Fortifiers

Human milk fortifiers (HMFs) contain proteins, carbohydrates, and minerals and are used to supplement breast milk in order to meet the nutritional needs of preterm infants fed human milk. They actually improve weight gain, linear growth, and head circumference growth without inducing major adverse effects (i.e., necrotizing enterocolitis) [47]. Since HMFs increase both energy and osmolality, a role in inducing or aggravating GER may be expected. A study evaluated whether standard fortification with different amounts of HMFs (3%, as the low dose, and 5% as the high 1) may affect GER features in symptomatic preterm infants [48]. It appeared that the addition of both concentrations of HMF, 3 and 5%, resulted in a significant increase of nonacid GERs, nonacid reflux index, and esophageal height of reflux; no difference was observed in acid GER pattern.

Alginate

Sodium alginate is likely to form in combination with gastric acidity a gel floating at the surface of the gastric content and preventing acid form going upward into the stomach. A study evaluated the effect of sodium alginate on gastroesophageal reflux features in preterm newborns by combined pH and impedance monitoring (pH-MII) [49]. Sodium alginate actually reduced the number of GER reaching the proximal esophagus (DG vs. DF, 5.50 vs. 7.50, $P = 0.030$). It also decreased the number of acid GER detected either by pH monitoring (DG vs. DF, median 17.00 vs. 29.00, $P = 0.002$) and MII (DG vs. DF, 4.0 vs. 6.00, $P = 0.050$) and also acid esophageal exposure (DG vs. DF, 4.0% vs. 7.6%, $P = 0.030$), without any influence on nonacid GER. Authors thus consider sodium alginate in preterm infants promising. However,

it must be kept in mind that alginate is derived from agar-agar, a thickening and gel-forming agent largely used in food preparations so that its role might not be very different from that of well-recognized thickening agents, mentioned above, the use of which might be dangerous in preterm babies.

Prokinetics

Promotility agents (cisapride, metoclopramide, and domperidone) belong to a family of drugs which have been widely employed in pediatric practice, in order to reduce the symptoms of GER. Cisapride has been removed from the market due to cardiac side effects. Domperidone, which belongs to the same therapeutic class, has never been tested in clinical trial in preterms. As for metoclopramide, a trial performed in preterm infants regarding metoclopramide's effectiveness failed to demonstrate the improvement of bradycardia clinically attributed to GER [50]. Eventually, metoclopramide's administration might be associated to adverse effects, especially dystonic reactions which make it quite unlikely to be given to preterms.

Erythromycin

Erythromycin is a common macrolide antibiotic, acting as a strong non-peptide motilin receptor agonist which contributes to enhance gastric emptying and induces phase III activity of the interdigestive migratory motor complex (MMC), propagating from the stomach to the ileum. It may thus help promote the passage of the digestive bolus from the upper digestive tract to the rectum. In a large randomized controlled trial in a preterm cohort, erythromycin demonstrated a significant improvement on parenteral nutrition-associated cholestasis: there was a quicker attainment of full enteral feeding, at the intermediate dose of erythromycin (5 mg/kg 4 times/day for 14 days), therefore resulting in a shorter duration of parental nutrition [51, 52]. However, the erythromycin's effectiveness on GER seems limited if not null, as mentioned in a trial, performed in a small number of preterm infants, which reported no significant improvement in GER indexes after the low-dose provision [53]. A recent developmental study on the effects of erythromycin on migrating motor complexes showed that these were induced only in infants with gestational ages of 32 weeks or older [54].

In addition, erythromycin has the potential to induce cardiac arrhythmias, pyloric stenosis, or septicemia from multiresistant organisms.

Anti H2 and PPIs

Histamine-2 (H2) blockers are a group of drugs which compete with histamine for the selective linkage to the H2 receptor, placed in the gastric wall. This bond leads

to a lowered secretion of the hydrochloric acid by the parietal cells in the stomach and, thus, to an increased intragastric pH. Several concerns as to the role of ranitidine in inducing NEC were confirmed by a clinical trial in a case control trial, where authors documented a higher incidence of NEC in preterm infants treated with ranitidine (17.2%) when compared to the control group (4.3%) [55]. The risk does not seem associated neither with the dose nor with the duration of treatment. This means that H2-blockers are probably overused in most of the NICUs to treat many clinical conditions, even though the evidence of benefits is low if any, and that adverse effects are probably largely underestimated in clinical practice.

Proton pump inhibitor (PPI) therapy is increasingly being used to treat premature infants with gastroesophageal reflux disease (GERD), even though their efficacy on both acid production has yet to be assessed in this patient.

In a randomized, double-blind, placebo-controlled, crossover design trial of omeprazole therapy in ten preterm infants (34–40 weeks postmenstrual age) was effective in reducing esophageal acid exposure in premature infants with pathological acid reflux on 24-h pH probe compared to placebo [56]. Omeprazole therapy significantly reduced gastric acidity (% time pH <4, 54% vs. 14%, $P < 0.0005$), esophageal acid exposure (% time pH <4, 19% vs. 5%, $P < 0.01$), and number of acid GER episodes (119 vs. 60 episodes, $P < 0.05$). However, there was a discrepancy between normalization of acid reflux and lack of effect on symptoms after PPI treatment. For authors, one explanation was that they had a minor acidic disease, so that symptoms may have been due to weakly acidic refluxes, in accordance with findings obtained in preterm infants with apnea of prematurity [57].

The investigation of pharmacodynamics and systemic exposure of esomeprazole in 26 preterm infants and term neonates with symptoms of gastroesophageal reflux and pathologic acid exposure was tested with oral esomeprazole 0.5 mg/kg once daily for 7 days and 24-h esophagogastric pH-impedance monitoring [58]. Treatment produces no change in bolus reflux characteristics despite significant acid suppression: there were no significant differences from baseline to day 7 of therapy in the frequency of bolus reflux, consistency of bolus reflux (liquid, mixed, or gas), extent of bolus reflux, or bolus clearance time. Acid bolus reflux episodes were reduced on therapy (median 30 vs. 8, $P < 0.001$), as was the reflux index (mean % time esophageal pH <4, 15.7% vs. 7.1%, $P < 0.001$). The number of gastroesophageal reflux symptoms recorded over 24 h was lower on therapy (median 22 vs. 12, $P < 0.05$). In another study, esomeprazole was well tolerated and reduced esophageal acid exposure and the number of acidic reflux events in neonates [59]. However, signs and symptoms of GERD traditionally attributed to acidic reflux in neonates were not significantly altered by esomeprazole treatment.

For all PPIs, the far more complex issues of safety and efficacy have yet to be addressed. Actually, the prolonged use of acid inhibitors in preterm infants significantly increases the risk of infections [60], so that they should be prescribed only for neonates with relevant clinical evidence of disease, i.e., with severe GERD.

Bullet Points

- GER is still poorly defined in premature infants.
- The relationship between GER and apneas remains poorly understood.
- Prone position is recommended in preterms with GER babies when heart rate is monitored.
- Milk thickening is inefficient and potentially dangerous, with a risk of NEC.
- Prokinetics have been either abandoned for side effects or not sufficiently tested in this age range.
- Anti-H2 drugs bear the risk of NEC.
- PPIs may be efficient but have side effects, especially infection.
- A conservative approach is always recommended.

Conclusion

GER is probably a frequent occurrence in the preterm, even though its exact frequency remains difficult to quantify and if the symptoms which should be attributed still remain debated. A major point is that none of the drug used in the preterm have a license in this age range, so that their efficacy and safety are poorly defined. "Primum non nocere" should be the mainstay of any medical decision, especially in respect to some adverse effects, non- recognized for some thickeners or some antacid drugs, such as anti-H2. A conservative and stepwise approach seems always advisable.

References

1. Dhillon AS, Ewer AK. Diagnosis and management of gastrooesophageal reflux in preterm infants in neonatal intensive care units. Acta Paediatr. 2004;93:88–93.
2. McGuire W, Henderson G, Fowlie PW. Feeding the preterm infant. BMJ. 2004;329(7476):1227–30.
3. Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2013;3:CD000504. doi:10.1002/14651858.CD000504.
4. Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low birth weight infants (VLBW). Cochrane Database Syst Rev. 2013;3:CD001241. doi:10.1002/14651858.CD001241.
5. Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotizing enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2013;5:CD001970.
6. SIFT Investigators group, Abbot J, Berrington JE, Boyle E, Dorling JS, Embleton NE, et al. Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews. Arch Dis Child Fetal Neonatal Ed. 2013;98:F470–2.
7. Basuki F, Hadiati DR, Turner T, McDonald S, Hakimi M. Dilute versus full strength formula in exclusively formula-fed preterm or low birth weight infants. Cochrane Database Syst Rev. 2013;11:CD007263. doi:10.1002/14651858.CD007263.
8. Shulman RJ, CN O, Smith EO. Evaluation of potential factors predicting attainment of full gavage feedings in preterm infants. Neonatology. 2011;99:38–44.

9. Sankar MJ, Agarwal R, Mishra S, Deorari AK, Paul VK. Feeding of low birth weight infants. Indian J Pediatr. 2008;75:459–69.
10. Omari TI, Barnett CP, Benninga A, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut. 2002;51:475–9.
11. Peter CS, Wiechers C, Bohnhorst B, Silny J, Poets CF. Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: a multiple intraluminal impedance study. J Pediatr. 2002;141:277–9.
12. Ewer AK. Can pH monitoring reliably detect gastro-oesophageal reflux in preterm infants?. (Commentary to article by Grant L, Cochran D). Arch Dis Child Fetal Neonatal Ed. 2001;85:F157–8.
13. Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? Pediatrics. 2002;110:972–84.
14. D'Netto MA, Herson VC, Hussain N, et al. Allergic gastroenteropathy in preterm infants. J Pediatr. 2000;137:480–6.
15. Coviello C, Rodriquez DC, Cecchi S, Tataranno ML, Farmeschi L, Mori A, et al. Different clinical manifestation of cow's milk allergy in two preterm twins newborns. J Matern Fetal Neonatal Med. 2012;25(Suppl 1):132–3.
16. Abdelhamid AE, Chuang SL, Hayes P, Fell JM. Evolution of in vitro cow's milk protein-specific inflammatory and regulatory cytokine responses in preterm infants with necrotising enterocolitis. J Pediatr Gastroenterol Nutr. 2013;56(1):5–11.
17. Baldassarre ME, Cappiello A, Laforgia N, Vanderhoof J. Allergic colitis in monozygotic preterm twins. Immunopharmacol Immunotoxicol. 2013;35(1):198–201.
18. Manuyakorn W, Benjaponpitak S, Siripool K, Prempunpong C, Singvijarn P, Kamchaisatian W, et al. Cow milk protein allergy presenting as feeding intolerance and eosinophilia: case reports of three preterm neonates. Paediatr Int Child Health. 2015;35(4):337–41.
19. Zachariassen G. Nutrition, growth, and allergic diseases among very preterm infants after hospital discharge. Dan Med J. 2013;60(2):B4588. Review
20. Corvaglia L, Mariani E, Aceti A, Galletti S, Faldella G. Extensively hydrolyzed protein formula reduces acid gastro-esophageal reflux in symptomatic preterm infants. Early Hum Dev. 2013;89(7):453–5.
21. Cordova J, Sriram S, Patton T, Jericho H, Gokhale R, Weinstein D, et al. Manifestations of cow's-milk protein intolerance in preterm infants. J Pediatr Gastroenterol Nutr. 2016;62(1):140–4.
22. Dupont C, Soulaines P, Lapillonne A, Donne N, Kalach N, Benhamou P. Atopy patch test for early diagnosis of cow's milk allergy in preterm infants. J Pediatr Gastroenterol Nutr. 2010;50(4):463–4.
23. Lucchini R, Bizzarri B, Giampietro S, DeCurtis M. Feeding intolerance in preterm infants: how to understand the warning signs. J Matern Fetal Neonatal Med. 2011;24(Suppl 1):72–4.
24. Poets CF. Myth: gastroesophageal reflux is a pathological entity in the preterm infant. Semin Fetal Neonatal Med. 2011;16:259–63.
25. Di Fiore J, Arko M, Herynk B, Martin R, Hibbs AM. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. J Perinatol. 2010;30:683–7.
26. Jadcherla SR, Gupta A, Fernandez S, Nelin LD, Castile R, Gest AL, et al. Spatiotemporal characteristics of acid refluxate and relationship to symptoms in premature and term infants with chronic lung disease. Am J Gastroenterol. 2008;103(3):720–8.
27. Dupont C, Kalach N, de Boissieu D, Barbet JP, Benhamou PH. Digestive endoscopy in neonates. J Pediatr Gastroenterol Nutr. 2005;40:406–20.
28. Bredenoord AJ, Weusten BL, Timmer R, et al. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. Am J Gastroenterol. 2006;101:453–9.
29. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. Am J Gastroenterol. 2006;101(9):1956–63.
30. López-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macías M, Silny J, et al. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. Pediatrics. 2006;118(2):e299–308.

31. Zhang J, Li Z, Ge Y, Wang K, Xu Z, Xia Z, et al. Role of the twenty-four-hour esophageal multichannel intraluminal impedance-pH monitoring in preterm infants. Zhonghua Er Ke Za Zhi. 2014;52(4):298–302.
32. Indrio F, Magistà AM, Cavallo L, Francavilla R. Gastroesophageal reflux in preterm infants: how acid should it be?. Omari TI, Haslam RR, Lundborg P. Author's response to letter. J Pediatr Gastroenterol Nutr. 2008;46(1):96.
33. Rudolph CD, Mazur LJ, Liptak GS, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 2001;32(Suppl 2):S1–31.
34. Vandenplas Y, Colin DR, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2009;49:498–547.
35. Corvaglia L, Martini S, Aceti A, Arcuri S, Rossini R, Faldella G. Nonpharmacological management of gastroesophageal reflux in preterm infants. Biomed Res Int. 2013;2013:141967. doi:10.1155/2013/141967. Review
36. Corvaglia L, Monari C, Martini S, Aceti A, Faldella G. Pharmacological therapy of gastroesophageal reflux in preterm infants. Gastroenterol Res Pract. 2013;2013:714564. doi:10.1155/2013/714564. Review
37. Blumenthal I, Lealman GT. Effect of posture on gastrooesophageal reflux in the newborn. Arch Dis Child. 1982;57:555–6.
38. Omari TI, Rommel N, Staunton E, et al. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr. 2004;145:194–200.
39. van Wijk MP, Benninga MA, Dent J, et al. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr. 2007;151:585–90.
40. Bhat RY, Rafferty GF, Hannam S, Greenough A. Acid gastroesophageal reflux in convalescent preterm infants: effect of posture and relationship to apnea. Pediatr Res. 2007;62(5):620–3.
41. Birch JL, Newell SJ. Gastrooesophageal reflux disease in preterm infants: current management and diagnostic dilemmas. Arch Dis Child Fetal Neonatal Ed. 2009;94(5):F379–83.
42. Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. Pediatrics. 2004;113(2):e128–32. Review
43. Corvaglia L, Ferlini M, Rotatori R, Paoletti V, Alessandroni R, Cocchi G, et al. Starch thickening of human milk is ineffective in reducing the gastroesophageal reflux in preterm infants: a crossover study using intraluminal impedance. J Pediatr. 2006;148(2):265–8.
44. Corvaglia L, Aceti A, Mariani E, Legnani E, Ferlini M, Raffaeli G, et al. Lack of efficacy of a starch-thickened preterm formula on gastro-oesophageal reflux in preterm infants: a pilot study. J Matern Fetal Neonatal Med. 2012;25(12):2735–8.
45. Clarke P, Robinson MJ. Thickening milk feeds may cause necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2004;89(3):F280.
46. Beal J, Silverman B, Bellant J, Young TE, Klontz K. Late onset necrotizing enterocolitis in infants following use of a xanthan gum-containing thickening agent. J Pediatr. 2012;161(2):354–6.
47. Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. Cochrane Database Syst Rev. 2004;(1):CD000343. Review Update in: Cochrane Database Syst Rev. 2016;(5):CD000343.
48. Aceti A, Corvaglia L, Paoletti V, Mariani E, Ancora G, Galletti S, et al. Protein content and fortification of human milk influence gastroesophageal reflux in preterm infants. J Pediatr Gastroenterol Nutr. 2009;49(5):613–8.
49. Corvaglia L, Aceti A, Mariani E, De Giorgi M, Capretti MG, Faldella G. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. Aliment Pharmacol Ther. 2011;33(4):466–70.
50. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. J Pediatr. 2009;155(4):516–21.

51. Ng PC, Lee CH, Wong SP, Lam HS, Liu FY, So KW, et al. High-dose oral erythromycin decreased the incidence of parenteral nutrition-associated cholestasis in preterm infants. Gastroenterology. 2007;132(5):1726–39.
52. Ng YY, PH S, Chen JY, Quek YW, JM H, Lee IC, et al. Efficacy of intermediate-dose oral erythromycin on very low birth weight infants with feeding intolerance. Pediatr Neonatol. 2012;53(1):34–40.
53. Ng SC, Gomez JM, Rajadurai VS, Saw SM, Quak SH. Establishing enteral feeding in preterm infants with feeding intolerance: a randomized controlled study of low-dose erythromycin. J Pediatr Gastroenterol Nutr. 2003;37(5):554–8.
54. Jadcherla SR, Berseth CL. Effect of erythromycin on gastroduodenal contractile activity in developing neonates. J Pediatr Gastroenterol Nutr. 2003;37(5):554–8.
55. Bilali A, Galanis P, Bartsocas C, Sparos L, Velonakis E. H2-blocker therapy and incidence of necrotizing enterocolitis in preterm infants: a case-control study. Pediatr Neonatol. 2013;54(2):141–2.
56. Omari TI, Haslam RR, Lundborg P, et al. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44:41–4.
57. Magistà AM, Indrio F, Baldassarre M, Bucci N, Menolascina A, Mautone A, et al. Multichannel intraluminal impedance to detect relationship between gastroesophageal reflux and apnoea of prematurity. Dig Liver Dis. 2007;39(3):216–21.
58. Omari T, Lundborg P, Sandström M, Bondarov P, Fjellman M, Haslam R, et al. Pharmacodynamics and systemic exposure of esomeprazole in preterm infants and term neonates with gastroesophageal reflux disease. J Pediatr. 2009;155(2):222–8.
59. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. J Pediatr. 2013;163(3):692–8.
60. Terrin G, Passariello A, Ruggieri A, et al. Increased risk of infections in gastric acidity inhibitors treated newborn. Dig Liver Dis. 2006;38:A94.

Gastroesophageal Reflux and the Neurologically Impaired Patient

9

Efstratios Saliakellis and Nikhil Thapar

Abstract

Gastroesophageal reflux (GER) and its associated complications (gastroesophageal reflux disease—GERD) are very common in children with neurological impairment (NI) and correlate with the severity of neurodisability. A number of causative mechanisms underlie GERD in this population, many of which are inherent to the neurodisability and irreversible. Diagnosis is often difficult and compounded by a limited ability of NI children to communicate their symptoms, variable presentation and poor correlation with objective testing. Unfortunately, as a result, management is often misdirected and/or suboptimal. Overall, a high index of suspicion is needed for GERD when managing children with NI. A wide range of treatments are available for managing GER/GERD in this population of children, although the mainstay remains pharmacological therapy, namely, PPIs. A systematic approach is advised starting at simpler 'conservative' treatments through dietary manipulation, pharmacotherapy to surgical interventions. At each step there should be careful consideration of the benefits and risks and carers of NI children appropriately counselled about these. There is evidence to suggest that although there is a place for pharmacotherapy, consideration should also be given to diet both in terms of type and method of administration. In this respect there is emerging benefit for the use of post-pyloric feeding even as an alternative to surgery. Surgery, namely, anti-reflux procedures, should be considered the last resort although it appears to have a clear benefit in a highly selective

E. Saliakellis
Great Ormond Street NHS Foundation Trust, London, UK

N. Thapar (✉)
Great Ormond Street NHS Foundation Trust, London, UK

UCL Great Ormond Street Institute of Child Health, London, UK
e-mail: n.thapar@ucl.ac.uk

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_9

group of NI children especially those with severe disability who have failed medical therapy. Overall, although there have been significant strides into understanding the management of NI children suffering problematic GER, there is a clear need for further robust studies in this challenging group.

Keywords
Gastroesophageal reflux • Gastroesophageal reflux disease • Neurologically impaired • Children • Cerebral palsy

Introduction

Normal functioning of the neuromusculature of the gastrointestinal tract is inextricably linked with that of the central and autonomic nervous systems, reflective of their shared developmental origins. It is perhaps not surprising, therefore, that not only are gastrointestinal motility disorders including gastroesophageal reflux (GER) and its related complications (gastroesophageal reflux disease—GERD) highly prevalent in children suffering neurological impairment (NI), their presence and severity appear to correlate with that of the motor disability. Indeed, gastrointestinal complaints, including GER, are reported to be present in up to 80–90% of children with cerebral palsy and other neurodevelopmental disabilities [1].

Although the true prevalence remains ill-defined [2], GER is frequently present in children with underlying neurological disorders with estimates of the incidence of GERD in children with NI such as cerebral palsy (CP) of between 15 and 75% [3–10].

It should be noted that GERD in a randomly selected cohort of intellectually disabled children was confirmed with both pH metry and upper GI endoscopy (oesophagogastroduodenoscopy) in approximately half of the population, even in the absence of overt symptomatology [11].

Pathophysiology

A number of mechanisms have been implicated in the pathophysiology of GER in NI children [12–17]. Dysfunction of the central nervous system leads to disruption of the coordination of upper GI neuromuscular function, with specific effects on the physiology of the lower oesophageal sphincter (LOS) and motility of the oesophagus and stomach [18, 19].

LOS factors include decreased resting pressure and increased frequency of transient lower oesophageal sphincter relaxations (TLESRs). Pensabene et al. conducted concurrent oesophageal manometry and pH monitoring in ten unoperated children with sequelae of birth asphyxia and showed that in 40% the LES pressure was largely undetectable [14]. A proportion of these children suffered TLESRs. Hiatal herniae appear more prevalent in these children and disrupt the integrity of the LOS further compounding the risk of GER and its complications [18].

Along with gastric emptying, oesophageal clearance of refluxate is one of the key mechanisms for protecting against GER. In normality, this is achieved by peristalsis of the oesophageal body, which is evoked by the presence of refluxate in the distal oesophagus and functions to empty virtually all the acid volume from the oesophagus. Children with NI show significant impairment of oesophageal motility. Gustafsson and Tibbling investigated the prevalence of pathological GER and oesophageal dysfunction in 32 children (0.7–19 years of age) with brain damage, mainly severe cerebral palsy and tetraplegia. More than two-thirds had evidence of GER and a third abnormal oesophageal manometry, including absence of propulsive motor activity in the oesophagus [19]. Others have reported similar findings [18].

The role of gastric emptying in GER in children suffering NI is less clear. Kawahara et al. evaluated acid/non-acid reflux episodes (RE) and gastric emptying using combined multichannel intraluminal impedance-pH (MII-pH) monitoring and (^{13}C)-breath test in 30 NI patients (age, 1–34 years; median, 6 years). Overall they found that NI patients showed a wide range of gastric emptying rates without any significant causal relationship between delayed gastric emptying and GER [20]. A similar lack of correlation has also been reported in healthy children with GER [21]. More studies are needed to elucidate the relationship between GER and aspects of gastric motility and emptying in NI children.

Although dysfunction of the LOS and upper GI motility are key causative factors for GER, others factors are likely to contribute to the development of GERD including increased intra-abdominal pressure (from spinal curvature, spasticity or seizures) and prolonged periods of time spent in the recumbent position due to limited mobility. Similar disturbances on function of the respiratory tract together with an impaired ability to protect the airway increase the risk of GERD-associated pulmonary aspiration.

Many NI children have trunk hypotonia, which predisposes to spinal curvature and raised intra-abdominal pressure when they are sitting upright. As time progresses especially in severe neurodisability, these spinal deformities are more likely to increase and become fixed often requiring surgical intervention. However, NI children may then develop gastric dysmotility post-surgery including post-prandial antral hypomotility further compounding problems with GER and vomiting [22]. The cause of this is not clear, but interference with autonomic innervation from the traction on nerves may contribute. Secondary malnutrition may further contribute to the gastrointestinal dysmotility.

Diagnosis

Ideally, the diagnosis of GER in NI children should be based on both clinical grounds (e.g. detailed medical history and meticulous clinical examination, observation of feeds) along with laboratory investigations where appropriate and feasible. Although typical GERD symptoms, such as frequent regurgitation and heartburn have been reported [17], in reality the diagnosis of GER/D in NI children is often difficult to make. Akin to issues faced in infants, children with severe NI are often unable to convey symptoms of GERD such as heartburn and regurgitation, which

remain unrecognised not infrequently until complications, e.g. oesophageal strictures, occur. For example, there is little agreement between studies as to the relationship between GERD and symptoms such as inconsolable crying, irritability or indeed behaviours such as aggression or agitation [23–26]. It is important to note that although objective investigations, e.g. pH metry ± combined with impedance and endoscopy, confirm the presence of GERD in the majority of NI children with GERD symptoms [11, 16, 27–30]; they have also shown GERD in a significant proportion of NI children without obvious symptoms [29]. There may also be considerable overlap of symptoms attributed to GERD with those of oropharyngeal dysfunction (OPD) where in addition to swallowing dysfunction children with NI may display coughing, gurgly voice, wet breathing, gagging and choking [31–33]. Multidisciplinary assessment utilising appropriately trained professionals such as speech and language therapists possibly together with investigations, e.g. videofluoroscopy, should be used to differentiate GERD and OPD especially where feed-related symptoms and uncertainty exist.

GERD in NI children carries important short-term and long-term implications both in terms of quality of life and long-term prognosis of NI patients. Inadequately or un-treated or indeed undiagnosed NI children with GERD may suffer complications such as the development of oesophageal strictures, Barrett's oesophagus or recurrent pneumonias. As a result a high index of suspicion is required to identify possible GERD, perhaps using, in addition, surrogate clinical parameters for its presence. de Veer et al., in a systematic review of the adult and paediatric literature relating to GERD symptoms in people with severe mental retardation, found that vomiting, rumination and haematemesis were most associated with GERD. Interestingly, they were unable to find support for a relationship between GERD and regurgitation, food refusal, failure to thrive or recurrent pneumonia [15]. Despite these findings several studies have suggested that the presence of GERD is associated with worse nutritional status of NI children when compared to NI children without GERD [16, 27]. More objective changes in NI children, such as dental erosion may be associated with GERD [17, 28].

Overall, there is little evidence that objective diagnostic tests for GERD should be routinely used in NI children any more than their utility in healthy children [3]. Investigation modalities include:

1. *Oesophageal pH metry* alone (to detect acid reflux) or combined with *oesophageal multichannel intraluminal impedance* (to detect acid, weakly acid and non-acid reflux). These modalities have been used in both healthy and NI child to quantify GER and attempt to define the temporal relationship between reported/observed GER symptoms/signs and reflux episodes [23, 27]. Although they are able to detect GER in NI children, the degree of reflux does not appear to correlate consistently with the presence of symptoms or their severity or with demonstrable complications. Alternative methods of investigation and/or analysis are needed to definitively associate pathologic reflux with complications such as aspiration pneumonia.

2. *Upper gastrointestinal (GI) contrast series*. Although such studies have little role to play in the actual diagnosis or GER or GERD, they should be used to determine the presence of anatomical abnormalities such as hiatal herniae or intestinal malrotation, which may be associated with isolated NI or where it is part of a more complex syndrome.
3. *Upper gastrointestinal endoscopy* (OGD or oesophagogastroduodenoscopy) with biopsies is used to delineate oesophageal anatomy (e.g. to rule out oesophageal stricture, hiatus hernia) and assesses for mucosal pathology (reflux oesophagitis, Barrett's oesophagus) [24]. Histological changes seen in reflux oesophagitis are described elsewhere in this book.
4. *Nuclear medicine studies (scintigraphy) and breath tests.* Assessment of gastric emptying time (GET) with either gastric emptying scintigraphy or (^{13}C)-breath test can be used to determine the presence of delayed gastric emptying, which has been suggested by some studies to contribute to GER [25, 26], although this is not supported by others [20]. Scintigraphy has also been used to assess for pulmonary aspiration but has a relatively low specificity [16].
5. *Oesophageal manometry* has been used in children suffering NI to define disruption of the structure and/or dynamics of the upper and lower oesophageal sphincter along with the contractile activity of the oesophageal body. These have increasingly been used to assess abnormalities in oesophageal motility that underlie OPD and GER in children with NI. Manometry has also been used prior to a surgical anti-reflux procedure or intraoperatively in patients undergoing anti-reflux surgery to determine the optimal type of the wrap [24, 28]. Further advances in technology are likely to further enhance assessment.

Treatment

Treatment options for GER in NI children include conservative (adjusting feeding regimes, posture), medical (e.g. medications, special means of alimentation such as post-pyloric feeding) and surgical options where GER is recalcitrant to other therapy.

Although children with NI are more likely to demonstrate intractable reflux, and indeed medical treatment of GER in this group of children is known to be notoriously ineffective, medical management using antacids (e.g. proton-pump inhibitors (PPIs), histamine-2 receptor antagonists) and prokinetic agents (e.g. domperidone, erythromycin) remains the first-line treatment [12].

'Simple' Measures

Akin to management in other non-NI children with GERD, and in the absence of severe complications, attention needs to be given to simpler conservative strategies. Assessment of feed volumes and rates of administration should be carried out using

a multidisciplinary approach ensuring at the same time that optimal nutrition and corresponding growth are not impacted. Attention also needs to be given to posture, especially in the post-prandial period, given the frequent trunk hypotonia and risk of kyphoscoliosis. There is some data in normal infants regarding reduction of GER by positioning (head elevation or left lateral) especially in infants [34, 35]. Although these positioning manoeuvres may be of benefit, no data exists for children with NI to provide a clear recommendation. Furthermore, a safe supine sleeping position is advised in infants to minimise the risk of sudden infant death syndrome.

Pharmacotherapy

Pharmacotherapy, namely, treatment with acid suppression medications, is the mainstay of management of GERD, with proton-pump inhibitors reported to be superior to histamine-2 receptor antagonists for both healing of erosive oesophagitis and relief of symptoms [11, 36]. It should be noted, however, that PPIs do not appear to exert significant effects on the volume of refluxate, the total number of reflux episodes and the reflux events reaching the proximal oesophagus [16, 37]. In keeping with this, GER symptoms such as regurgitation and 'vomiting' still occur in NI children adequately treated with PPIs [6, 17]. A small study, however, prospectively assessing the frequency of vomiting in a cohort of neurologically handicapped children, demonstrated a reduction of vomiting after PPI treatment was initiated [27, 38]. The effect of PPIs in NI children needs to be further elucidated especially in view of more recent concerns over an increased risk of complications from PPI use in children such as gastroenteritis, pneumonia and adverse bone health [39, 40].

Until its withdrawal from the market in most countries across the world given cardiac concerns over the risk of fatal cardiac arrhythmias/sudden death, cisapride, a serotonin 5-HT_4 receptor agonist, was widely used in children as a prokinetic agent. Although some studies suggested that not only was it tolerated well but also resulted in symptomatic improvement and reduced acid GER. Others, however, showed no reduction in GERD in CP patients compared to those without neurologic disorders [41, 42]. In 2010, a Cochrane review found no clear evidence that cisapride results in a reduction of GER symptoms in children [43]. Recently, a newer selective 5-HT_4 agonist mosapride used in a small number of NI children with GERD (0.3 mg/kg/day in 11 patients, 5 male, median age 12.3 years) showed a decreased reflux index (17.5% before and 8.2% after mosapride treatment; $p = 0.02$) suggesting its potential in this population [29]. There are insufficient studies on the efficacy and safety of other prokinetic drugs, such as domperidone, erythromycin and metoclopramide.

Using 24 h oesophageal pH monitoring, Kawai et al. studied the effect of the $GABA_B$ (*gamma*-aminobutyric acid) receptor agonist baclofen on GERD in eight NI children [44]. Baclofen administered orally or via nasogastric tube at a dose of 0.7 mg/kg/day resulted in a significant reduction of emesis ($p = 0.03$), total number of acid reflux episodes during 24 h ($p = 0.01$) and post-prandial ($p = 0.049$) periods, as well as number of acid refluxes longer than 5 min ($p = 0.02$). It was well tolerated with minimal side effects [30].

Diet and Feeding Route

It is clear that optimising nutrition is key in the management of children with NI and GERD. Campanozzi et al. showed a considerable improvement of GERD in children with cerebral palsy following a 6-month hypercaloric diet with a concomitant increase of body weight and BMI [27, 45].

Apart of overall nutrition, dietary modifications such as feed consistency and constituents also appear to be of value. The use of thickeners, such as pectin, decreased the amount of GER, as measured by pH metry, in children with cerebral palsy. Specifically, a high-pectin diet significantly decreased the reflux index, total number of reflux episodes, duration of the longest reflux episode as well as cough score [46]. NI children presenting with GER disease symptoms resistant to standard anti-reflux treatment may benefit from a trial of a hydrolysed or elemental diet; such an approach may be considered prior to making definitive decisions for anti-reflux surgery, as it may improve GER symptomatology [14, 47–49]. A significant reduction in the number of reflux episodes and duration of reflux was demonstrated in a study by Koshoo et al. of ten neurologically impaired children exclusively fed via a gastrostomy, while consuming a whey-based formula [14, 48]. Savage et al. in a pilot study showed that in children who have severe CP with a gastrostomy and fundoplication, gastric emptying of whey-based enteral formula is significantly faster than those based on casein. The acceleration in gastric emptying, however, did not alter the frequency of GER episodes [49]. Predominant whey-based formulas therefore appear to have a faster gastric emptying in children that have underlying GER. Further studies are required to address this definitively.

Finally, the feeding regime and location of delivery of feeds may have value. A significant number of NI children, especially those with severe neurological impairment, are fed by enteral tube. Enteral tube feeding can be administered by bolus, intermittently or continuously and feeding regime based on type of enteral tube, nutritional requirements, symptoms and tolerance to feeds [50].

In NI children with GERD, there is an emerging evidence base for the use of post-pyloric (jejunal) feeding in NI children with GERD even as an alternative to surgery. The rationale is limiting GER and its related complications and improving enteral nutrition in children unable to feed effectively, orally or gastrically. Jejunal access can be gained trans-nasally, via a gastrostomy or via a surgical jejunostomy. Ideally, the jejunal tube needs to be passed beyond the ligament of Treitz to minimise the risk of backfilling the stomach. Jejunal feeding is less invasive, appears safe and effective, requires less recovery time compared to fundoplication and is easily reversible. It, however, requires continuous feeding regimes and carries a risk of intussusception (20%), perforation (2–3%) and small intestinal obstruction as well as frequent complications of clogging (29%) and dislodgement (66%) requiring replacement [6, 51–53].

The outcomes of fundoplication with gastrostomy insertion were compared to percutaneous gastrojejunostomy in children with neurological impairment, in a recent systematic review and meta-analysis [54]. No differences were identified in the rates of pneumonia and mortality; of note, a non-significant trend towards major complications (e.g. small bowel obstruction, peritonitis, deep wound

infection, need for reoperation due to failure of the initial procedure) was revealed in the fundoplication group compared to those that underwent percutaneous gastrojejunostomy. Although the quality of available evidence comparing them is arguably still too low to allow for a definitive recommendation [52, 54], there are large robust studies in NI children suggest that rates of GERD complications are comparable between those receiving transpyloric feedings and those who underwent fundoplication, even in the presence of greater rates of comorbidities in the former group [55, 56].

Surgery

The indications for anti-reflux surgery in NI children, as in non-NI children, include failure of optimal medical management, presence of an anatomical abnormality (e.g. hiatus hernia), development of severe related complications (e.g. oesophageal stricture) and ALTE secondary to documented GER [57].

Fundoplication is the anti-reflux procedure of choice as it is proven to be safe and effective in NI children with GERD. Although gagging and retching can be frequently present following surgery, a high percentage of caregivers reported improvement in nutrition, reflux-related symptomatology and overall levels of satisfaction [44, 58–60]. Surgical therapy appears more effective in alleviating oesophageal inflammation than aspiration. Factors such as swallow incoordination and pharyngo-oesophageal dysmotility, however, may persist, or symptoms may indeed worsen accounting for the persistence of respiratory symptoms in neurologically handicapped children that underwent surgery [61]. Overall, the decision to undertake fundoplication in NI children should not be taken lightly and occur only after careful consideration of the clinical picture and alternative less invasive management strategies. In a recent analysis of survival post fundoplication in children, Wockenforth et al. found that the lowest 5-year survival (59%) was in children with cerebral palsy and gastrostomy [62]. It is important to adequately explain to patients' families the expected benefits and risks from surgery. It is imperative that the diagnosis of GER disease is confirmed prior to surgery and that the anticipated benefit is weighted against the risk of potential complications of surgery, as children with severe neurologic disability have an increased risk for operative morbidity and postoperative failure with persistence/recurrence of reflux symptoms [63, 64]. Age below 6 years at the time of the operation, presence of preoperative hiatal hernia, postoperative retching and oesophageal dilatation were identified as risk factors for recurrence of reflux post fundoplication in paediatric patients with neurologic impairment [65].

Surgical procedures most commonly performed are Nissen fundoplication (open or laparoscopic) and less frequently Thal or Toupet partial fundoplication [30]; partial fundoplication is the procedure of choice by some experts in NI children with oesophageal dysmotility, as they preserve the ability to belch or vomit; however, they are associated with a higher incidence of GER recurrence when compared to Nissen fundoplication [60]. Of note, it is now recognised that percutaneous endoscopic gastrostomy tube placement does not induce or exacerbate

GER; thus, routinely performing an anti-reflux operation with gastrostomy insertion is not recommended [66–70].

Total oesophagogastric dissociation represents a more radical surgical approach advocated for NI children with intractable GERD. First described 20 years ago, it involves total disconnection of the oesophagus from the stomach and anastomosis with the jejunum. Gastric feeding can then be continued into the stomach without the risk of reflux. A number of early studies suggested a comparable morbidity and mortality to fundoplication and a particular utility in NI children with severe neurological compromise and complete dependence on tube feeding especially where anti-reflux procedures have failed and in cases with a combination of pharyngeal neuromuscular incoordination and severe GERD [71–73].

In more recent studies, however, total oesophagogastric dissociation has been reported to require more and prolonged postoperative care and is associated with a number of early and late complications including nutritional (malabsorption), metabolic (dumping) and Barrett's oesophagus as well as the need for prolonged enteral feeding and further operative procedures (dilatations, reoperation) [74–78].

At present it is likely to provide a viable option for a small highly selective group of patients ensuring an adequate process of balancing risks and benefits has occurred as well as counselling of the family.

Summary and Conclusions

Gastroesophageal reflux (GER) and its associated complications (gastroesophageal reflux disease—GERD) are very common in children with neurological impairment (NI) and correlate with the severity of neurodisability. A number of causative mechanisms underlie GERD in this population, many of which are inherent to the neurodisability and irreversible. Diagnosis is often difficult and compounded by limited ability of NI children to communicate their symptoms, variable presentation and poor correlation with objective testing. Unfortunately as a result management is often misdirected and/or suboptimal. Overall, a high index of suspicion is needed for GERD when managing children with NI. A wide range of treatments are available for managing GER/GERD in this population of children, although the mainstay remains pharmacological therapy, namely, PPIs. A systematic approach is advised starting at simpler 'conservative' treatments through dietary manipulation, pharmacotherapy to surgical interventions. At each step there should be careful consideration of the benefits and risks and carers of NI children appropriately counselled about these. There is evidence to suggest that although there is a place for pharmacotherapy, consideration should also be given to diet both in terms of type and method of administration. In this respect there is emerging benefit for the use of post-pyloric feeding even as an alternative to surgery. Surgery, namely, anti-reflux procedures, should be considered the last resort although it appears to have a clear benefit in a highly selective group of NI children especially those with severe disability who have failed medical therapy. Overall, although there have been significant strides into understanding the management of NI children suffering problematic GER, there is a clear need for further robust studies in this challenging group.

References

1. Del Giudice E, Staiano A, Capano G, et al. Gastrointestinal manifestations in children with cerebral palsy. Brain Dev. 1999;21:307–11.
2. Reyes AL, Cash AJ, Green SH, et al. Gastrooesophageal reflux in children with cerebral palsy. Child Care Health Dev. 1993;19:109–18.
3. Sondheimer JM, Morris BA. Gastroesophageal reflux among severely retarded children. J Pediatr. 1979;94:710–4.
4. Ravelli AM, Milla PJ. Vomiting and gastroesophageal motor activity in children with disorders of the central nervous system. J Pediatr Gastroenterol Nutr. 1998;26:56–63.
5. Wadie GM, Lobe TE. Gastroesophageal reflux disease in neurologically impaired children: the role of the gastrostomy tube. Semin Laparosc Surg. 2002;9:180–9.
6. Sullivan PB. Gastrointestinal disorders in children with neurodevelopmental disabilities. Dev Disabil Res Rev. 2008;14:128–36.
7. Bohmer CJ, Klinkenberg-Knol EC, Niezen-de Boer RC, et al. The prevalence of gastro-oesophageal reflux disease based on non-specific symptoms in institutionalized, intellectually disabled individuals. Eur J Gastroenterol Hepatol. 1997;9:187–90.
8. Wesley JR, Coran AG, Sarahan TM, et al. The need for evaluation of gastroesophageal reflux in brain-damaged children referred for feeding gastrostomy. J Pediatr Surg. 1981;16: 866–71.
9. de Veer AJ, Bos JT, Niezen-de Boer RC, et al. Symptoms of gastroesophageal reflux disease in severely mentally retarded people: a systematic review. BMC Gastroenterol. 2008;8:23.
10. Gangil A, Patwari AK, Bajaj P, et al. Gastroesophageal reflux disease in children with cerebral palsy. Indian Pediatr. 2001;38:766–70.
11. Bohmer CJ, Niezen-de Boer MC, Klinkenberg-Knol EC, et al. Gastro-oesophageal reflux disease in institutionalised intellectually disabled individuals. Neth J Med. 1997;51:134–9.
12. Quitadamo P, Thapar N, Staiano A, et al. Gastrointestinal and nutritional problems in neurologically impaired children. Eur J Paediatr Neurol. 2016;20:810–5.
13. Kawahara H, Nakajima K, Yagi M, et al. Mechanisms responsible for recurrent gastroesophageal reflux in neurologically impaired children who underwent laparoscopic Nissen fundoplication. Surg Endosc. 2002;16:767–71.
14. Pensabene L, Miele E, Del Giudice E, et al. Mechanisms of gastroesophageal reflux in children with sequelae of birth asphyxia. Brain Dev. 2008;30:563–71.
15. Miki K, Harada T, Kozaiwa K, et al. Antroduodenal motor function and gastro-oesophageal reflux in neurologically impaired children, adolescents and young adults. Eur J Pediatr. 1998;157:695–6.
16. Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med. 1982;307:1547–52.
17. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? Ann Intern Med. 1992;117:977–82.
18. Staiano A, Cucchiara S, Del Giudice E, et al. Disorders of oesophageal motility in children with psychomotor retardation and gastro-oesophageal reflux. Eur J Pediatr. 1991;150:638–41.
19. Gustafsson PM, Tibbling L. Gastro-oesophageal reflux and oesophageal dysfunction in children and adolescents with brain damage. Acta Paediatr. 1994;83:1081–5.
20. Kawahara H, Tazuke Y, Soh H, et al. Causal relationship between delayed gastric emptying and gastroesophageal reflux in patients with neurological impairment. Pediatr Surg Int. 2015;31:917–23.
21. Knatten CK, Avitsland TL, Medhus AW, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. J Pediatr Surg. 2013;48:1856–61.
22. Stevenson RD, Conaway M, Chumlea WC, et al. Growth and health in children with moderate-to-severe cerebral palsy. Pediatrics. 2006;118:1010–8.
23. Fukahori S, Asagiri K, Ishii S, et al. Pre and post-operative evaluation of gastroesophageal reflux and esophageal motility in neurologically impaired children using combined pH-multichannel intraluminal impedance measurements. Pediatr Surg Int. 2013;29:545–51.

24. Mauritz FA, van Herwaarden-Lindeboom MY, Stomp W, et al. The effects and efficacy of antireflux surgery in children with gastroesophageal reflux disease: a systematic review. J Gastrointest Surg. 2011;15:1872–8.
25. Spiroglou K, Xinias I, Karatzas N, et al. Gastric emptying in children with cerebral palsy and gastroesophageal reflux. Pediatr Neurol. 2004;31:177–82.
26. Okada T, Sasaki F, Asaka M, et al. Delay of gastric emptying measured by 13C-acetate breath test in neurologically impaired children with gastroesophageal reflux. Eur J Pediatr Surg. 2005;15:77–81.
27. Wenzl TG, Benninga MA, Loots CM, et al. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. J Pediatr Gastroenterol Nutr. 2012;55:230–4.
28. Inge TH, Carmeci C, Ohara LJ, et al. Outcome of Nissen fundoplication using intraoperative manometry in children. J Pediatr Surg. 1998;33:1614–7.
29. Komura M, Kanamori Y, Tanaka Y, et al. Mosapride for gastroesophageal reflux disease in neurologically impaired patients. Pediatr Int. 2016;59(3):347–51.
30. Kawai M, Kawahara H, Hirayama S, et al. Effect of baclofen on emesis and 24-hour esophageal pH in neurologically impaired children with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2004;38:317–23.
31. Erkin G, Culha C, Ozel S, et al. Feeding and gastrointestinal problems in children with cerebral palsy. Int J Rehabil Res. 2010;33:218–24.
32. Waterman ET, Koltai PJ, Downey JC, et al. Swallowing disorders in a population of children with cerebral palsy. Int J Pediatr Otorhinolaryngol. 1992;24:63–71.
33. Benfer KA, Weir KA, Bell KL, et al. Clinical signs suggestive of pharyngeal dysphagia in preschool children with cerebral palsy. Res Dev Disabil. 2015;38:192–201.
34. Vandenplas Y, De Schepper J, Verheyden S, et al. A preliminary report on the efficacy of the Multicare AR-Bed in 3-week-3-month-old infants on regurgitation, associated symptoms and acid reflux. Arch Dis Child. 2010;95:26–30.
35. Loots C, Smits M, Omari T, et al. Effect of lateral positioning on gastroesophageal reflux (GER) and underlying mechanisms in GER disease (GERD) patients and healthy controls. Neurogastroenterol Motil. 2013;25:222–9, e161-2.
36. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
37. Turk H, Hauser B, Brecelj J, et al. Effect of proton pump inhibition on acid, weakly acid and weakly alkaline gastro-esophageal reflux in children. World J Pediatr. 2013;9:36–41.
38. Cheung KM, Tse PW, Ko CH, et al. Clinical efficacy of proton pump inhibitor therapy in neurologically impaired children with gastroesophageal reflux: prospective study. Hong Kong Med J. 2001;7:356–9.
39. Canani RB, Cirillo P, Roggero P, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006;117:e817–20.
40. Safe M, Chan WH, Leach ST, et al. Widespread use of gastric acid inhibitors in infants: are they needed? Are they safe? World J Gastrointest Pharmacol Ther. 2016;7:531–9.
41. Bozkurt M, Tutuncuoglu S, Serdaroglu G, et al. Gastroesophageal reflux in children with cerebral palsy: efficacy of cisapride. J Child Neurol. 2004;19:973–6.
42. Brueton MJ, Clarke GS, Sandhu BK. The effects of cisapride on gastro-oesophageal reflux in children with and without neurological disorders. Dev Med Child Neurol. 1990;32:629–32.
43. Maclennan S, Augood C, Cash-Gibson L, et al. Cisapride treatment for gastro-oesophageal reflux in children. Cochrane Database Syst Rev. 2010;(4):CD002300.
44. Horwood JF, Calvert W, Mullassery D, et al. Simple fundoplication versus additional vagotomy and pyloroplasty in neurologically impaired children–a single centre experience. J Pediatr Surg. 2015;50:275–9.

45. Campanozzi A, Capano G, Miele E, et al. Impact of malnutrition on gastrointestinal disorders and gross motor abilities in children with cerebral palsy. Brain Dev. 2007;29:25–9.
46. Miyazawa R, Tomomasa T, Kaneko H, et al. Effects of pectin liquid on gastroesophageal reflux disease in children with cerebral palsy. BMC Gastroenterol. 2008;8:11.
47. Miele E, Staiano A, Tozzi A, et al. Clinical response to amino acid-based formula in neurologically impaired children with refractory esophagitis. J Pediatr Gastroenterol Nutr. 2002;35:314–9.
48. Khoshoo V, Zembo M, King A, et al. Incidence of gastroesophageal reflux with whey- and casein-based formulas in infants and in children with severe neurological impairment. J Pediatr Gastroenterol Nutr. 1996;22:48–55.
49. Savage K, Kritas S, Schwarzer A, et al. Whey- vs casein-based enteral formula and gastrointestinal function in children with cerebral palsy. JPEN J Parenter Enteral Nutr. 2012;36:118S–23S.
50. Marchand V, Motil KJ, Nutrition NCo. Nutrition support for neurologically impaired children: a clinical report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2006;43:123–35.
51. Friedman JN, Ahmed S, Connolly B, et al. Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children. Pediatrics. 2004;114:458–61.
52. Wales PW, Diamond IR, Dutta S, et al. Fundoplication and gastrostomy versus image-guided gastrojejunal tube for enteral feeding in neurologically impaired children with gastroesophageal reflux. J Pediatr Surg. 2002;37:407–12.
53. Campwala I, Perrone E, Yanni G, et al. Complications of gastrojejunal feeding tubes in children. J Surg Res. 2015;199:67–71.
54. Livingston MH, Shawyer AC, Rosenbaum PL, et al. Fundoplication and gastrostomy versus percutaneous gastrojejunostomy for gastroesophageal reflux in children with neurologic impairment: a systematic review and meta-analysis. J Pediatr Surg. 2015;50:707–14.
55. Srivastava R, Berry JG, Hall M, et al. Reflux related hospital admissions after fundoplication in children with neurological impairment: retrospective cohort study. BMJ. 2009;339:b4411.
56. Srivastava R, Downey EC, O'Gorman M, et al. Impact of fundoplication versus gastrojejunal feeding tubes on mortality and in preventing aspiration pneumonia in young children with neurologic impairment who have gastroesophageal reflux disease. Pediatrics. 2009;123:338–45.
57. Spitz L, McLeod E. Gastroesophageal reflux. Semin Pediatr Surg. 2003;12:237–40.
58. Fukahori S, Yagi M, Ishii S, et al. Laparoscopic Nissen fundoplication mainly reduces the volume of acid reflux and potentially improves mucosal integrity up to the middle esophagus in neurologically impaired children detected by esophageal combined pH-multichannel intraluminal impedance measurements. J Pediatr Surg. 2016;51:1283–7.
59. Miyano G, Yamoto M, Morita K, et al. Laparoscopic Toupet fundoplication for gastroesophageal reflux: a series of 131 neurologically impaired pediatric cases at a single children's hospital. Pediatr Surg Int. 2015;31:925–9.
60. O'Loughlin EV, Somerville H, Shun A, et al. Antireflux surgery in children with neurological impairment: caregiver perceptions and complications. J Pediatr Gastroenterol Nutr. 2013;56:46–50.
61. Kawahara H, Okuyama H, Kubota A, et al. Can laparoscopic antireflux surgery improve the quality of life in children with neurologic and neuromuscular handicaps? J Pediatr Surg. 2004;39:1761–4.
62. Wockenforth R, Gillespie CS, Jaffray B. Survival of children following Nissen fundoplication. Br J Surg. 2011;98(5):680.
63. Pearl RH, Robie DK, Ein SH, et al. Complications of gastroesophageal antireflux surgery in neurologically impaired versus neurologically normal children. J Pediatr Surg. 1990;25:1169–73.
64. Martin K, Deshaies C, Emil S. Outcomes of pediatric laparoscopic fundoplication: a critical review of the literature. Can J Gastroenterol Hepatol. 2014;28:97–102.
65. Ngerncham M, Barnhart DC, Haricharan RN, et al. Risk factors for recurrent gastroesophageal reflux disease after fundoplication in pediatric patients: a case-control study. J Pediatr Surg. 2007;42:1478–85.

66. Toporowska-Kowalska E, Gebora-Kowalska B, Jablonski J, et al. Influence of percutaneous endoscopic gastrostomy on gastro-oesophageal reflux evaluated by multiple intraluminal impedance in children with neurological impairment. Dev Med Child Neurol. 2011;53:938–43.
67. Ponsky TA, Gasior AC, Parry J, et al. Need for subsequent fundoplication after gastrostomy based on patient characteristics. J Surg Res. 2013;179:1–4.
68. Kawahara H, Mitani Y, Nose K, et al. Should fundoplication be added at the time of gastrostomy placement in patients who are neurologically impaired? J Pediatr Surg. 2010;45:2373–6.
69. Kakade M, Coyle D, McDowell DT, et al. Percutaneous endoscopic gastrostomy (PEG) does not worsen vomiting in children. Pediatr Surg Int. 2015;31:557–62.
70. Heuschkel RB, Gottrand F, Devarajan K, et al. ESPGHAN position paper on management of percutaneous endoscopic gastrostomy in children and adolescents. J Pediatr Gastroenterol Nutr. 2015;60:131–41.
71. Gatti C, di Abriola GF, Villa M, et al. Esophagogastric dissociation versus fundoplication: which is best for severely neurologically impaired children? J Pediatr Surg. 2001;36:677–80.
72. Goyal A, Khalil B, Choo K, et al. Esophagogastric dissociation in the neurologically impaired: an alternative to fundoplication? J Pediatr Surg. 2005;40:915–8. discussion 918-9
73. Morabito A, Lall A, Lo Piccolo R, et al. Total esophagogastric dissociation: 10 years' review. J Pediatr Surg. 2006;41:919–22.
74. Peters RT, Goh YL, Veitch JM, et al. Morbidity and mortality in total esophagogastric dissociation: a systematic review. J Pediatr Surg. 2013;48:707–12.
75. Lansdale N, McNiff M, Morecroft J, et al. Long-term and 'patient-reported' outcomes of total esophagogastric dissociation versus laparoscopic fundoplication for gastroesophageal reflux disease in the severely neurodisabled child. J Pediatr Surg. 2015;50:1828–32.
76. Gottrand M, Michaud L, Guimber D, et al. Barrett esophagus and esophagojejunal anastomotic stenosis as complications of esophagogastric disconnection in children with esophageal atresia. J Pediatr Gastroenterol Nutr. 2013;57:93–5.
77. Lall A, Morabito A, Dall'Oglio L, et al. Total oesophagogastric dissociation: experience in 2 centres. J Pediatr Surg. 2006;41:342–6.
78. Madre C, Serhal L, Michaud L, et al. Prolonged enteral feeding is often required to avoid long-term nutritional and metabolic complications after esophagogastric dissociation. J Pediatr Gastroenterol Nutr. 2010;50:280–6.

GERD and Dysphagia

10

Nathalie Rommel and Gigi Veereman

Abstract

Dysphagia describes any type of difficulty with feeding and swallowing and was recently classified by the World Health Organization in the International Statistical Classification of Diseases and Related Health Problems (ICD). However, there is no specific pediatric definition. Dysphagia has age-specific presentations in children: in the youngest it manifests itself by food refusal, whereas older children are able to describe their swallowing difficulties. Gastroesophageal reflux disease (GERD) was demonstrated in 53% of young children with feeding difficulties and should always be excluded or treated appropriately when documented. Advanced manometry techniques have revealed causes of dysphagia other than GERD. Oropharyngeal or esophageal dysfunction can now be demonstrated even in infants and young children. Understanding the underlying physiopathology of dysphagia leads to targeted treatment.

Keywords

Dysphagia • Gastroesophageal reflux • Children

This chapter aims at guiding the clinician to identify the symptoms and underlying pathophysiology of dysphagia in infants and children with GERD.

N. Rommel
Department of Neurosciences, Experimental Otorhinologyngology, Deglutology, University of Leuven, Leuven, Belgium

Department of Gastroenterology, Neurogastroenterology, and Motility, University Hospitals Leuven, Leuven, Belgium

G. Veereman (✉)
Pediatric Gastroenterology and Nutrition, UZ Brussels, Free University Brussels, Brussels, Belgium
e-mail: gveereman@gmail.com

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_10

Abbreviations

EGJ	Esophagogastric junction
GERD	Gastroesophageal reflux disease
HRM	High-resolution manometry
ICD	International Classification of Diseases
UES	Upper esophageal sphincter

Defining Dysphagia

In clinical practice, the term "dysphagia" is used to describe any type of difficulty with feeding and swallowing. Dysphagia is very common in the pediatric population within a wide range of disorders and hinders the provision of adequate nutrition, affecting growth and development [1, 2]. Dysphagia has recently been specifically classified by the World Health Organization in the International Statistical Classification of Diseases and Related Health Problems (ICD), 787.2 in ICD-9 and R13.10 in ICD-10 [3]. There is no specific pediatric definition given. Through this classification scheme, dysphagia is approached as a specific clinical entity and thereby includes dysphagia as a defined pathology rather than as comorbidity to other medical pathology. Nevertheless, dysphagia is frequently seen in children with neurological disorders, developmental abnormalities, and congenital anatomical defects.

This chapter will focus on the link between GERD and dysphagia in typically developing children, with "dysphagia" referring to both abnormal oropharyngeal and esophageal function.

Clinical Presentation of Dysphagia Differs According to Age

Food Refusal

Whereas older children can clearly describe the difficulty they experience to swallow food or liquids, infants and toddlers express their distress by crying and food refusal. It is distressing to parents when their infants refuse to feed. Depending on the duration of the symptoms, failure to gain adequate weight may ensue. It is of utmost importance that the physician obtains a clear description of what exactly happens during the feeding: does the infant regurgitate, take the bottle, and cry afterward or show distress from the moment it has "to swallow."

The best option is to observe a feeding during the consultation, possibly together with a feeding therapist. Nowadays parents often videotape the feeding at home on their smartphone and bring it to the consultation. "A picture is worth a thousand words," and the physician should then record observations in the medical records.

Difficult Swallow

Older children, at least from six years onward, can clearly describe the difficulty they experience to swallow food or liquids. They describe that food "gets stuck" in their throat and experience the sensation usually with non-solvable solids such as meat. The physician should take a careful history, finding out when the experience occurs and with what type of food, knowing that solids are more difficult to swallow than liquids. It is important to discriminate between regurgitation, heartburn, or pyrosis and difficult swallowing or dysphagia. Pain does not need to be present for a diagnosis of dysphagia. Painful swallowing is defined as odynophagia.

These symptoms can occur in different circumstances, at first presentation, after GERD treatment, e.g., Nissen fundoplication or in combination with other pathologies (e.g., neurological or cardiac disease).

GERD and Dysphagia

In 2003, we published a prospective cohort of 700 young children with feeding difficulties in which food refusal linked to GERD was documented in 53% [2]. It was also demonstrated that appropriate treatment led to the resolution of the symptoms in 73% of the entire cohort [2]. Therefore, it was concluded that a workup for GERD should be an integral part of the first-line assessment of a child with food refusal or dysphagia.

Despite this being current practice, we failed to identify any additional studies or systematic review on the relationship between dysphagia or food refusal as presenting symptom and GERD in pediatrics.

Most available pediatric literature linking GERD and dysphagia focuses on dysphagia after Nissen fundoplication. Typical symptoms of post-Nissen dysphagia are early satiety, inability to eat semisolid and solid bolus consistencies, food obstruction in the esophagus, or retrosternal pain, gagging, and excessive salivation. It is generally accepted that esophageal manometry testing is required to rule out esophagogastric outflow obstruction as well as to determine the esophageal peristaltic reserve which reflects the ability to clear esophageal content as well as to overcome the surgically increased esophagogastric barrier. An esophageal outflow obstruction can be present immediately postsurgery due to inappropriate tightness of the wrap or can occur later due to altered tonus in the EGJ, herniation, or fibrosis. Irrespective of the timing when the post-Nissen dysphagia occurs, in case an esophagogastric outflow obstruction is documented, intervention is needed. Treatment options are pneumatic dilatation or in case of failure partially or completely undo of the wrap.

Bolus obstruction in the mid-distal esophagus leading to dysphagia can be secondary to inadequate motor function of the esophageal body or due to increased or

incomplete deglutitive relaxation of the esophagogastric junction including the lower esophageal sphincter and the diaphragmatic crura. In case of dysphagia, both aspects of esophageal function can occur jointly or separately. In case the esophageal motor function is inadequate, intervention at the level of the wrap is not going to solve the dysphagia symptoms. Therefore, it is essential to perform esophageal function testing before the surgery as dysphagia could be induced in patient with ineffective esophageal motility due to the resistance to bolus flow that is inherent to a Nissen or Toupet fundoplication.

Non-GERD Causes of Dysphagia

Despite the fact that many of the pediatric patients referred for dysphagia with suggestive symptoms have underlying GERD, not all dysphagia or food refusal is associated with GERD. Dysphagia in infants and young children can be the consequence of either oropharyngeal or esophageal dysfunction or a combination of both.

In typically developing children, oropharyngeal dysphagia, defined as difficulty to manipulate food throughout the oral cavity, can either be anatomical, inflammatory, or motor or sensory based. Besides well-described anatomical abnormalities such as cleft palate and micrognathia, inflammatory lesions such as oral candida, herpes, or allergic reactions can interfere with oral intake. Medical or nutritional treatment will in that case mostly lead to resolution of the food refusal.

Oral motor abnormalities are defined as the inadequate function of tongue, jaw, lips, and palate in relation to sucking, chewing, and drinking. Oral sensory-based feeding difficulties present as a hyperresponsiveness to tactile stimulation and increased bolus consistencies. This includes gagging, food refusal, collecting bolus in the buccal cheek, etc. In case these symptoms of oral hyperresponsiveness occur, any other pharyngeal or esophageal motor dysfunction has to be ruled out before starting further oral treatment. Clinical practice has revealed that detection and appropriate treatment of these potentially related dysfunctions often resolve symptoms initially read as oral hyperresponsiveness or oral aversion. Nevertheless, some of the patients with a severe oral aversion secondary to needed, but invasive medical oropharyngeal interventions such as long-term intubation for ventilation or nasogastric tube feeding, need specific and systematic oral therapy to decrease their oral aversive symptoms.

Pharyngeal dysphagia in infants and children relates to the lack of safe and effective bolus transport into the esophagus. Safe oropharyngeal transport is dependent on closure of the true vocal folds. Inadequate closure of the infant airway can lead to aspiration before, during, and after the swallow. Effective bolus transport depends on adequate nasopharyngeal closure, pharyngeal contractility, and UES opening

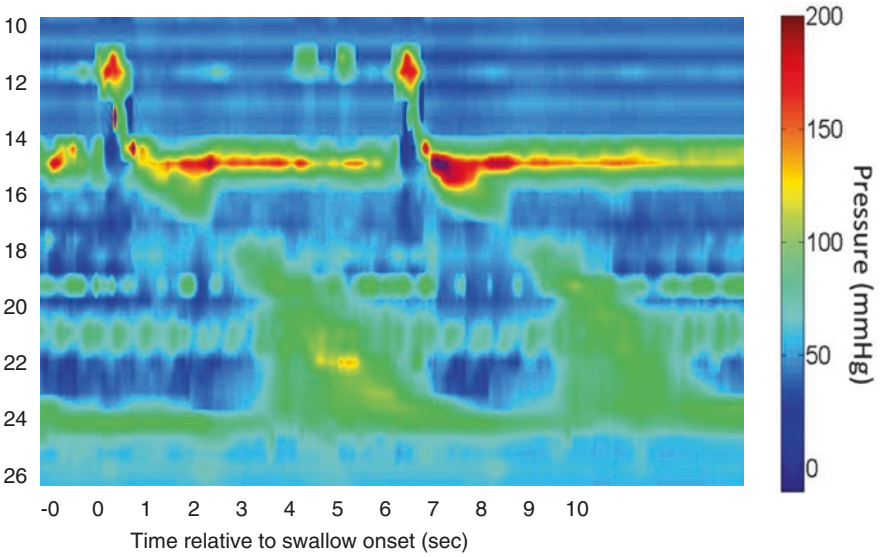


Fig. 10.1 Esophageal high-resolution manometry (HRM) color plot of a semisolid swallow in a 6-year-old boy with GERD referred for pre-Nissen fundoplication manometric evaluation because of frequent vomiting and regurgitation on semisolids and solids during and after a mealtime. Pressures are indicated according to color code illustrated. This child presented with symptoms of dysphagia on semisolid and solids leading to early satiety and insufficient oral intake. HRM showed adequate contractility of the esophageal body combined with inadequate deglutitive relaxation of the esophagogastric junction (EGJ). Increased pressurization in distal esophagus indicates increased resistance to bolus flow. This manometric signature corresponds with the diagnosis of EGJ outflow obstruction according to the Chicago Classification of Esophageal Motility Disorders [6]. This case illustrates that the GERD symptom of regurgitation can occur on residue in the esophageal body due to esophagogastric outflow obstruction and can be confused with regurgitation or backflow of gastric content due to a hypotonic EGJ. Therefore, a mealtime-related or three-type bolus (liquids, semisolids, and solids) manometric evaluation is warranted to differentiate the pathophysiology of the event of 'regurgitation'. Patient was treated with Savary dilatation, and a Nissen fundoplication was no longer recommended

and their timing. Ineffective pharyngeal transport results in bolus residue and potentially obstruction with potential respiratory compromise.

Esophageal dysphagia in relation to GERD can either be obstructive or non-obstructive. Patients with GERD can, for example, present with obstructive dysphagia in case of excessive tightness of a Nissen fundoplication. Two examples are illustrated in Figs. 10.1 and 10.2. Non-obstructive dysphagia is defined as dysphagia not related to a mechanical obstruction and has been described in patients with eosinophilic esophagitis [4] and other forms of esophageal inflammation leading to dysmotility. The two most commonly described esophageal motor patterns in patients with GERD are distal esophageal spasm and ineffective esophageal motility [5].

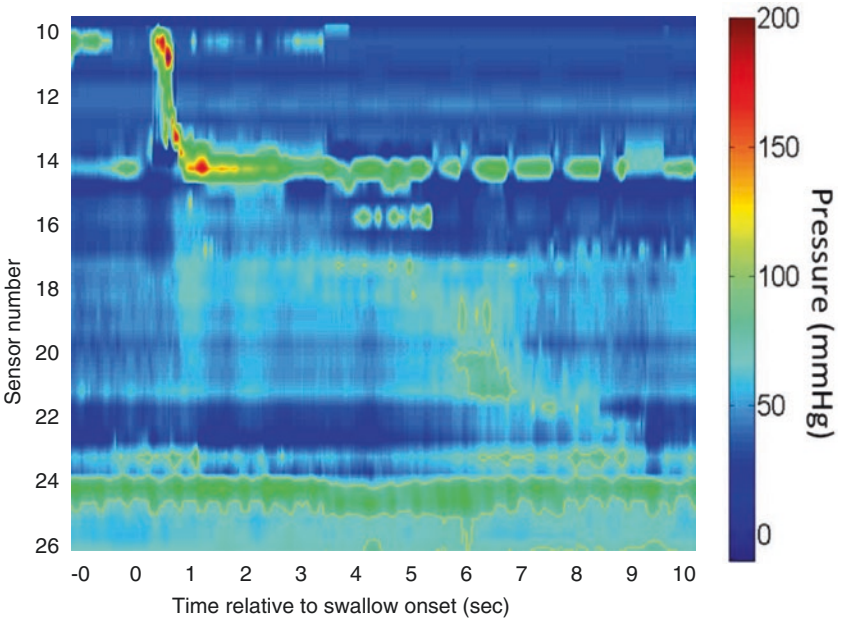


Fig. 10.2 HRM color plot of a solid bread swallow in a 12-year-old child. Pressures are indicated according to color code illustrated. This boy was referred because of severe post-Nissen dysphagia on liquids, semisolids, and solids. Manometry shows ineffective esophageal motility and non-relaxing EGJ esophagogastric junction. Due to the weak esophageal contractions, no increased pressurization in the mid-distal esophagus is observed despite bolus residue on impedance confirmed by the clinical perception of the child. This manometric trace corresponds to the diagnosis of EGJ outflow obstruction according to the Chicago Classification of Esophageal Motility Disorders [6]. In this case the outflow obstruction is mechanical secondary to a tight Nissen fundoplication. Treatment with EGJ Savary dilatation improved the symptoms of dysphagia of this patient markedly

Treatment

If treating GERD is not indicated based on the workup, alternatives should be explored. Targeted treatment can be attempted when an underlying dysfunction has been demonstrated. Such has been the case in our practices with young children presenting with dysphagia and EGJ outflow obstruction. Dilatation or injections of the LES with Botox (25 E per quadrant) resulted in resolution of the obstruction.

References

1. Estrem HH, Pados BF, Park J, Knafl KA, Thoyre SM. Feeding problems in infancy and early childhood: evolutionary concept analysis. J Adv Nurs. 2017;73(1):56–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27601073
2. Rommel N, De Meyer A-M, Feenstra L, Veereman-Wauters G. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. J Pediatr Gastroenterol Nutr. 2003;37(1):75–84.

3. Clavé P, Shaker R. Dysphagia: current reality and scope of the problem. Nat Rev Gastroenterol Hepatol. 2015;12(5):259–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25850008
4. Roman S, Hirano I, Kwiatek MA, Gonsalves N, Chen J, Kahrilas PJ, et al. Manometric features of eosinophilic esophagitis in esophageal pressure topography. Neurogastroenterol Motil. 2011;23(3):208–e111. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3036777&tool=pmcentrez&rendertype=abstract
5. Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying esophageal peristalsis with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol. 2006;290(5):G988–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16410365
6. Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJPM, et al. The Chicago classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27(2):160–74. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4308501&tool=pmcentrez&rendertype=abstract

Gastroesophageal Reflux and Esophageal Atresia

11

Frederic Gottrand, Madeleine Gottrand, Rony Sfeir, and Laurent Michaud

Abstract

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is one of the most common digestive malformations. Although mortality decreased dramatically to less than 10%, 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 gastroesophageal reflux (GER) and its complications, as anastomotic strictures, esophagitis, failure to thrive, and Barrett's esophagus. Concerns in adults include esophageal adenocarcinoma and epidermoid carcinoma which have been recently been reported. Although there was a lack of recommendation, a recent guideline for the management of GI complications has been published to help formulate clinical practice guidelines for the care of EA patients. It is recommended that GER be treated with PPI in all EA patients in the neonatal period up to the first year of life or longer depending on persistence of GER. Endoscopy with biopsies is mandatory for routine monitoring of GERD in patients with EA. All EA patients (including asymptomatics) should undergo monitoring of GER (impedance/pH-metry, and/or endoscopy) at time of discontinuation of antiacid 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, one at transition to adulthood). Patients with EA need a systematic follow-up with a multidisciplinary team.

F. Gottrand (✉) • M. Gottrand • R. Sfeir • L. Michaud
National Reference Center for Congenital Malformation of the Esophagus,
Department of Pediatrics, CHU Lille, Univ. Lille, F-59000 Lille, France
e-mail: frederic.gottrand@chru-lille.fr; madgotte@hotmail.com; rony.sfeir@chru-lille.fr; laurent.michaud@chru-lille.fr

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_11

Introduction

EA is one of the most common digestive malformations occurring in 1 in 2400–4500 births worldwide [1], and the life birth prevalence is 1.8 per 10,000 births in France [2]. 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 [3–5]. EA is no more just a neonatal surgical problem but a lifelong problem. Other than respiratory problems, nutritional and GI issues are prevalent not only in the first years of life but also in adolescence and adulthood. Gastroesophageal reflux (GER), peptic esophagitis, gastric metaplasia and Barrett's esophagus, anastomotic strictures, feeding disorders, dysphagia, and esophageal dysmotility 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 been recently reported [4].

A recent guideline for the management of GI complications has been published by ESPGHAN/NASPGHAN and the International Network on Esophageal Atresia to help formulate clinical practice guidelines for the care of these patients [6]. Statements (all expert opinions) concerning GER are reported in gray boxes at the end of each chapter when appropriate.

Why Is GER a Concern in Patients with EA?

Patients with EA are at major risk of presenting GER [7]. Several factors contribute to the physiopathology of GER in EA (Table 11.1).

In EA patients, GER is the most frequent digestive complication with a reported prevalence in literature ranging between 22 and 63%, especially in infants and children with isolated EA in whom GER is reported in almost all patients [20] (Table 11.2).

Table 11.1 Potential mechanisms of GER 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 cardioesophageal junction	[8, 9]
Abnormal esophageal motility	– Reduction of esophageal clearance – Longer acid and bolus clearing times – Transient lower esophageal sphincter relaxation	[10–12]
Slow gastric emptying (controversial)	– Congenital – Surgically induced vagal nerve injury	[7, 13–15]
Abnormal gastric myoelectrical activity (minor role)	– Disturbed neuromuscular function – Antral hypomotility	[14, 16, 17]
Gastrostomy as an aggravating role (controversial)	– Gastrostomy can worsen GER – Long-gap EA worsens GER – Long-gap EA often necessitates gastrostomy (selection bias)	[18, 19]

Table 11.2 Prevalence of GER, esophagitis, and antireflux surgery in EA patients

Authors	Number	Age at evaluation	Prevalence of GER	Diagnosis of GER	Prevalence of esophagitis	Prevalence of antireflux surgery
Curci and Dibbins [21]	36	NA	NA	NA	NA	45%
Montgomery and Frenckner [22]	110	NA	30%	Barium study	NA	8%
Engum et al. [23]	227	1 month–22 years (mean: 6)	58%	NA	NA	44%
Chetcuti et al. [24]	125	>18 years	46% (11% > one episode a week)	Clinical signs (heartburn)	NA	NA
Somppi et al. [25]	42	3–30 years (mean: 12.6)	22%	pH-metry	6% 51% (histo)	8%
Krug et al. [26]	39	18–26 years	33%	Clinical score	23%	NA
Bergmeijer et al. [27]	125	NA	NA	NA	NA	23%
Yanchar et al. [8]	90 excluding type A	NA	46%	NA	NA	33%
Deurloo et al. [28]	371	1–54 years	40%	pH-metry	NA	23%
Deurloo et al. [29]	40	28–45 years (mean: 34)	52%	Heartburn Retrosternal pain	9% (90% histo)	2.5%
Koivusalo et al. [30]	50	2.5–95 months (mean: 9.2)	20%	pH-metry	26%	24%
Konkin et al. [31]	144	Postoperative period	31%	NA	NA	12%
Taylor et al. [32]	132	20–48 years (mean: 33)	63%	Symptoms	58% (histo)	11%
Koivusalo et al. [33]	61 type C	1–10 years (median 5 years)	46%	Fundoplication or pH-metry or endoscopy	NA	30%

(continued)

Table 11.2 (continued)

Authors	Number	Age at evaluation	Prevalence of GER	Diagnosis of GER	Prevalence of esophagitis	Prevalence of antireflux surgery
Castilloux et al. [5]	134	0.3–16 years (mean: 5)	<1 year 34% >1 year 43%	Severe GER: moderate to severe esophagitis on biopsy and/or intestinal metaplasia on esophageal biopsies and/or need of fundoplication and/or need of jejunal feeding	NA	NA
Castilloux et al. [34]	45	0.5–18 years (median: 7.3)	20% 13%	Regurgitation Pyrosis	31% (histo)	44%
Sistonen et al. [35]	101	21–56 months (mean: 36)	34%	Clinical symptoms	8% (25% histo)	10%
Catalano et al. [12]	22	3–40 months (median: 15)	45.5% (acidic)	Impedance-pH-metry	NA	0%
Legrand et al. [36]	81 type C	9.5–18.5 years (mean: 13.3)	35%	Heartburn/regurgitation and/or pH-metry, endoscopy	NA	39%
Pedersen et al. [37]	59	5–15 years (mean: 10.2)	56% 55%	Clinical symptoms pH-metry	49% (44% histo)	NA
Shah et al. [19]	110	6±3.5 years	39%	Symptoms ± pH-impedancemetry ± endoscopy	40% histo	17%
Bouguermouh and Salem [38]	45	3 months–10 years	49%	NA	NA	18%

NA not available

Table 11.3 Complications of GER 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	3 cases reported

GER is associated with complications in neonates and infants operated on for EA (Table 11.3). Noncontrolled studies suggest that GER is a major factor for recurrent anastomotic stricture [28, 39, 40]. Starting a routine screening of GER in infancy and an aggressive treatment of GER (including antireflux surgery), Deurloo et al. observed a dramatic fall in the number of patients requiring multiple dilations of an anastomotic stricture (10 to 2%) [28].

Pulmonary complications associated with GER are persistent atelectasis, aspiration pneumonia, asthma/increased airway reactivity, chronic lung disease with bronchiectasis, and worsened tracheomalacia [28, 39]. Airway obstruction and/or acute life-threatening episodes (ALTE) can result from either proximal GER reaching the larynx or GER in the lower esophagus that could be reflexively responsible for respiratory symptoms [41].

What Is the Natural History of GER in EA Patients?

There are few longitudinal studies about natural history of GER in EA population, and the risk of recurrence has not been assessed. GER seems to be particularly frequent during the first months of age, especially within the first 5 years in type C EA patients (Table 11.2). Koivusalo assessed longitudinally GER with pH-metry and histology in 61 children and showed that the prevalence of GER increased gradually from 16% at age 6 months to 51% at age of 5 years, while 44% of children still have GER at the age of 10 years [33]. After 3 years of age, new cases of GER are rare and most of the patients presenting GER are symptomatic [33].

How Should GER Be Diagnosed in EA Patients (Table 11.4)?

Although 24-hour pH monitoring quantifies the esophageal acid burden, which is highly correlated with peptic esophagitis, the main use of pH-impedance monitoring is not to diagnose pathologic reflux but rather to try to correlate extra-esophageal symptoms with reflux events. Although specific norms are not available in EA patients, a pH-metry study including 13 EA infants aged 12 weeks, with an uneventful

Table 11.4 Recommendations related to GER in EA patients (from [6])

Statements
It is recommended that GER be treated with acid suppression in all EA patients in the neonatal period
PPIs should be the first-line therapy for GER/GERD
It is recommended that GER be systematically treated for prevention of peptic complications and anastomotic stricture up to the first year of life or longer depending on persistence of GER
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, GER 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 asymptomatics) should undergo monitoring of GER (impedance/pH-metry, and/or endoscopy) at time of discontinuation of antiacid 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, 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 increase 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 presence of dysphagia, GER, 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

follow-up and no clinical sign of GER, showed a mean reflux index of 4.08% (range, 1–9.8%; median, 3.3%), 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) [42]. These figures are very similar to those found in normal infants from the same age by Vandenplas and Sacre-Smits [43]. One of the limitations of pH-impedance 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 [44] with a high risk of underreporting of reflux. Experience with pH-impedancemetry is increasing in patients with EA showing that reflux events are equally as likely to be due to nonacid reflux as acid reflux in these patients [11, 12, 19, 37, 44]. Since there are currently no medications which are effective in treating nonacid reflux, there is no practical therapeutic consequence of demonstrating nonacid reflux in EA patients except consideration for fundoplication.

Esophagitis is very frequent in EA patients (Table 11.2). Multilevel esophageal biopsies are recommended for screening for peptic and eosinophilic esophagitis. The number of biopsies should be increased in the presence of macroscopic abnormalities or for screening for Barrett's esophagus (at least four biopsies in each quadrant 1 cm above the Z line). Endoscopy is also useful in children post-fundoplication since the recurrence of GER and peptic esophagitis is possible [20, 45, 46].

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, GER symptoms with normal pH probe and endoscopy).

Endoscopy with biopsies is mandatory for routine monitoring of GERD in patients with EA.

How Should GER Be Treated in EA Patients?

A recent systematic review addressed the management of GERD in EA [47]. 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 number of dose.

There are no efficient prokinetic drugs currently available; moreover, there are 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 + alginate and suggest a nonsignificant reduction of mean index reflux from 3.8 to 1.47% after 6 weeks of treatment [48]. Intrinsic abnormal motility of the esophagus is a constant feature in EA where prokinetics should not be as efficient as in a normal

child [49]. 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 GER, only reduce the regurgitations (although not studied specifically in EA patients), and therefore are not recommended in EA patients for the treatment of GER.

Positioning has not been studied in EA patients and therefore 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 GER in patients with EA. Although the quality of literature regarding the use of antireflux medication in children with EA is extremely poor [47], medical management of GER with proton pump inhibitors (PPIs) and H2 receptor antagonists has been reported to be successful by reducing GI and/or respiratory symptoms or by achieving demonstrable weight gain [47]. 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 11.4).

PPIs should be the first-line therapy for GER/GERD.

Should GER Systematically Be Treated in All EA Patients?

Although there are currently no controlled studies on the benefit of systematic acid suppression in EA patients, due to the high prevalence of GER in this cohort and the potential for GER-associated complications, the panel recommended that GER should be systematically treated with acid suppression in all EA patients starting in the neonatal period (Table 11.4). A recent study comparing infants receiving PPI for the first 12 months compared to a historical cohort of EA infant treated systematically for only 3 months showed no difference in the incidence of anastomotic stricture, but when needed initial balloon dilation procedures were performed later in infants who were treated longer [50]. However, 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 GI and respiratory infections have recently been highlighted.

It is recommended that GER be treated with acid suppression in all EA patients in the neonatal period.

How Long Should GER 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. GER is very common during infancy but can persist long term (Table 11.2). Complications due to GER 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 on. A recent study showed that GERD tended to be more prevalent after 1 year of age (43%) compared to before (34%), and significant complications could develop after 1 year of age even in children who were previously asymptomatic [5]. GERD is one of the factors contributing to failure to thrive in infancy [36]. The prevalence of peptic esophagitis is high throughout childhood and adulthood (Table 11.2). Barrett's esophagus is a long-term complication of EA [20, 51]. GERD also contributes to dysphagia in EA patients [39] and can negatively influence quality of life [36, 52]. GER remains frequent in EA children after the age of 2 years, even in asymptomatic patients, and can persist lifelong (Table 11.2). 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.

It is recommended that GER be systematically treated for prevention of peptic complications and anastomotic stricture up to the first year of life or longer, depending on persistence of GERD.

All EA patients (including asymptomatic patients) should undergo monitoring of GER (impedance/pH-metry, and/or endoscopy) at time of discontinuation of antiacid 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 EA patients. However, GER can be asymptomatic, and several studies have shown the absence of correlation between symptoms and esophagitis in this population [19, 26, 29, 33–35] (Table 11.4). Esophageal mucosal abnormalities can be observed in up to 35% of EA patients at endoscopy despite the absence of symptoms [34, 35] making the recommendation of endoscopic assessment based solely on symptomatology inappropriate. A retrospective study analyzed the results of esophageal biopsies performed during routine esophagoscopy in 72 EA children (all grade C or D) followed up from 6 months to 19 years (mean 10 years) [53]. 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 "good" biopsies was very low [53]. 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 [54]), esogastric 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 an endoscopy is performed and even macroscopically normal, at least four biopsies, in quadrant, one centimeter above the Z line, and one biopsy in the middle part of the esophagus, are recommended for Barrett's and eosinophilic esophagitis screening. The number of biopsies should be increased in presence of macroscopic abnormalities. In children who underwent a fundoplication (see below), repeated systematic endoscopy is recommended, as recurrence of GER and peptic esophagitis or Barrett is possible for these patients [20, 45, 46].

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 years, and one at transition to adulthood).

When Do We Perform Fundoplication in EA Patients with GER?

There is no controlled trial on the role of surgical management of GER in patients with EA. Cumulative risk of having a fundoplication performed in children with EA ranges from 0 to 45% (Table 11.2). In long-gap EA, GER is particularly frequent and severe and leads to a high risk of anastomotic stricture, suggesting that fundoplication should be considered in a large proportion of these children [27, 55, 56]. In patients with EA who have poor motility and esophageal clearance, fundoplication may worsen esophageal stasis by preventing gravity-driven esophageal clearance which may, in turn, worsen respiratory symptoms, so the decision to proceed with fundoplication for respiratory symptoms alone should be made with caution.

In a recent systematic review on the management of GER in EA patients, reasons stated for the need for antireflux surgery included failure of maximum conservative therapy for GER, failure to thrive, acute life-threatening event, esophagitis, and a recurrent anastomotic stenosis [30]. Timing of fundoplication varies from a center to another but is often performed during infancy. In one series, 92% of the Nissen fundoplication were performed between 1 and 24 months after the atresia repair (median, 4 months) [27]. However, performing fundoplication early in life exposes to a higher risk of failure. In a recent series of 360 children who underwent Nissen fundoplication (including 50 EA patients), age at surgery was negatively associated with Nissen failure [57].

The failure rate of fundoplication is high in this population varying from 6 to 47% [27]. 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) [57]. A redo Nissen was required in 29% of patients within 16 months after the first one in a population of

long-gap EA [55]. In a series of 148 children receiving fundoplication (87 had EA), the recurrence rate was 16.1% in the children with EA and 6.5% in the other cases [46]. In another study, failure rate of partial fundoplication (15%) was significantly higher than that (4.2%) in non EA-TEF patients. The presence of gastrostomy and long-gap or prior myotomy differed significantly in children with fundoplication failure compared to those with successful fundoplication suggesting that short esophagus and esophageal dysmotility might have contributed to this [56].

Severe esophageal dysmotility predisposes EA patients to post-fundoplication complications. However, EA patients may benefit from fundoplication in:

- Recurrent anastomotic strictures, especially in long-gap EA
- Poorly controlled GERD despite maximal PPI therapy
- Long-term dependency on transpyloric feeding
- Dying spells

What Evaluations Should Be Performed Prior to Fundoplication?

The preoperative evaluation should include reflux testing (24-hour pH-metry or pH-MII testing), upper gastrointestinal series, and endoscopy [58] (Table 11.4). pH-metry is required to confirm and quantify acid reflux; barium contrast study allows the diagnosis of hiatal hernia, associated congenital stenosis, the assessment of the anatomy of the cardiac region, and exclusion of other intestinal malformations. Endoscopy is required because it allows macroscopic evaluation and biopsies of the esophageal mucosa, for screening for peptic esophagitis and eosinophilic esophagitis or Barrett's esophagus. To date, esophageal manometry, pH-metry, and pH-impedancemetry have not been shown to be predictive for determining the risk of postoperative dysphagia [59, 60]. There is currently no data on the predictive value of high-resolution esophageal manometry for the occurrence of post-fundoplication complications in EA patients.

Barium contrast study, endoscopy with biopsies, and pH-metry should at least be performed prior to fundoplication.

Are There Extra-esophageal Manifestations of Reflux in EA Patients?

Extra-esophageal symptoms are common in children and adults with EA, and these symptoms are associated with significant morbidity, especially in childhood [5, 24, 38, 39, 61–64]. Up to 40% of patients have respiratory symptoms which include tracheomalacia [34, 39], cough [36, 62, 63], wheezing [62, 63], dyspnea [36],

bronchitis [24, 36, 62], recurrent infections [38, 65], bronchiectasis [39], and pneumonia [24, 62], resulting in restrictive lung disease [36, 39] and/or obstructive lung disease [36, 39]; on top of GER, the gastrointestinal causes of pulmonary symptoms are variable and include aspiration due to mucus or food retention in the proximal pouch or distal esophagus, anastomotic stricture, impaired esophageal motility, congenital esophageal stenosis, aspiration during swallowing, recurrent or missed fistulae, eosinophilic esophagitis, and esophageal pooling over a fundoplication.

There are no studies which systematically evaluate respiratory symptoms in children to determine the frequency of GER for pulmonary symptoms. There are also no studies to determine the impact of dysmotility, independently of reflux, on respiratory symptoms.

Symptoms of aspiration during swallowing may be identical to GER symptoms in young children.

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.

What Are the Long-Term GERD Morbidities of EA in Adulthood?

In adult EA patients, ongoing 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 living with a degree of dysphagia and reflux symptoms and often do not consider them problematic enough to seek medical attention. This can result in suboptimal management of GER. Up to six case series reported GI symptoms in adult patients older than 18 years [24, 32, 51, 66, 67]. The prevalence of symptomatic GER is significantly higher among the patients than among controls (34% vs. 8%), as reported by Sistonen [51]. Taylor et al. found that GER symptoms were reported by 63% of subjects, and 25% of these had severe reflux symptoms, defined as occurring at least 3 days per week [32].

Sistonen et al. describe 101 patients with their native esophagus who systematically underwent upper GI endoscopy. GER symptoms and dysphagia were equally common in individuals with normal histology, histological esophagitis, or epithelial metaplasia [51]. Overall, endoscopic esophagitis was reported in 8–58%, histological esophagitis in 24–90%, and macroscopic Barrett's esophagus 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 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 development of epithelial metaplasia. A recent multicenter prospective study included 120 EA patients aged 15–19 years who underwent an upper endoscopy with multistaged esophageal biopsies.

Barrett was suspected after endoscopy in 37% and was confirmed by histology for 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 dilation ($P = 0.04$), and histological esophagitis ($P = 0.02$) [68].

Eight case reports of esophageal cancer (three adenocarcinoma [69–71], five squamous cell carcinoma [29, 32, 72, 73]) occurring between 20 and 46 years have so far been reported. One cohort study in Finland showed that the relative risk of esophageal cancer in adults operated for EA was lower than the calculated 500-fold higher risk when compared with the normal control population [74]. A retrospective review of the EA database from the Royal Children's Hospital in Melbourne (798 patients [309 patients older than 40 years]) was performed to identify cases of esophageal cancer developing in this cohort. At the time of the publication, 4 of 309 patients had developed esophageal squamous cell carcinoma, over the age of 40 years. The cumulative incidence of esophageal squamous cell carcinoma in this age group was 50 times that expected in the general population [73]. There is no adequately powered study which measures the risk of developing cancer in adults with EA. Mitomycin, usually classified as an alkylating agent, which is used to promote anastomotic dilations and prevent strictures, may be an additional long-term risk factor, and patients who have been treated with it warrant additional specific surveillance.

There is no study reporting the benefit of a systematic surveillance in adults with EA. However, since early treatment can prevent the development of esophageal malignancy, endoscopic surveillance should be performed (Table 11.4): (1) systematically every 5–10 years, (2) if a new esophageal symptom occurs, and (3) if regular symptoms (such as dysphagia) worsen.

Early evidence of squamous cell carcinoma and adenocarcinoma of the esophagus are generally small, subtle mucosal abnormalities. Therefore, to optimize detection rates, advanced mucosal imaging techniques should be used. Acetic acid staining is a cheap and sensitive technique to accentuate the squamocolumnar junction. Chromoendoscopy with Lugol's iodine sprayed onto the mucosal surface improves visualization of subtle squamous dysplasia from the surrounding normal mucosa because the iodine is not taken up by the dysplastic mucosa. Narrowband imaging has also been described for detection of early squamous cell carcinoma. In case of endoscopic Barrett's esophagus, four-quadrant biopsies should be taken at every centimeter.

Symptoms of GER continue into adulthood in EA patients and are more frequent in EA survivors than in the general population.

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 increase 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 presence of dysphagia, GER, 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

References

1. Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology. J Med Genet. 2006;43(7):545–54.
2. Sfeir R, Bonnard A, Khen-Dunlop N, Auber F, Gelas T, Michaud L, Podevin G, Breton A, Fouquet V, Piolat C, Lemelle JL, Petit T, Lavrand F, Becmeur F, Polimerol ML, Michel JL, Elbaz F, Habonimana E, Allal H, Lopez E, Lardy H, Morineau M, Pelatan C, Merrot T, Delagausie P, de Vries P, Levard G, Buisson P, Sapin E, Jaby O, Borderon C, Weil D, Gueiss S, Aubert D, Echaieb A, Fourcade L, Breaud J, Laplace C, Pouzac M, Duhamel A, Gottrand F. Esophageal atresia: data from a national cohort. J Pediatr Surg. 2013;48(8):1664–9.
3. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest. 2004;126(3):915–25.
4. Rintala RJ, Pakarinen MP. Long-term outcome of esophageal anastomosis. Eur J Pediatr Surg. 2013;23(3):219–25.
5. Castilloux J, Noble AJ, Faure C. Risk factors for short- and long-term morbidity in children with esophageal atresia. J Pediatr. 2010;156(5):755–60.
6. Krishnan U, Mousa H, Dall'Oglio L, Homaira N, Rosen R, Faure C, Gottrand F. ESPGHAN-NASPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with esophageal atresia-tracheoesophageal fistula. J Pediatr Gastroenterol Nutr. 2016;63(5):550–70.

7. Jolley SG, et al. Patterns of gastroesophageal reflux in children following repair of esophageal atresia and distal tracheoesophageal fistula. J Pediatr Surg. 1980;15:857–62.
8. Yanchar NL, Gordon R, Cooper M, Dunlap H, Soucy P. Significance of the clinical course and early upper gastrointestinal studies in predicting complications associated with repair of esophageal atresia. J Pediatr Surg. 2001;36:815–22.
9. Montedonico S, Diez-Pardo JA, Possögel AK, Tovar JA. Effects of esophageal shortening on the gastroesophageal barrier: an experimental study on the causes of reflux in esophageal atresia. J Pediatr Surg. 1999;34:300–3.
10. Kawahara H, et al. Lack of distal esophageal contractions is a key determinant of gastroesophageal reflux disease after repair of esophageal atresia. J Pediatr Surg. 2007;42:2017–21.
11. van Wijk M, Knüppe F, Omari T, de Jong J, Benninga M. Evaluation of gastroesophageal function and mechanisms underlying gastroesophageal reflux in infants and adults born with esophageal atresia. J Pediatr Surg. 2013;48:2496–505.
12. Catalano P, Di Pace MR, Caruso AM, Casuccio A, De Grazia E. Gastroesophageal reflux in young children treated for esophageal atresia: evaluation with pH-multichannel intraluminal impedance. J Pediatr Gastroenterol Nutr. 2011;52:686–90.
13. Lopes MF, Botelho MF. Midterm follow-up of esophageal anastomosis for esophageal atresia repair: long-gap versus non-long-gap. Dis Esophagus. 2007;20:428–35.
14. Romeo C, et al. Gastric motility disorders in patients operated on for esophageal atresia and tracheoesophageal fistula: long-term evaluation. J Pediatr Surg. 2000;35:740–4.
15. Montgomery M, Escobar-Billing R, Hellström PM, Karlsson KA, Frenckner B. Impaired gastric emptying in children with repaired esophageal atresia: a controlled study. J Pediatr Surg. 1998;33:476–80.
16. Yagi M, et al. Electrogastrography after operative repair of esophageal atresia. Pediatr Surg Int. 1997;12:340–3.
17. Bókay J, Kis E, Verebély T. Myoelectrical activity of the stomach after surgical correction of esophageal atresia. J Pediatr Surg. 2005;40:1732–6.
18. Black TL, et al. The effect of tube gastrostomy on gastroesophageal reflux in patients with esophageal atresia. J Pediatr Surg. 1991;26:168–70.
19. Shah R, Varjavandi V, Krishnan U. Predictive factors for complications in children with esophageal atresia and tracheoesophageal fistula. Dis Esophagus. 2015;28:216–23.
20. Lindahl H, Rintala R. Long-term complications in cases of isolated esophageal atresia treated with esophageal anastomosis. J Pediatr Surg. 1995;30(8):1222–3.
21. Curci MR, Dibbins AW. Problems associated with a Nissen fundoplication following tracheoesophageal fistula and esophageal atresia repair. Arch Surg. 1988;123(5):618–20.
22. Montgomery M, Frenckner B. Esophageal atresia: mortality and complications related to gastroesophageal reflux. Eur J Pediatr Surg. 1993;3(6):335–8.
23. Engum SA, Grosfeld JL, West KW, Rescorla FJ, Scherer LR III. Analysis of morbidity and mortality in 227 cases of esophageal atresia and/or tracheoesophageal fistula over two decades. Arch Surg. 1995;130(5):502–8. discussion 8–9
24. Chetcuti P, Myers NA, Phelan PD, Beasley SW. Adults who survived repair of congenital oesophageal atresia and tracheo-oesophageal fistula. BMJ. 1988;297(6644):344–6.
25. Somppi E, Tammela O, Ruuska T, Rahnasto J, Laitinen J, Turjanmaa V, et al. Outcome of patients operated on for esophageal atresia: 30 years' experience. J Pediatr Surg. 1998;33(9):1341–6.
26. Krug E, Bergmeijer JH, Dees J, de Krijger R, Mooi WJ, Hazebroek FW. Gastroesophageal reflux and Barrett's esophagus in adults born with esophageal atresia. Am J Gastroenterol. 1999;94(10):2825–8.
27. Bergmeijer JH, Tibboel D, Hazebroek FW. Nissen fundoplication in the management of gastroesophageal reflux occurring after repair of esophageal atresia. J Pediatr Surg. 2000;35(4):573–6.
28. Deurloo JA, Ekkelkamp S, Schoorl M, Heij HA, Aronson DC. Esophageal atresia: historical evolution of management and results in 371 patients. Ann Thorac Surg. 2002;73(1):267–72.
29. Deurloo JA, Ekkelkamp S, Bartelsman JF, Ten Kate FJ, Schoorl M, Heij HA, et al. Gastroesophageal reflux: prevalence in adults older than 28 years after correction of esophageal atresia. Ann Surg. 2003;238(5):686–9.

30. Koivusalo A, Pakarinen M, Rintala RJ, Lindahl H. Does postoperative pH monitoring predict complicated gastroesophageal reflux in patients with esophageal atresia? Pediatr Surg Int. 2004;20(9):670–4.
31. Konkin DE, O'Hali WA, Webber EM, Blair GK. Outcomes in esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2003;38(12):1726–9.
32. Taylor AC, Breen KJ, Auldist A, Catto-Smith A, Clarnette T, Crameri J, et al. Gastroesophageal reflux and related pathology in adults who were born with esophageal atresia: a long-term follow-up study. Clin Gastroenterol Hepatol. 2007;5(6):702–6.
33. Koivusalo A, Pakarinen MP, Rintala RJ. The cumulative incidence of significant gastrooesophageal reflux in patients with oesophageal atresia with a distal fistula--a systematic clinical, pH-metric, and endoscopic follow-up study. J Pediatr Surg. 2007;42(2):370–4.
34. Castilloux J, Bouron-Dal Soglio D, Faure C. Endoscopic assessment of children with esophageal atresia: Lack of relationship of esophagitis and esophageal metaplasia to symptomatology. Can J Gastroenterol. 2010;24(5):312–6.
35. Sistonen SJ, Pakarinen MP, Rintala RJ. Long-term results of esophageal atresia: Helsinki experience and review of literature. Pediatr Surg Int. 2011;27(11):1141–9.
36. Legrand C, Michaud L, Salleron J, Neut D, Sfeir R, Thumerelle C, et al. Long-term outcome of children with oesophageal atresia type III. Arch Dis Child. 2012;97(9):808–11.
37. Pedersen RN, Markow S, Kruse-Andersen S, Qvist N, Hansen TP, Gerke O, et al. Esophageal atresia: gastroesophageal functional follow-up in 5–15 year old children. J Pediatr Surg. 2013;48(12):2487–95.
38. Bouguermouh D, Salem A. Esophageal atresia: a critical review of management at a single center in Algeria. Dis Esophagus. 2015;28(3):205–10.
39. Banjar HH, Al-Nassar SI. Gastroesophageal reflux following repair of esophageal atresia and tracheoesophageal fistula. Saudi Med J. 2005;26(5):781–5.
40. McKinnon LJ, Kosloske AM. Prediction and prevention of anastomotic complications of esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 1990;25(7):778–81.
41. Cozzi DA, Zani A, Conforti A, Colarizi P, Moretti C, Cozzi F. Pathogenesis of apparent life-threatening events in infants with esophageal atresia. Pediatr Pulmonol. 2006;41(5):488–93.
42. Bergmeijer JH, Bouquet J, Hazebroek FW. Normal ranges of 24-hour pH-metry established in corrected esophageal atresia. J Pediatr Gastroenterol Nutr. 1999;28(2):162–3.
43. Vandenplas Y, Sacre-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old. J Pediatr Gastroenterol Nutr. 1987;6(2):220–4.
44. Frohlich T, Otto S, Weber P, Pilic D, Schmidt-Choudhury A, Wenzl TG, et al. Combined esophageal multichannel intraluminal impedance and pH monitoring after repair of esophageal atresia. J Pediatr Gastroenterol Nutr. 2008;47(4):443–9.
45. Lindahl H, Rintala R, Louhimo I. Failure of the Nissen fundoplication to control gastroesophageal reflux in esophageal atresia patients. J Pediatr Surg. 1989;24(10):985–7.
46. Holschneider P, Dubbers M, Engelskirchen R, Trompelt J, Holschneider AM. Results of the operative treatment of gastroesophageal reflux in childhood with particular focus on patients with esophageal atresia. Eur J Pediatr Surg. 2007;17(3):163–75.
47. Shawyer AC, D'Souza J, Pemberton J, Flageole H. The management of postoperative reflux in congenital esophageal atresia-tracheoesophageal fistula: a systematic review. Pediatr Surg Int. 2014;30(10):987–96.
48. Bergmeijer JH, Hazebroek FW. Prospective medical and surgical treatment of gastroesophageal reflux in esophageal atresia. J Am Coll Surg. 1998;187(2):153–7.
49. Tovar JA, Diez Pardo JA, Murcia J, Prieto G, Molina M, Polanco I. Ambulatory 24-hour manometric and pH metric evidence of permanent impairment of clearance capacity in patients with esophageal atresia. J Pediatr Surg. 1995;30(8):1224–31.
50. Stenström P, Anderberg M, Börjesson A, Arnbjornsson E. Prolonged use of proton pump inhibitors as stricture prophylaxis in infants with reconstructed esophageal atresia. Eur J Pediatr Surg. 2016;27(2):192–5.

51. Sistonen SJ, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, et al. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. Ann Surg. 2010;251(6):1167–73.
52. Peetsold MG, Heij HA, Deurloo JA, Gemke RJ. Health-related quality of life and its determinants in children and adolescents born with oesophageal atresia. Acta Paediatr. 2010;99(3):411–7.
53. Schalamon J, Lindahl H, Saarikoski H, Rintala RJ. Endoscopic follow-up in esophageal atresia-for how long is it necessary? J Pediatr Surg. 2003;38(5):702–4.
54. Georges A, et al. Inlet patch: clinical presentation and outcome in children. J Pediatr Gastroenterol Nutr. 2011;52:419–23.
55. Foker JE, Kendall Krosch TC, Catton K, Munro F, Khan KM. Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results. Semin Pediatr Surg. 2009;18(1):23–9.
56. Snyder CL, Ramachandran V, Kennedy AP, Gittes GK, Ashcraft KW, Holder TM. Efficacy of partial wrap fundoplication for gastroesophageal reflux after repair of esophageal atresia. J Pediatr Surg. 1997;32(7):1089–91; discussion 92.
57. Lopez-Fernandez S, Hernandez F, Hernandez-Martin S, Dominguez E, Ortiz R, De La Torre C, et al. Failed Nissen fundoplication in children: causes and management. Eur J Pediatr Surg. 2014;24(1):79–82.
58. Esposito C, Langer JC, Schaarschmidt K, Mattioli G, Sauer C, Centonze A, et al. Laparoscopic antireflux procedures in the management of gastroesophageal reflux following esophageal atresia repair. J Pediatr Gastroenterol Nutr. 2005;40(3):349–51.
59. Cullu F, Gottrand F, Lamblin MD, Turck D, Bonnevalle M, Farriaux JP. Prognostic value of esophageal manometry in antireflux surgery in childhood. J Pediatr Gastroenterol Nutr. 1994;18(3):311–5.
60. Loots C, van Herwaarden MY, Benninga MA, VanderZee DC, van Wijk MP, Omari TI. Gastroesophageal reflux, esophageal function, gastric emptying, and the relationship to dysphagia before and after antireflux surgery in children. J Pediatr. 2013;162(3):566–73.e2.
61. Lindahl H, Rintala R, Sariola H. Chronic esophagitis and gastric metaplasia are frequent late complications of esophageal atresia. J Pediatr Surg. 1993;28(9):1178–80.
62. Chetcuti P, Phelan PD. Respiratory morbidity after repair of oesophageal atresia and tracheo-oesophageal fistula. Arch Dis Child. 1993;68(2):167–70.
63. Chetcuti P, Phelan PD, Greenwood R. Lung function abnormalities in repaired oesophageal atresia and tracheo-oesophageal fistula. Thorax. 1992;47(12):1030–4.
64. Legrand C, Michaud L, Neut D, Sfeir R, Thumerelle C, Bonnevalle M, et al. Long term outcome of children with esophageal atresia. J Pediatr Gastroenterol Nutr. 2010;50:E133–E4.
65. Little DC, Rescorla FJ, Grosfeld JL, West KW, Scherer LR, Engum SA. Long-term analysis of children with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg. 2003;38(6):852–6.
66. Gatzinsky V, Jonsson L, Johansson C, Gothberg G, Sillen U, Friberg LG. Dysphagia in adults operated on for esophageal atresia–use of a symptom score to evaluate correlated factors. Eur J Pediatr Surg. 2011;21(2):94–8.
67. Huyn-Trudeau V, Maynard S, Terzic T, Soucy G, Bouin M. Dysphagia among adult patients who underwent surgery for esophageal atresia at birth. Can J Gastroenterol Hepatol. 2015;29(5):91–4.
68. Schneider A, Gottrand F, Bellaiche M, Becmeur F, Lachaux A, Bridoux-Henno L, Michel JL, Faure C, Philippe P, Vandenplas Y, Dupont C, Breton A, Gaudin J, Lamireau T, Muyshont L, Podevin G, Viola S, Bertrand V, Caldari D, Colinet S, Wanty C, Sauleau E, Leteurtre E, Michaud L. Prevalence of barrett esophagus in adolescents and young adults with esophageal atresia. Ann Surg. 2015;264(6):1004–8.
69. Adzick NS, Fisher JH, Winter HS, Sandler RH, Hendren WH. Esophageal adenocarcinoma 20 years after esophageal atresia repair. J Pediatr Surg. 1989;24(8):741–4.

70. Alfaro L, Bermas H, Fenoglio M, Parker R, Janik JS. Are patients who have had a tracheoesophageal fistula repair during infancy at risk for esophageal adenocarcinoma during adulthood? J Pediatr Surg. 2005;40(4):719–20.
71. Pultrum BB, Bijleveld CM, de Langen ZJ, Plukker JT. Development of an adenocarcinoma of the esophagus 22 years after primary repair of a congenital atresia. J Pediatr Surg. 2005;40(12):e1–4.
72. Deurloo JA, van Lanschot JJ, Drillenburg P, Aronson DC. Esophageal squamous cell carcinoma 38 years after primary repair of esophageal atresia. J Pediatr Surg. 2001;36(4):629–30.
73. Jayasekera CS, Desmond PV, Holmes JA, Kitson M, Taylor AC. Cluster of 4 cases of esophageal squamous cell cancer developing in adults with surgically corrected esophageal atresia--time for screening to start. J Pediatr Surg. 2012;47(4):646–51.
74. Sistonen SJ, Koivusalo A, Lindahl H, Pukkala E, Rintala RJ, Pakarinen MP. Cancer after repair of esophageal atresia: population-based long-term follow-up. J Pediatr Surg. 2008;43(4):602–5.

GOR(D) and Apnoea

12

Silvia Salvatore and Yvan Vandenplas

Abstract

Several mechanisms can contribute to respiratory manifestations in patients with gastro-oesophageal reflux (GOR), but pathological and causal relationship is uncommon. In most infants apnoea of short duration is a physiologic phenomenon occurring frequently in relation to an episode of GOR and a protective mechanism to prevent aspiration. Diagnostic gold standard, cut-off values and follow-up data are currently lacking making the relation between GOR or GOR disease and respiratory system difficult to clarify. When compared with pH monitoring, oesophageal impedance with simultaneous polysomnography can better demonstrate the temporal association in selected patients but should be reserved to severe or recurrent otherwise unexplained respiratory events. Empirical treatment for GOR is not recommended due to lack of evidence of efficacy and possible pharmacologically related adverse events.

Keywords

Reflux • GOR • GOR(D) • Regurgitation • Apnoea • ALTE • Infants • Children

Introduction

Gastro-oesophageal reflux (GOR) has been associated with all chronic respiratory disorders, but in the vast majority of cases, neither temporal nor causal relation with apnoea or apparent life-threatening event (ALTE) (an episode characterized by some combination of apnoea, colour change, marked change in muscle tone,

S. Salvatore (✉)
Department of Paediatrics, Ospedale "F. Del Ponte", Università dell'Insubria, Varese, Italy
e-mail: silvia.salvatore@uninsubria.it

Y. Vandenplas
Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussels, Brussels, Belgium

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_12

choking or gagging, i.e. frightening to the observer) is demonstrated [1, 2]. However, coexistence of GOR may occur in many infants, particularly in preterms and in postprandial time [3, 4], mainly because apnoeas and regurgitations are frequent physiologic events in the first months of life. Outcomes of studies are difficult to compare because of heterogeneity in the population recruited and diagnostic criteria of both apnoea and GOR or GOR disease GOR(D) [1, 2]. Intervention trials and follow-up data are needed to clarify the relation between the two phenomena.

Pathophysiology

The two major theories that attribute respiratory symptoms to GOR are (micro) aspiration of gastric contents during a reflux episode and vagal reflex arc. The neural theory is based on stimulation of oesophageal afferent receptors by oesophageal distention, inflammation or irritation caused by GOR with subsequent laryngospasm or bronchospasm (triggered by airway efferents) via vagal pathways. However, the association between GOR and respiratory system is more complex and not completely clarified. Negative intrathoracic pressure (i.e. in tracheomalacia), congenital malformation (i.e. oesophageal atresia and/or fistula, laryngomalacia) or other comorbidities (i.e. neurological impairment, cystic fibrosis, achalasia) or swallowing disorders or impaired oesophageal peristalsis or increased abdominal pressure (due to recurrent cough or obesity) all can facilitate reflux. Thus, in each patient with recurrent respiratory events, all the following mechanisms should be considered: presence or coexistence of (micro)aspiration, stimulation of laryngeal (chemo)reflexes, alteration of vagal response, oesophageal and/or laryngeal inflammation, oesophageal or respiratory hyperreactivity or hypersensitivity, increased negative intrathoracic or positive abdominal pressure, impaired airway protection, reduced oesophageal sphincter tone, anatomic abnormalities or congenital malformation and abnormal motility (Fig. 12.1). Because no diagnostic gold standard

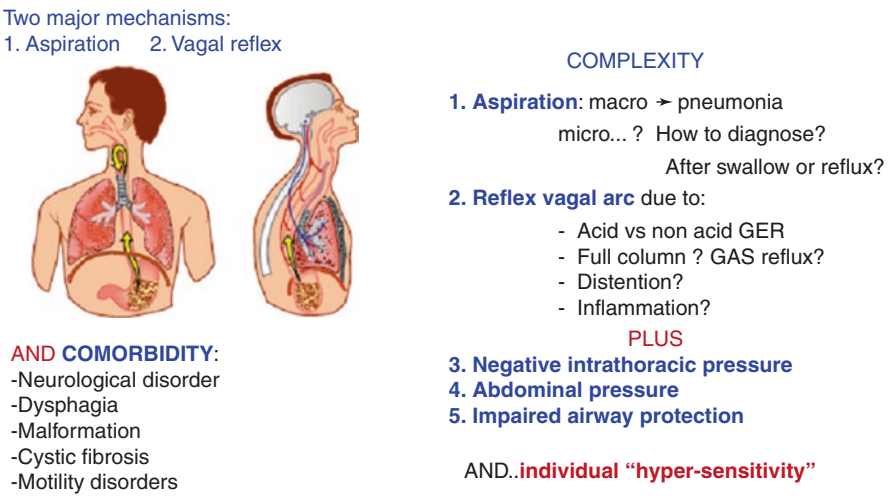


Fig. 12.1 Possible mechanisms and uncertain cofactors of respiratory manifestations in GOR

exists for any of these variables, pathophysiology of respiratory symptoms in GOR(D) is far to be elucidated.

Furthermore, GOR can occur as a consequence of apnoea, facilitated by a negative intrathoracic pressure or as a preceding event that causes apnoea as an exaggerated laryngeal reflex or a natural protective mechanism for the respiratory airways [1, 5]. GOR can even be considered as a protective concurrent disorder for ALTE and SIDS as reflux facilitates arousals [6, 7]. Both acid and nonacid refluxes have been reported to be associated with apnoea. However, the temporal relation and specific association with obstructive apnoea (compared to central or mixed apnoeas) are still controversial.

In healthy individuals, a series of barriers and protective responses prevent refluxed gastric contents from entering the airway. These protective mechanisms include the upper oesophageal sphincter, oesophageal-glottal closure reflex (with consequent apnoea), pharyngeal clearance, cough and airway clearance of aspirated materials [8]. The consequence of oesophageal distension is also complex and difficult to measure. In normal subjects, when GOR is of small volume, the upper oesophageal sphincter contracts, whilst after a large volume reflux, oesophageal distention leads to vagal reflexes that cause vocal cord closure, central apnoea and upper oesophageal sphincter relaxation which allow the entry of gastric contents into the pharynx, followed by a swallow to clear the pharynx and rapid resumption of respiration [8]. If reflux enters the larynx, normally, a cough burst expels the material from the airway and bronchoconstriction prevents aspirated material from reaching the alveolar spaces [8]. If any of this complex sequence occurs out of order or abnormally, there is a high risk of aspiration and respiratory complications [8].

To complicate even more the relationship between respiratory system and GOR, several studies suggested a primary or secondary autonomic or parasympathetic alteration.

A 24 h analysis of heart rate variability showed that in (adult) patients with GOR(D), the function of the autonomic nervous system is altered and vagal tone is (primary?) reduced [9–11]. Similarly, lower rate of heart high frequency HF was reported in patients with laryngopharyngeal reflux compared to healthy adults [12].

Data in children are lacking, but in neonates short-term GOR-related changes of vagal activity, with lower parasympathetic tone in the minutes preceding GOR, have been reported [13]. A significant increase in the sympathovagal ratio (+32%, $p = 0.013$) was observed in the period immediately prior to reflux (due to a 15% reduction in parasympathetic activity ($p = 0.017$)), relative to the control period. This phenomenon was observed during both wakefulness and active sleep and suggests that a pre-reflux change in autonomic nervous system activity is one of the factors contributing to the mechanism of reflux in neonates [13]. Parasympathetic dysfunction has also long been implicated in GOR(D) through an impaired regulation of the lower oesophageal sphincter (LOS) [14].

However, the potential role of inflammation has not been clarified, and distinguishing between cause and effect is challenging also because (individual) hypersensitivity to oesophageal stimuli produces changes in autonomic nervous system even in healthy subjects [15, 16].

The vigilance state also significantly influenced the distribution of GOR events, with 53% observed during wakefulness, 38% observed during active sleep and only 9% observed during quiet sleep [13]. Poor quality of sleep characterized by irregular breathing patterns is associated with reflux [3, 17–23]. GOR is a frequent cause of interrupting sleep among infant patients [3], and nonacid GOR proved to be equally important as acid GOR for causing arousals and awakenings in infants [24]. Pain or discomfort also occurs both with weakly acid and acid reflux episodes [25] and may mediate GOR and arousals.

Physiologic data suggest that when there is a temporal relationship, apnoea is more likely to predispose to GOR via oesophageal sphincter relaxation than vice versa [26].

When compared with pH monitoring [3], combined pH-oesophageal impedance (pH-MII), detecting both acid and nonacid GOR, could better demonstrate that apnoea of short duration following GOR is a physiologic protective phenomenon to prevent aspiration.

In children and adults, GOR 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 [27]. In adults, OSA has been associated with increased occurrence of nocturnal symptoms of GOR [28] as well as increased number and length of overnight GOR episodes (2000). In children the relation has not been investigated so far.

Continuous positive airway pressure (CPAP), the mainstay therapy for OSA (in adults), may reduce reflux events and improve symptoms of nocturnal GOR [28] through a beneficial effect (increase pressure and/or reduced transient relaxations) on LOS [29].

However, adult studies reported an association between nocturnal GOR episodes and apnoea or hypopnea in a range of 54–70% [27, 30–32], suggesting a (mild) causal relationship between obstructive respiratory events and nocturnal GOR 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 GOR event occurring in proximity to any given respiratory event [27].

The arousal accompanying the re-establishment of upper airway patency after occlusion and the associated stimulation of sympathetic nervous activity as well as the apnoea-associated increased parasympathetic (vagal) nervous activity [33] do not appear to influence significantly transient LOS relaxation in adults [27].

Conversely, obesity predisposes to OSA and GOR(D) both in adults [27] and in children [1].

The clinical relevance of the proximal extension of a reflux in generating respiratory events or other symptoms is still unclear. A stronger association between symptoms and proximal reflux than with non-proximal reflux was sustained by some authors [34, 35] but could not be confirmed by others [36–38]. The majority of reflux events in asymptomatic preterms reached the proximal oesophagus or pharynx, and there were no differences between acid and nonacid reflux [39]. The lack

of differences between asymptomatic and diseased infants contravenes the hypothesis for macro- or microaspiration but does not exclude hypersensitivity to reflux as a cause for respiratory symptoms [39]. In our population, symptoms were associated with proximal reflux in 70% of all the reflux-related episodes without influence of age [38]. However, proximal extension of reflux was not a necessary condition to cause symptoms. As expected, the proportion of proximal reflux was higher for "vomiting" as a symptom than for all the other occurring symptoms [38].

A recent report investigated 20 preterm infants (10 with ALTE and 10 controls) with simultaneous pharyngo-oesophageal manometry, respiratory plethysmography and nasal thermistors and suggested a possible role of oesophageal motility. The analysis showed more frequent and prolonged spontaneous respiratory events (defined as apnoea >2″ with ≥2 "missing" breathing), less amplitude of protective contraction of upper oesophageal sphincter, more frequent disturbed oesophageal propagation, mixed apnoea and gasping in patients with ALTE compared to controls [40].

Apnoea, ALTE and GOR(D)

Current knowledge on the relationship between apnoea or ALTE and GOR(D) in infants is limited because of the small number of patients investigated, differences in methodology and controversial results. Furthermore, patient selection and grouping are made difficult by the absence of "gold standard" diagnostic criteria both for apnoea and GOR(D) in infant population.

First, relation between apnoea or ALTE and GOR was based on concurrent clinical symptoms of regurgitation and/or results of pH monitoring. Pathological pH monitoring has been overall reported in a range of 20% [41] to 77% [19] of infants with ALTE and of 32% [20, 21, 42] to 100% [43] of infants with apnoeas.

ALTE and GOR(D)

GOR(D) is the most commonly attributed cause of ALTE in a range of 31–55% of ALTE cases [44, 45]. However, in most studies proper investigations for GOR(D) were not performed, and diagnosis of GOR(D) was based simply on reported regurgitations concomitant to the episode or even just in previous weeks.

In old studies, patients with ALTEs had a 60–70% prevalence of recurrent regurgitation or emesis [46, 47], and case reports and series described ALTEs triggered by overt regurgitation into the oropharynx, by aspiration of refluxed gastric contents and by reflux induced by positional change after feedings [43, 48–50]. In selected patients with ALTE, acid perfusion of the oesophagus induced obstructive apnoea [49] or oxygen desaturation [51], suggesting that one mechanism for ALTE is acid stimulation of laryngeal, pharyngeal or oesophageal chemoreceptors with subsequent laryngospasm. Three small studies showed no significant difference in terms of acid reflux percentage or duration between infants who had experienced an

ALTE and controls [18, 52, 53]. However, in a previous report, abnormal pH-metry results were found in 42% of 62 infants with episodes of paleness possibly suggestive of an ALTE, compared with 8.5% of the 378 control infants [3]. In 67 infants with ALTE investigated with pH monitoring for ≥10 ore, Arad-Cohen reported pathological GOR in 53% of infants, but 81% of apnoeic events were not associated with GOR. In the minority of cases with demonstrated association, apnoeas preceded GOR in nearly all (94%) of the episodes [54]. A large study reported the prevalence of ALTE to be less (20%) in a sample of 173 infants with GOR(D) (defined as a reflux index greater than 5% on pH monitoring) than in 169 healthy controls (31%, $p < 0.12$) [41].

In 2008 retrospectively reviewed records from a large group of 313 infants hospitalized for ALTE showed a discharge diagnosis of GOR(D) as the most common (49%) diagnosis, but that again was not based on pH monitoring except that in one patient. Interestingly, within 6 months, 14 patients (9%) of this subgroup had recurrent ALTE [55]. A large revision of 12,067 infants discharged with a diagnosis of ALTE in the USA confirmed that the most common associated diagnosis was GOR (37%) but with a considerable hospital-based variation particularly in the evaluation and diagnosis of GOR. An increased likelihood of readmission for patients discharged with a diagnosis of cardiovascular disorders (odds ratio [OR] = 1.68; 95% confidence interval [CI] = 1.30–2.16) and GOR (OR = 1.32; 95% CI = 1.03–1.69) compared with other discharge diagnoses was also reported [44].

Another retrospective cohort study of 469 infants admitted for ALTE found that adverse outcomes associated with GOR(D) (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 [2].

In the last two decades, many studies analysed the temporal association between reflux episodes and ALTE or apnoea in infants using 24 h pH-impedance monitoring (pH-MII) which offers a higher diagnostic sensitivity for GOR compared to pH monitoring, particularly in the first months of life and in postprandial period when nonacid (pH >4) reflux is more common.

Mousa et al. [56] analyzed the temporal relationship between apnoea and GOR by pH-MII in a group of 25 infants who presented with an ALTE event or pathologic apnoea. In this report a time interval of as long as 5 min between apnoea and reflux during pH-MII investigation was considered acceptable to demonstrate a "temporal link" between the two phenomena. In total, 527 episodes of apnoea were recorded, but only 80 (15.2%) were temporally linked to a reflux episode (despite the large criterion of 5 min). Of these 80 episodes, 37 (7% of the total number of apnoea events) were related to an acid reflux episode and 43 (8%) were related to a nonacid reflux episode. Thus, even considering both acid and nonacid GOR and a time interval of as long as 5 min, the relation between reflux and apnoea appears rare [56]. Recently, the analysis of 39 infants with ALTE reported abnormal GOR parameters in 33 (85%) with combined pH impedance reduced to 14 (36%) when only pH monitoring was considered, confirming an increased frequency of nonacid reflux events and usefulness of combined investigation to detect underlying GOR(D) [57].

As all studies were retrospective regarding the episode of ALTE, they could not document the rate of ALTEs that occurred during reflux or vice versa but only the underlying condition of GOR and possible temporal association between GOR and apnoeas occurring during GOR investigation.

Medical therapy of ALTEs suspected of being GOR related has not been adequately studied. Avoidance of overfeeding and approaches that decrease the frequency of regurgitation and the volume of reflux such as thickened feeding is suggested in infants with frequent regurgitation [1]. Pharmacotherapy has not been shown to be effective and the use of acid inhibitors has been related to an increased risk of infections in infants. Furthermore, the incidence of ALTEs diminishes significantly with age and without therapy in most cases, suggesting that anti-reflux therapy should be reserved in the rare infant in whom ALTEs are truly life threatening and are shown to be clearly related to GOR [1].

Similarly, even if supine position is associated with increased rate of reflux events, prone sleeping should be avoided in infants because of related increased risk of SIDS.

Although rare, SIDS has been reported to occur in patients with a previous ALTE and documented GOR [7, 22, 58]. However, in none of these patients, a correlation between oesophageal 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 GOR(D).

In a recent review on ALTE [59] Tieder concluded that routine investigation for GOR is not necessary, but patients with recurrent ALTEs or symptoms of GOR not responsive to behaviour and diet treatment can benefit from pH (or, better, impedance pH) monitoring combined with symptom (and polysomnography) registration to establish a cause-effect relation or another aetiology [59].

In the new classification of ALTE, in case of brief resolved unexplained events (BRUE) and infant at low risk, GOR can be associated with or without overt regurgitation and should be considered as a (co)factor for respiratory abnormalities and recurrent BRUE events [60].

It is clear that ALTE is the preceding referring manifestation and investigation for GOR(D) can only reveal an underlying excessive oesophageal acid exposure or GOR-associated apnoea/desaturation that occurred during the (impedance)-pH monitoring. As ALTE rarely recurs during the diagnostic test, the causal relation with the episode of ALTE is impossible to prove as well as the related benefit of GOR treatment unless follow-up data are available.

Apnoea and GOR(D): Studies in Infants

In highly selected cases, reflux is temporally associated with pathological, central and obstructive apnoea [7] but no study has conclusively shown a cause and effect relation between reflux and pathologic apnoea.

In one old report, short apnoea or bradycardia was tightly tied to vomit or regurgitation, whereas the majority of prolonged apnoea spells (>20 s) were not [61]. Using

pH monitoring to assess GOR, several studies reported an occasional correlation of GOR with obstructive or short-mixed central apnoeas (5–15 s) [3, 20, 21, 23, 62] but also showed that all of the patients presented episodes of apnoea unrelated to episodes of GOR, suggesting a primary impairment in the regulation of respiration. Large case series did not find a significant relation between GOR and pathologic apnoea or ALTEs [17, 18].

To examine the temporal relationship between apnoea and GOR and its effect on apnoea duration, 119 preterm infants underwent 12 h cardiorespiratory monitoring studies using respiratory inductance plethysmography, heart rate, oxygen saturation and oesophageal pH monitoring [63]. Among 6255 episodes of acid GOR detected by pH monitoring, only 1% were associated with apnoea >15 s. There was also no difference in rate of apnoea >10 s before versus during GOR, but a decrease in apnoea rate was found immediately after GOR. The presence of reflux during apnoea did not prolong apnoea duration, and GOR had no effect on the lowest oxygen saturation or heart rate during apnoea. Hence, there was no evidence of a temporal relationship between acid-based GOR and apnoea in these preterm infant cohorts [63].

One retrospective study showed that GOR-related apnoea improved rapidly following commencement of gastrojejunal feeding, suggesting that in some cases reflux may cause apnoea [64].

A strong temporal association between acid and nonacid GOR and respiratory abnormalities was reported in 1 study using 6 h combined pH-MII that recorded 364 episodes of reflux, of which only 11% were acid, in a group of 22 infants who presented with repetitive regurgitation and chronic respiratory symptoms [65]. Of these reflux episodes, 312 (85%, 12% of which were acid) could be associated with irregular breathing. In a minority of these episodes (n:19), oxygen desaturations of 10% occurred (19% [3 of 19] of these episodes were acid). Analysis of the polysomnographic recording revealed 165 episodes of apnoea (>5 s), of which 49 (30%) were associated with a reflux episode. Again, the majority (78%) of reflux episodes were detected with impedance only [65].

In the last years, although some authors suggested a relation between (long, >30 s) apnoea or bradycardias of prematurity and reflux [66, 67], most studies did not support reflux as a cause of pathologic apnoea in (premature) infants [39, 63, 68, 69]. Nineteen preterm infants (gestational age, 30 weeks) who presented with apnoea were studied at a mean age of 26 days, and 2039 episodes of apnoea (median, 67; range, 10–346), 188 oxygen desaturations (median, 6; range, 0–25), 44 bradycardias (median, 0; range, 0–24) and 524 episodes of GOR (median, 25; range 8–62) were detected by pH-MII lasting 6 h [68]. The frequency of apnoea (≥4 s) in a 20 s period before and after an episode of GOR was not different from the frequency of apnoea not related to a reflux episode (0.19/min (range, 0.00–0.85/min) vs. 0.25/min (range, 0.00–1.15/min)) [68]. The analysis and conclusions were identical for oxygen desaturations and bradycardias [68].

In a small group of 6 premature infants with apnoea (defined as abnormal respiratory pause ≥20 s or of shorter duration if associated with cyanosis or marked pallor or hypotonia or bradycardia <80 beats/min) or hypoxaemia (defined as pulse

oximeter saturation ≤80%) not responsive to caffeine treatment, a total of 405 reflux events (306 (76%) weakly acid and 99 acid reflux) and 142 apnoeas were detected. The sub-analysis based on chemical composition and duration of refluxate showed that the frequency of apnoeas associated with nonacid reflux events was significantly greater than the one calculated for reflux-free period (0.416/min (0.00–1.30) vs. 0.016/min (0.003–0.028), respectively; $p < 0.05$) and that the frequency of apnoeas occurring during reflux events longer than 30 s was significantly higher than those occurring during shorter reflux events (22% vs. 11%; $p < 0.004$) [67].

Corvaglia et al. investigated 52 preterm infants with simultaneous polysomnography and combined 24 h pH-MII and showed that 154 (14%) apnoeas out of 1136 were related in time to GOR. The frequency of apnoea during the 1 min time (30 s before and after) within the onset of GOR was significantly higher than the apnoea in GOR-free periods ($p = 0.03$). Furthermore, the frequency of apnoea in the 30 s after GOR (GOR-triggered apnoeas) was greater than that detected in the 30 s before ($p = 0.01$) suggesting that a number of apnoeas were induced by GOR [66].

In a subsequent report, the same authors confirmed in 58 preterm infants with recurrent apnoeas an increased frequency of apnoea after (both acid and nonacid) GOR compared to periods before or without GOR [70]. No difference was found regarding proximal extension or duration of GOR between reflux events associated or not associated with apnoea [70].

The influence of body position on GOR has also been assessed in a number of studies. In ten healthy preterm infants, a "crossover position study" and postprandial evaluation showed more liquid GOR 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/h; $p = 0.002$). Conversely, gastric emptying was faster in the right than in the left lateral position (37.0 + 21.1 vs. 61.2 + 24.8 min; $p = 0.006$) [71]. Similar findings were reported by another group in 22 preterm babies presenting with regurgitation and postprandial desaturations: the number of acid and nonacid reflux episodes was significantly smaller when the subjects were in the prone and left-side sleeping position in comparison with the supine and right-side positions [72]. The left-side position showed the lowest oesophageal acid exposure in the early postprandial period, whereas in the prone position acid reflux was smallest in the late postprandial period [73].

History and physical examination are still important, in infants with ALTE, to exclude warning signs (for GOR and other extra-oesophageal diseases), but the presence or absence of regurgitation is not sufficient to discriminate physiological reflux from GOR(D). Regurgitation is neither specific (even if associated to crying or back arching or feeding problem) nor sufficient to make a diagnosis of GOR(D). Indeed regurgitation is extremely common in the first months of life and represents a physiological manifestation in most infants who do not need any investigation or pharmacological treatment. Similarly, desaturation or apnoea or laryngeal inflammation does not imply GOR(D) [5]. Conversely, malformation (such as laryngomalacia) or respiratory disease can facilitate (secondary) GOR by negative intrathoracic pressure or increased abdominal pressure caused by cough. No specific symptom or cluster of symptoms for GOR(D) and response to acid inhibitors

have been identified in infants and young children so far. Therefore, empirical pharmacological treatment is not recommended in infants because of lack of symptomatic efficacy and possible adverse events (i.e. increased incidence of infections with acid inhibitors and cardiac problems with prokinetics) [1]. Domperidone is also not beneficial for GOR in newborns because it increases GER episodes per hour compared to the baseline despite reducing the duration without modifying the pH value or the proximal extent reached by the refluxes [74].

In accordance with the ESPGHAN-NASPGHAN guidelines [1], the NICE guidelines, after reviewing 13 studies, confirmed that GOR only rarely causes episodes of apnoea or ALTEs and recommended specialist investigations if GOR(D) is suspected as a possible factor following a general paediatric assessment or in cases of unexplained apnoeas [75]. MII/pH oesophageal monitoring in combination with polysomnographic recording and precise, synchronous symptom recording may aid in establishing the relationship between apnoea and GOR [1].

A recent systematic review [76] has highlighted the limited data available on the association between GOR and apnoea with small patients recruited, heterogeneous inclusion and diagnostic criteria and therapeutic outcomes. Only one study was considered eligible using pH-MII recording [77] which found, in 71 preterms, no association between GOR and apnoeas with only 3% of apnoea (>10 s) following GOR and only 9% respiratory events preceding reflux considering a time window of 30 s [77]. Based on the current literature, the authors concluded that there is insufficient evidence to prove an association between the two disorders.

However, the association between pathologic central, obstructive and mixed apnoea has never been demonstrated (but has also not been well studied yet), and clear cut-off values discriminating normal from pathologic children still need to be determined.

In conclusion, the available evidence suggests that in the vast majority of infants, GOR is not related to pathologic apnoea or to ALTE [1, 2, 26], and thus there is no evidence to support an empirical treatment of GOR in infants presenting with apnoea or ALTE. However, a clear temporal association based on history, observation or testing occurs in individual infants. pH-MII in combination with polysomnographic recording is recommended to demonstrate the relation in these infants [1].

Studies in Children

In one study that analysed 28 children (mean age, 6.5 ± 5.6 years) with chronic respiratory symptoms (on treatment with antacid medications), multivariate analysis confirmed a stronger association between respiratory symptoms with nonacid reflux episodes than with acid reflux episodes and pointed out the importance of the height of the refluxate: the higher the reflux, the stronger the association [78].

The complexity in understanding the role of acid and nonacid GOR in respiratory symptoms still exists and involves the possible presence of primary or secondary reflux in different subjects, the low chance of occurrence of respiratory symptoms

(especially if they have no daily frequency) during the investigation (making the association impossible to be determined) and the difficulty in identifying the correct temporal sequence of "respiratory reflux" or "reflux respiratory" or "respiratory reflux-reflux respiratory" without combined sensitive investigation tool.

In a selected group of 22 adults, a relation between chronic coughing and GER has been, for the first time, accurately studied by combined manometry and pH-MII in 2005 [79]. Using a time frame of 2 min and symptom association probability, 69% of the coughing episodes were considered "independent" of a reflux episode. When a "reflux-cough" sequence occurred, the reflux in 65% of the cases was acid, weakly acid in 29% and weakly alkaline in 6% [79].

The feasibility and accuracy of these combined investigations for cough were then confirmed in children [80].

No similar method has been reported for the temporal detection of apnoea and GOR. Polysomnography has demonstrated a better accuracy compared to transcutaneous oxygen saturimeter to detect and define apnoeas, but it has not been a widespread use because of the cost and complexity of the analysis [81]. Furthermore most studies used synchronization of the internal clock of the two instruments (polysomnography and impedance), but the related tracings do not appear on the same screen of the computer limiting the accuracy of the temporal association and sequence between apnoea and GOR.

OSAS and GOR

It is estimated that 9–10% of children are habitual snorers or have sleep-disordered breathing-related illnesses [82]. 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 hypopnoea [81]. Snoring and occasional apnoeic breath holding in sleep are common, but only when witnessed repetitive apnoeas and symptoms of sleep fragmentation, such as excessive daytime sleepiness, occur, a diagnosis of obstructive sleep apnoea syndrome (OSAS) can be made [81]. In adult, sleep studies measure the apnoea/hypopnoea index (AHI), which is the number of respiratory events an hour. Excessive sleepiness becomes more prevalent once the AHI exceeds five events an hour, and this value has become a lower cut-off for the diagnosis of OSAS [81].

The ideal method for diagnosis of sleep apnoeas is full polysomnography, which involves overnight admission for supervised multichannel recording, including electroencephalography. Restricted availability of polysomnography and the cost mean that oximetry and limited respiratory monitoring are more widely used [81]. Overnight oximetry is widely available, but oxygen desaturation is an inexact surrogate for apnoeic events, and the ideal frequency and depth of desaturation events are still debated although an oxygen desaturation of 4% is conventionally used to indicate apnoea [81]. Obstructive sleep apnoea occurs in approximately 3% of children, most frequently aged from 2 to 6 years [83]. OSAS diagnosis is clinically relevant because recurrent episodes of air flow cessation, oxygen desaturation and

sleep disruption are associated with behaviour disorders, neurocognitive deficits, disturbances of somatic development as well as cardiovascular and metabolic sequelae [78, 84].

The aetiology of OSAS is multifactorial consisting of a complex interplay between airway anatomical characteristics and dynamic control of upper airway muscular tone [85]. Obstructive sleep apnoea is hypothesized to be influenced by genes involved with obesity, craniofacial development, inflammation and ventilator control [86]. Adenotonsillar hypertrophy is recognized as the most frequent cause of OSAS in childhood [87]. The association between GOR and OSAS in children has been less explored compared to apnoea in infants and, as well as in adults, remains controversial.

In several studies acidification of the distal oesophagus was suggested in the mechanism of OSA in children and adults and in persisting OSAS after adenoidectomy [88–92]. The role of GOR in OSAS in infants has been less investigated and in residual OSA among young children is unclear.

A report in 18 children with adenotonsillar hypertrophy and OSAS evaluated the OSA-18 questionnaire, nasofibrolaringoscopy and full overnight polysomnography performed simultaneously with oesophageal pH monitoring. Seven children (41%) presented episodes of acid reflux during the registered sleep time. The authors concluded that GOR is frequent and should be assessed in children from 6 to 12 years with OSAS [91]. However, reflux parameters did not correlate to OSAS severity and a temporal relationship between GOR and apnoea-hypopnea events was not observed [91].

The main treatment options of OSAS are essentially physical solutions to narrowing of the upper airway, namely, continuous positive airway pressure (CPAP), oral appliances and upper airway surgery. Weight loss and bariatric surgery may also be appropriate interventions in adults [81].

Treatment of GOR has been shown to improve OSAS [90, 93], and OSAS therapy with CPAP has been demonstrated to reduce GOR [94] confirming a bidirectional association between these two conditions. The favourable effect of CPAP on nocturnal GOR is possibly due to an increase in nadir LOS pressure and decrease in the duration of LOS relaxation [27].

In eight newborn lambs, continuous oesophageal pH-impedance monitoring and polysomnography were performed for 6 h during both spontaneous breathing and nCPAP application at 6 cm H2O (nCPAP6, of common usage in newborns), in a randomized order. CPAP6 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 against GOR [95]. Hence, CPAP may reduce in patients with OSAS both acid and nonacid GOR and, eventually, proximal refluxes, which are especially prominent in infants and can be responsible for cardiorespiratory inhibition via the laryngeal chemoreflexes [96].

However, temporal relationship between GOR and apnoea-hypopnea events was not clearly demonstrated, and heterogeneity for both apnoea and GOR definition and detection does not allow a general conclusion. Even in studies when a simultaneous recording of pH monitoring and polysomnography was applied, the

registration from the two investigations was not integrated. Additionally, since a pH probe and not a pH-MII was used to assess GOR in many studies, it is possible that GOR has been underestimated in these patients. Prospective studies assessing natural evolution of patients with concomitant GOR and apnoeas and benefit of GOR treatment are lacking.

Low basal pressure of LOS detected in some OSA patients raises the possibility of weakening of the gastro-oesophageal junction from repetitive strain associated with obstructed breathing events.

Conclusions

Several authors have suggested an association between GOR and apnoea in infants. However, current studies present low number of patients, high heterogeneity in terms of population recruited, diagnostic tools, definition of apnoeas, GOR and GOR(D), means of association and time intervals, hampering a direct comparison among results. Most studies fail to show a temporal link between apnoea or ALTE and GOR, and when an association is found, apnoea episodes more frequently precede GOR, than follow GOR. Empirical treatment for GOR is not recommended due to lack of evidence of efficacy and possible pharmacologically related adverse events. In selected patients with recurrent idiopathic respiratory events, pH-MII with simultaneous polysomnography recording should be performed to detect underlying GOR(D) and to prove the relationship with apnoeas.

References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–597.
2. Zimbric G, Bonkowsky JL, Maloney CG, Srivastava R. Adverse outcomes associated with gastroesophageal reflux disease are rare following an apparent life-threatening event. J Hosp Med. 2012;7:476–81.
3. Sacre L, Vandenplas Y. Gastroesophageal reflux associated with respiratory abnormalities during sleep. J Pediatr Gastroenterol Nutr. 1989;9:28–33.
4. Wenzl TG, Schneider S, Scheele F, et al. Effects of thickened feeding on GER in infants: a placebo-controlled crossover study using intraluminal impedance. Pediatrics. 2003;114:e355–9.
5. Tolia V, Vandenplas Y. Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. Aliment Pharmacol Ther. 2009;29(3):258–72.
6. Kahn A, Rebuffat E, Sottiaux M, et al. Prevention of airway obstructions during sleep in infants with breath-holding spells by means of oral belladonna: a prospective double-blind crossover evaluation. Sleep. 1991;14(5):432–8.
7. Vandenplas Y, Hauser B. Gastro-oesophageal reflux, sleep pattern, apparent life threatening event and sudden infant death. The point of view of a gastroenterologist. Eur J Pediatr. 2000;159:726–9.

8. Lang IM, Medda BK, Shaker R. Mechanisms of reflexes induced by esophageal distension. Am J Phys. 2001;281:G1246–63.
9. Cuomo R, De Giorgi F, Adinolfi L, et al. Oesophageal acid exposure and altered neurocardiac function in patients with GERD and idiopathic cardiac dysrhythmias. Aliment Pharmacol Ther. 2006;24:361–70.
10. Dobrek L, Nowakowski M, Mazur M, et al. Disturbances of the parasympathetic branch of the autonomic nervous system in patients with gastroesophageal reflux disease (GERD) estimated by short-term heart rate variability recordings. J Physiol Pharmacol. 2004;55(S2):77–90.
11. Milovanovic B, Filipovic B, Mutavdzin S, et al. Cardiac autonomic dysfunction in patients with gastroesophageal reflux disease. World J Gastroenterol. 2015;21:6982–9.
12. Huang W-J, Shu C-H, Chou K-T, et al. Evaluating the autonomic nervous system in patients with laryngopharyngeal reflux. Otolaryngol—Head Neck Surg. 2013;148:997–1002.
13. Djeddi D-D, Kongolo G, Stéphan-Blanchard E, et al. Involvement of autonomic nervous activity changes in gastroesophageal reflux in neonates during sleep and wakefulness. PLoS One. 2013;8:e83464.
14. Heatley RV, Collins RJ, James PD, Atkinson M. Vagal function in relation to gastro oesophageal reflux and associated motility changes. Br Med J. 1980;280:755–7.
15. Sharma A, Paine P, Rhodes S, et al. The autonomic response to human esophageal acidification and the development of hyperalgesia. Neurogastroenterol Motil. 2012;24:e285–93.
16. Tougas G, Spaziani R, Hollerbach S, et al. Cardiac autonomic function and oesophageal acid sensitivity in patients with non-cardiac chest pain. Gut. 2001;49:706–12.
17. Ariagno RL. Evaluation and management of infantile apnea. Pediatr Ann. 1984;13:210–3. 216–217
18. Kahn A, Rebuffat E, Sottiaux M, et al. Lack of temporal relation between acid reflux in the proximal oesophagus and cardiorespiratory events in sleeping infants. Eur J Pediatr. 1992;151(3):208–12.
19. Newman LJ, Russe J, Glassman MS, et al. Patterns of gastroesophageal reflux (GER) in patients with apparent life-threatening events. J Pediatr Gastroenterol Nutr. 1989;8:157–60.
20. Paton JY, Nanayakkara CS, Simpson H. Observations on gastroesophageal reflux, central apnoea and heart rate in infants. Eur J Pediatr. 1990;149:608–12.
21. Paton JY, Macfadyen U, Williams A, et al. Gastro-oesophageal reflux and apnoeic pauses during sleep in infancy – no direct relation. Eur J Pediatr. 1990;149:680–6.
22. Veereman-Wauters G, Bochner A, Van Caillie-Bertrand M. Gastroesophageal reflux in infants with a history of near-miss sudden infant death. J Pediatr Gastroenterol Nutr. 1991;12:319–23.
23. Walsh JK, Farrell MK, Keenan WJ, et al. Gastroesophageal reflux in infants: relation to apnea. J Pediatr. 1981;99:197–201.
24. Machado R, Woodley FW, Skaggs B, et al. Gastroesophageal reflux causing sleep interruptions in infants. J Pediatr Gastroenterol Nutr. 2013;56:431–5.
25. Cresi F, Castagno E, Storm H, et al. Combined esophageal intraluminal impedance, pH and skin conductance monitoring to detect discomfort in GERD infants. PLoS One. 2012;7:e43476.
26. Abu Jawdeh EG, Martin RJ. Neonatal apnea and gastroesophageal reflux (GER): is there a problem? Early Hum Dev. 2013;89(Suppl 1):S14–6.
27. Shepherd K, Hillman D, Holloway R, Eastwood P. Mechanisms of nocturnal gastroesophageal reflux events in obstructive sleep apnea. Sleep Breath. 2011;15(3):561–70.
28. Green BT, Broughton WA, O'Connor B. Marked improvement in nocturnal gastroesophageal reflux in a large cohort of patients with obstructive sleep apnea treated with continuous positive airway pressure. Arch Intern Med. 2003;163:41–5.
29. Shepherd KL, Holloway RH, Hillman DR, Eastwood PR. The impact of continuous positive airway pressure on the lower esophageal sphincter. Am J Physiol Gastrointest Liver Physiol. 2007;292(5):G1200–5.
30. Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. Am J Med. 2000;108(Suppl. 4A):120S–5S.
31. Ozturk O, Ozturk L, Ozdogan A, et al. Variables affecting the occurrence of gastroesophageal reflux in obstructive sleep apnea patients. Eur Arch Otorhinolaryngol. 2004;261(4):229–32.

32. Penzel T, Becker HF, Brandenburg U, et al. Arousal in patients with gastro-oesophageal reflux and sleep apnoea. Eur Respir J. 1999;14:1266–70.
33. Urata M, Fukuno H, Nomura M, et al. Gastric motility and autonomic activity during obstructive sleep apnea. Aliment Pharmacol Ther. 2006;24(S 4):132–40.
34. Jadcherla SR, Gupta A, Fernandez S, et al. Spatiotemporal characteristics of acid refluxate and relationship to symptoms in premature and term infants with chronic lung disease. Am J Gastroenterol. 2008;103:720–8.
35. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol. 2004;99:2452–8.
36. Condino AA, Sondheimer JM, Pan Z, et al. Evaluation in infantile acid and non-acid gastroesophageal reflux utilizing combined pH monitoring and impedance measurement. J Pediatr Gastroenterol Nutr. 2006;42:16–21.
37. Condino AA, Sondheimer J, Pan Z, et al. Evaluation of GER in pediatric patients with asthma using impedance-pH monitoring. J Pediatr. 2006;149:216–9.
38. Salvatore S, Arrigo S, Luini C, Vandenplas Y. Esophageal impedance in children: symptom-based results. J Pediatr. 2010;157:949–54.e1-2.
39. Lopez-Alonso M, Moya MJ, Cabo JA, et al. 24-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastro-esophageal reflux. Pediatrics. 2006;118:e299–308.
40. Hasenstab KA, Jadcherla SR. Respiratory events in infants presenting with apparent life threatening events: is there an explanation from esophageal motility? J Pediatr. 2014;165:250–5.
41. Tolia V, Wuerth A, Thomas R. Gastroesophageal reflux disease: review of presenting symptoms, evaluation, management, and outcome in infants. Dig Dis Sci. 2003;48(9):1723–9.
42. Barrington KJ, Tan K, Rich W. Apnea at discharge and gastro-esophageal reflux in the preterm infant. J Perinatol. 2002;22(1):8–11.
43. Spitzer AR, Boyle JT, Tuchman DN, et al. Awake apnea associated with gastroesophageal reflux: a specific clinical syndrome. J Pediatr. 1984;104:200–5.
44. Tieder JS, Cowan CA, Garrison MM, Christakis DA. Variation in inpatient resource utilization and management of apparent life-threatening events. J Pediatr. 2008;152(5):629–35.
45. Okada K, Miyako M, Honma S, et al. Discharge diagnoses in infants with apparent life-threatening event. Pediatr Int. 2003;45(5):560–3.
46. Rosen CL, Frost JD Jr, Harrison GM. Infant apnea: polygraphic studies and follow-up monitoring. Pediatrics. 1983;71:731–6.
47. Tirosh E, Kessel A, Jaffe M, et al. Outcome of idiopathic apparent life-threatening events: infant and mother perspectives. Pediatr Pulmonol. 1999;28:47–52.
48. Herbst JJ, Book LS, Bray PF. Gastroesophageal reflux in the “near miss” sudden infant death syndrome. J Pediatr. 1978;92:73–5.
49. Herbst JJ, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. J Pediatr. 1979;95:763–8.
50. Leape LL, Holder TM, Franklin JD, et al. Respiratory arrest in infants secondary to gastroesophageal reflux. Pediatrics. 1977;60:924–8.
51. Friesen CA, Streed CJ, Carney LA, et al. Esophagitis and modified Bernstein tests in infants with apparent life-threatening events. Pediatrics. 1994;94:541–4.
52. Gorrotxategi P, Eizaguirre I, Saenz de Ugarte A, et al. Characteristics of continuous esophageal pH-metering in infants with gastroesophageal reflux and apparent life-threatening events. Eur J Pediatr Surg. 1995;5(3):136–8.
53. Kahn A, Rebuffat E, Sottiaux M, et al. Sleep apneas and acid esophageal reflux in control infants and in infants with an apparent life-threatening event. Biol Neonate. 1990;57(3–4):144–9.
54. Arad-Cohen N, Cohen A, Tirosh E. The relationship between gastroesophageal reflux and apnea in infants. J Pediatr. 2000;137:321–6.
55. Doshi A, Bernard-Stover L, Kuelbs C, et al. Apparent life-threatening event admissions and gastroesophageal reflux disease: the value of hospitalization. Pediatr Emerg Care. 2012;28(1):17–21.

56. Mousa H, Woodley FW, Metheney M, Hayes J. Testing the association between gastroesophageal reflux and apnea in infants. J Pediatr Gastroenterol Nutr. 2005;41:169–77.
57. Blasco-Alonso J, Yun-Castilla C, Girón-Fernández-Crehuet F, et al. Esophageal multichannel intraluminal impedance and pH testing in the study of apparent life threatening episode incidents in infants. Rev Esp Enferm Dig. 2014;106:159–64.
58. Jolley SG, Halpern LM, Tunell WP, et al. The risk of sudden infant death from gastroesophageal reflux. J Pediatr Surg. 1991;26(6):691.
59. Tieder JS, Altman RL, Bonkowsky JL, et al. Management of apparent life-threatening events in infants: a systematic review. J Pediatr. 2013;163(1):94–9.
60. Tieder JS, Bonkowsky JL, Etzel RA, Subcommittee on apparent life threatening events, et al. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. Pediatrics. 2016;137(5):e20160590.
61. Menon AP, Schefft GL, Thach BT. Apnea associated with regurgitation in infants. J Pediatr. 1985;106:625–9.
62. de Ajuriaguerra M, Radvanyi-Bouvet MF, Huon C, Moriette G. Gastroesophageal reflux and apnea in prematurely born infants during wakefulness and sleep. Am J Dis Child. 1991;145:1132–6.
63. Di Fiore JM, Arko M, Hitehouse M, et al. Apnea is not prolonged by acid gastroesophageal reflux in preterm infants. Pediatrics. 2005;116:1059–63.
64. Misra S, Macwan K, Albert V. Transpyloric feeding in gastroesophageal-reflux-associated apnea in premature infants. Acta Paediatr. 2007;96:1426–9.
65. Wenzl TG, Silny J, Schenke S, et al. Gastro-esophageal reflux and respiratory phenomena in children: status of the intraluminal impedance technique. J Pediatr Gastroenterol Nutr. 1999;28:423–8.
66. Corvaglia L, Zama D, Gualdi S, et al. Gastro-oesophageal reflux increases the number of apnoeas in very preterm infants. Arch Dis Child Fetal Neonatal Ed. 2009;94:F188–92.
67. Magistà A, Indio F, Baldassarre M, et al. Multichannel intraluminal impedance to detect relationship between gastroesophageal reflux and apnoea of prematurity. Dig Liver Dis. 2007;39:216–21.
68. Peter CS, Sprodowski N, Bohnhorst B, et al. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. Pediatrics. 2002;109:8–11.
69. Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. Pediatrics. 2004;113:e128–32.
70. Corvaglia L, Zama D, Spizzichino M, et al. The frequency of apneas in very preterm infants is increased after non-acid gastro-esophageal reflux. Neurogastroenterol Motil. 2011;23:303–7.
71. van Wijk MP, Benninga MA, Dent J, et al. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr. 2007;151:585–90.
72. Corvaglia L, Rotatori R, Ferlini M, et al. The effect of body positioning on gastroesophageal reflux in premature infants: evaluation by combined impedance and pH monitoring. J Pediatr. 2007;151:591–6.
73. van Wijk MP, Benninga MA, Davidson GP, et al. Small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral position in infants. J Pediatr. 2010;156:744–8.
74. Cresi F, Marinaccio C, Russo MC, et al. Short-term effect of domperidone on gastroesophageal reflux in newborns assessed by combined intraluminal impedance and pH monitoring. J Perinatol. 2008;28:766–70.
75. National Institute of Health and Care Excellence (NICE) Clinical Knowledge Summaries on Gastroesophageal reflux disease in children available on www.nice.org.uk/guidance/NG1.
76. Smits MJ, Van Wijk MP, Langendam MW, et al. Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review. Neurogastroenterol Motil. 2014;26:1527–38.
77. Di Fiore J, Arko M, Herynk B, et al. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. J Perinatol. 2010;30:683–7.

78. Rosen CL, Storfer-Isser A, Taylor HG, et al. Increased behavioral morbidity in school-aged children with sleep-disordered breathing. Pediatrics. 2004;114:1640–8.
79. Sifrim D, Dupont I, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54:449–54.
80. Blondeau K, Mertens V, Dupont L, et al. The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings. Pediatr Pulmonol. 2011;46(3):286–94.
81. Greenstone M, Hack M. Ostructive sleep apnoea. BMJ. 2014;348:g3745.
82. Ali NJ, Pitson D, Stradling JR. Natural history of snoring and related behaviour problems between the ages of 4 and 7 years. Arch Dis Child. 1994;71(1):74–6.
83. Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. American Academy of Pediatrics. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2002;109:704–12.
84. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. Am J Respir Crit Care Med. 2010;182:676–83.
85. Katz ES, D'Ambrosio CM. Pathophysiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc. 2008;5:253–62.
86. Larkin EK, Patel SR, Goodloe RJ, et al. A candidate gene study of obstructive sleep apnea in European Americans and African Americans. Am J Respir Crit Care Med. 2010;182:947–53.
87. Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol. 2000;119:2–3.
88. Berg S, Hoffstein V, Gislason T. Acidification of distal esophagus and sleep related breathing disturbances. Chest. 2004;125:2101–6.
89. Carr MM, Poje CP, Ehrig D, Brodsky LS. Incidence of reflux in young children undergoing adenoidectomy. Laryngoscope. 2001;111:2170–2.
90. Friedman M, Gurpinar B, Lin HC, et al. Impact of treatment of gastroesophageal reflux on obstructive sleep apnea–hypopnea syndrome. Ann Otol Rhinol Laryngol. 2007;116:805–11.
91. Noronha AC, de Bruin AC, Nobre e Souza VM, et al. Gastroesophageal reflux and obstructive sleep apnea in childhood. Int J Pediatr Otorhinolaryngol. 2009;73(3):383–9.
92. Stapleton A, Brodsky L. Extra-esophageal acid reflux induced adenotonsillar hyperplasia: case report and literature review. Int J Pediatr Otorhinolaryngol. 2008;72:409–13.
93. Bortolotti M, Gentilini L, Morselli C, Giovannini M. Obstructive sleep apnoea is improved by a prolonged treatment of gastroesophageal reflux with omeprazole. Dig Liver Dis. 2006;38(2):78–81.
94. Tawk M, Goodrich S, Kinasewitz G, Orr W. The effect of 1 week of continuous positive airway pressure treatment in obstructive sleep apnea patients with concomitant gastroesophageal reflux. Chest. 2006;130(4):1003–8.
95. Djeddi D, Cantin D, Samson N, Praud JP. Nasal continuous positive airway pressure inhibits gastroesophageal reflux in newborn lambs. PLoS One. 2014;9(9):e107736.
96. Praud JP. Upper airway reflexes in response to gastric reflux. Paediatr Respir Rev. 2010;11:208–12.

Gastroesophageal Reflux and Respiratory Tract Symptoms

13

Daniel R. Duncan and Rachel L. Rosen

Abstract

Gastroesophageal reflux has been held responsible for a variety of respiratory symptoms including asthma, recurrent pneumonia, and myriad upper airway symptoms in the pediatric population. The focus of much of the early research has been on proving the association between esophageal reflux events and extraesophageal symptoms though recent studies have explored the role of biomarkers as novel diagnostic tests. Because of the lack of sensitive diagnostic tests for extraesophageal reflux disease, many clinicians continue to prescribe or recommend empiric medical and surgical reflux therapies though there is again a lack of convincing data showing benefit to these therapies and some studies even suggesting harm. The field of reflux-related respiratory disorders continues to evolve, however, and the challenge of caring for these pediatric patients requires a multidisciplinary team-based approach.

Keywords

Gastroesophageal reflux disease • Extraesophageal reflux • Reactive airway disease • Asthma • Recurrent pneumonia • Upper airway symptoms • Multichannel impedance with pH • Pepsin • Microbiome • Proton pump inhibitor • Fundoplication

D.R. Duncan • R.L. Rosen (✉)
Aerodigestive Center, Center for Motility and Functional Gastrointestinal Disorders, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, MA 02115, USA
e-mail: rachel.rosen@childrens.harvard.edu

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_13

Introduction

There is perhaps no other manifestation of reflux that has been subjected to more study and debate than respiratory tract symptoms. Gastroesophageal reflux has been postulated to cause respiratory symptoms in the pediatric population for many years due to the concern that either distal esophageal reflux triggers reflex bronchospasm or, more recently and perhaps more likely, that full-column refluxate reaches the oropharynx and causes direct and/or indirect damage to the larynx, trachea, and/or lungs [1, 2]. Even with improved technology, proving causality is difficult, and many patients undergo a variety of diagnostic tests and empiric therapies which result in significant cost and effect on quality of life. Children who suffer from extraesophageal symptoms of reflux often have decreased quality of life and see multiple specialists at great expense in the evaluation and treatment of their symptoms [3]. Recognizing the difficulty these families face in this experience is essential since children's symptoms can sometimes be debilitating, highlighting the significance of taking a multidisciplinary team-based approach that combines gastroenterologists with otolaryngologists, pulmonologists, and other supportive team members including speech language pathologists and dieticians. This approach has been shown to decrease both healthcare costs and burden in the pediatric population [4]. This communication is essential to not only coordinate testing and treatments.

Epidemiology of Extraesophageal Reflux Disease

Signs and symptoms of extraesophageal reflux disease are varied and are shown in Table 13.1. Reflux has been implicated as a cause of up to 57% of these signs and symptoms [5]. Multiple cross-sectional studies and systematic reviews in adults and children have shown possible associations between GERD and these respiratory disorders, but causality remains difficult to establish with clarity [5–8]. Because of the varied signs and symptoms of reflux and the number of specialists involved in

Table 13.1 Proposed symptoms and signs of extraesophageal reflux

Symptom/sign
Reactive airway disease/asthma/wheezing
Cough or nocturnal cough
Stridor
Hoarseness
Recurrent pneumonia
Laryngeal/pharyngeal inflammation
Dental erosions
Sinusitis
Recurrent otitis media
Apnea spells
Apparent life-threatening events/brief resolved unexplained events

the patient's care, there is often a costly workup for patients; while no pediatric data exists, the cost for diagnosing and managing these patients is upward of 50 billion dollars per year, on par with cancer diagnosis and management. These tremendous costs are driven by testing (on average 5 diagnostic tests per patient) and empiric therapies with proton pump inhibitors.

Respiratory tract symptoms most frequently attributed to reflux include reactive airway disease, recurrent pneumonia, and an assortment of upper airway symptoms. The epidemiology and evidence for these proposed symptoms will be presented briefly followed by a discussion of diagnostic testing and treatment options.

Reactive Airway Disease

As one of the most common chronic medical problems affecting children, asthma is a cause of great morbidity in pediatrics, resulting in more than 20,000 hospitalizations each year [9]. In the current era, asthma is not thought to be a single simple disease entity but rather a complex interplay between multiple individual diseases and pathways [10]. In younger children in particular, it is thought that reflux might be an important mediator or even cause of reactive airway disease in select patients [11].

Reflux has been proposed to play a role in reactive airway disease and asthma for many years, and a recent systematic review of 20 well-designed pediatric studies suggests that the average prevalence of GERD (diagnosed by testing or symptoms) in children with asthma was 22% compared to 4.8% of controls [12, 13]. While acid infusion has been shown in adults to induce bronchospasm in patients with asthma, no comparable pediatric studies have been performed, and more recent studies have suggested the microaspiration may be a more significant mechanism [14–17]. Studies of children with asthma and subsequent reflux testing have mixed results. In a study of 21 children using oropharyngeal pH monitoring, Banaszkiewicz et al. suggested that pharyngeal pH may correlate with poorer asthma control in children though the technology used in this study may not be reliable [18]. Kilic et al. studied 50 children with controlled and uncontrolled asthma and found no relationship between esophageal acidification and asthma control [19]. Additionally, Condino et al. studied 24 asthmatic children with multichannel impedance with pH and concluded that most asthma symptoms occur in the absence of a reflux event, and Chang et al. used an ambulatory pHmetry-cough logger to analyze 5628 coughs in 20 children with chronic cough and found that 84% of coughs were independent of a reflux event [20, 21]. Despite reports in the adult literature about the impact of nocturnal reflux on asthma symptoms, no similar pediatric association has been found [22]. While case control studies support that patients with asthma may experience asthma improvement after reflux therapies, well-designed randomized controlled studies have failed to show any benefit of reflux therapies in asthma outcomes [23–25].

While most of the studies support an association between asthma and GERD, it is not clear if the GERD causes the asthma or rather that asthma triggers the GERD. There is a mechanistic basis for this latter theory. Chronic lung

hyperinflation can effectively lower the lower esophageal sphincter pressure and promote the occurrence of reflux events [26, 27]. Additionally, while beta-agonists have not been associated with reflux, oral corticosteroids have been shown to promote reflux in adults though their impact in children is not known [28, 29]. Other asthma medications such as theophylline have been shown to inhibit lower esophageal sphincter pressure in studies utilizing pressure recordings in adults, thus predisposing patients to reflux, but Berquist et al. combined theophylline administration with 24-h pH monitoring in 10 asthmatic children and found no increase in reflux episodes [30, 31].

Recurrent Pneumonia

Reflux has classically been thought to cause recurrent pneumonia by way of gastric aspiration or microaspiration of full-column reflux, typically in patients with impaired airway protective mechanisms [32]. Unfortunately proving that pneumonias are resulting from gastric aspiration is almost impossible as these patients typically also have oropharyngeal dysphagia with salivary aspiration as well. The impact of GERD on pneumonias is largely gleaned from the fundoplication data in which reduction in pneumonia risk after fundoplication has been reported to range from 0 to 83% in neurologically impaired children, but there has been difference seen in hospitalization rates for recurrent pneumonia in these children [33–35]. In studies that compared rates of respiratory complications after gastrostomy tube with fundoplication to gastrostomy tube placement alone, there were no differences in pneumonia risk, suggesting reflux is not a significant contributor [33, 36]. In a study by Duncan et al. of 116 children undergoing multichannel intraluminal impedance with pH testing (pH-MII), he found that there was no increased risk of pulmonary hospitalizations in children with pathologic reflux, even after adjustment for aspiration risk, again suggesting gastroesophageal reflux may not be a significant contributor to pulmonary disease [37].

Upper Airway Symptoms

Reflux is typically thought to be a cause of hoarseness, chronic cough, and globus sensation, but the evidence for a clear association with these symptoms is weak [38]. A systematic review by Rosbe et al. found a relationship between reflux and upper airway symptoms in children but noted marked heterogeneity between the studies that were analyzed [39]. There is frequent discussion of upper airway symptoms in the otolaryngology literature, where this clinical entity is frequently referred to as laryngopharyngeal reflux, differentiating it from reflux that does not pass the upper esophageal sphincter [40]. Otolaryngologists frequently cite findings of erythema, edema, and cobblestoning seen on laryngoscopy as evidence of reflux causing upper airway symptoms, but the correlation of these findings with reflux testing is poor, and these findings are therefore generally felt to be unreliable. Most recently,

Rosen et al. studied 77 children with pH-MII testing and airway exams blindly scored by otolaryngologists and found no relationship between any of the reflux parameters including the type of reflux (acid/nonacid) or the height of the reflux and the appearance of the airways [41].

Cystic Fibrosis

Studies have shown that the rate of pathologic gastroesophageal reflux in patients with cystic fibrosis is as high as 54% and these patients have been shown to have poor acid clearance and inadequate acid suppression responsiveness [42, 43]. As with all respiratory disease, it is not clear if the pulmonary pathology causes the increased reflux or vice versa. In patients with cystic fibrosis, gastroesophageal reflux could be exacerbated by chronic coughing increasing the intra-abdominal pressure, poor motility due to required high-fat diets, or changes in the role of the diaphragm in reinforcing the lower esophageal sphincter. Furthermore, some studies have even suggested that gastroesophageal reflux may modify the lung microbiome of children with cystic fibrosis which then may result in functional declines [44]. Sometimes even therapies for cystic fibrosis may worsen gastroesophageal reflux; for example, studies vary about the impact of chest physiotherapy on gastroesophageal reflux with the number of reflux events varying depending on the position of the patient during the therapy [45, 46].

While studies have shown a correlation between pathologic gastroesophageal reflux and worse pulmonary function, proving causality is again difficult because both decline in lung function and worsening gastrointestinal function may merely represent that the patient is sicker in general [44, 47]. Studies of fundoplication in patients with cystic fibrosis show no apparent benefit to lung function postoperatively, and similar results are seen in the lung transplant population [48–51].

Diagnostic Testing

While some of the diagnostic tests for typical symptoms of gastroesophageal reflux are used for the diagnosis of extraesophageal reflux disease, some of the options differ, and there are a number of new potential modalities. Prospective studies have shown a high yield to reflux testing in children presenting with chronic cough and wheezing, but the yield of each test varies depending on the symptom under evaluation. Each of the commonly used approaches to testing will be discussed below.

Impedance Testing

Functional testing utilizing multichannel intraluminal impedance with pH monitoring (pH-MII) has become the test of choice in evaluating patients with both typical and atypical symptoms. In contrast to traditional pH probe studies, pH-MII allows

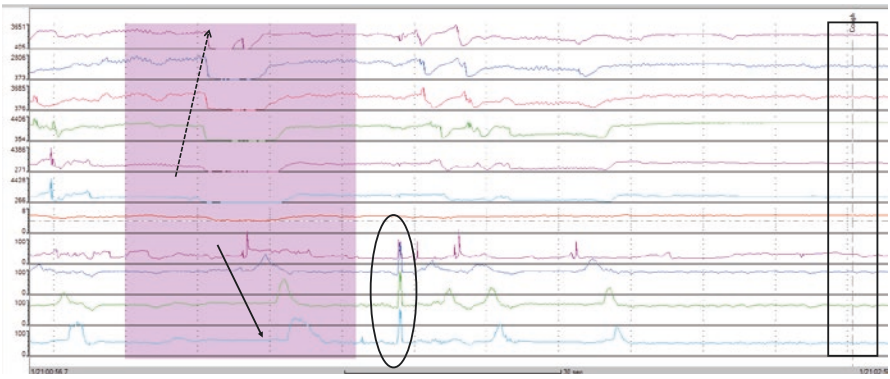
for the measurement of both acid and nonacid reflux and the height of the refluxate. The measurement of nonacid reflux is particularly important in pediatrics since up to 50% of pediatric reflux episodes are nonacid events, and there is some evidence to suggest that respiratory symptoms occur more frequently with nonacid events [52, 53]. The measurement of full-column reflux is also important because the presumed mechanism of many extraesophageal symptoms is full-column reflux causing laryngeal or bronchial inflammation, bronchospasm, or laryngospasm. In a prospective study of 112 children with respiratory symptoms, up to 58% of patients were found to have abnormal reflux testing with the most common pH-MII finding being an abnormal symptom association between cough and reflux [54]. Rosen et al. found, in a study of 28 children with respiratory symptoms, that nonacid reflux events and full-column events were more likely to cause respiratory symptoms than acid reflux or distal esophageal reflux [52]. Jadcherla et al. found, in a study of nine preterm infants, that full-column events were more likely to trigger respiratory symptoms [55]. Borrelli et al. prospectively analyzed 21 children with suspected pulmonary aspiration who underwent pH-MII testing and found a correlation between nonacid reflux and lipid-laden macrophage index, but, as discussed below, this specificity of the lipid-laden macrophage index has been called into question [56]. Finally, studies of the lung microbiome suggest that full-column, nonacid reflux in children may be associated with positive lung cultures which may impact lung function and symptoms [57].

pH-MII testing has also served as the gold standard tool to disprove the role of reflux in extraesophageal reflux disease. For example, there is perhaps no better studied population than infants presenting with apparent life-threatening event (ALTE) or brief resolved unexplained event (BRUE), a cohort of patients who have choking and even cyanotic episodes. Multiple studies using pH-MII testing have failed to show a consistent relationship between reflux events [58–60]. Similarly, pH-MII has been used to disprove the relationship between reflux events and airway erythema and proposed extraesophageal reflux disease biomarkers [61].

While pH-MII testing offers significantly more insight into esophageal physiology compared to standard pH probe testing, there are still several limitations to this and all esophageal-based technology. It is not clear that measuring esophageal reflux burden reflects the amount of reflux seen by extraesophageal sites. Second, it is not clear how much reflux is considered pathologic for extraesophageal sites, so the normal values for reflux burden in the esophagus may not apply to extraesophageal sites. Third, extraesophageal symptoms and signs are sporadic, so correlating symptoms with reflux events can be difficult.

Intraesophageal Pressure Recording and Acoustic Cough Recording

It is important to note that symptom recording, an essential component of impedance testing, can be flawed by frequent reporting errors by both parents and patients. In adult studies, patients fail to report up to 61% of symptoms during pH-MII



Dashed arrow: Reflux event. Solid arrow: Normal peristalsis. Circle: Cough detected by manometry. Rectangle: Patient reported cough. Note the time difference between pressure-recorded cough and patient reported cough.

Fig. 13.1 Example of intraesophageal pressure recording detecting cough combined with pH-MII

testing [62]. Similar studies have been performed in pediatrics and suggest that up to 60% of cough episodes during pH-MII testing are not reported by parents [63]. To overcome this inaccurate symptom reporting, manometry sensors can be placed in the esophagus alongside the pH-MII catheters. These pressure sensors measure coughs which appear as simultaneous high-pressure spikes. The addition of these pressure sensors increases cough detection by more than 100% and changes the reflux-symptom association in 20% of patients; the manometry catheter detects 94% of coughs compared to only 48% recorded by the family [64]. An example of intraesophageal pressure recording detecting coughs combined with pH-MII is shown in Fig. 13.1. Because the passage of the manometry catheter (cough catheter) in addition to the pH-MII catheter can be uncomfortable, another option for measurement of symptoms is the use of tracheal and chest wall microphones to detect sound and synch respiratory sounds with reflux events. As with the cough catheter, the addition of acoustic sound recording increases cough detection by more than 100% and improved reflux-cough correlation.

Reflux Finding Score

The reflux finding score is a clinical composite based on flexible laryngoscopy findings by otolaryngologists that was initially validated against pH probe results before and after acid suppression treatment for use in adults [65]. The score involves such findings as erythema, edema, and other markers of suspected reflux-related injury in the pharynx and has the benefit of being relatively noninvasive. This approach remains widely used by pediatric otolaryngology providers to guide therapy for aerodigestive patients in clinical practice. However, recent studies have questioned the reliability of this scoring system, showing that none of the airway findings correlate with any reflux parameters by pH-MII testing or endoscopy [66].

Oropharyngeal pH Monitoring

Oropharyngeal pH monitoring is a newer approach that utilizes a small probe placed through the nose into the posterior oropharynx behind the palate. Initial studies in adults showed a high degree of concordance with traditional pH probes and that oropharyngeal probes are perhaps more sensitive for detecting laryngopharyngeal reflux [67, 68]. However, in a definitive pediatric study in which both pH-MII and oropharyngeal probes were placed simultaneously in the same patient, there was no correlation between esophageal events or oropharyngeal drops in pH suggesting that the oropharyngeal probe was not, in fact, measuring esophageal events [69]. Subsequently, adult studies have shown similar findings, and for this reason, oropharyngeal pH monitoring is not recommended for the diagnosis of extraesophageal reflux disease [70, 71].

Esophageal Manometry

High-resolution esophageal manometry (HRM) testing does not have a role in the diagnosis of extraesophageal disease, but it does have a role in the diagnosis of gastroesophageal reflux mimickers. For typical reflux symptoms, HRM with impedance is important in the diagnosis of rumination syndrome [72]. For atypical symptoms, HRM with impedance is important in the diagnosis of causing esophageal stasis (which puts patients at risk for aspiration) and for cricopharyngeal dysfunction which causes oropharyngeal dysphagia (with symptoms of coughing and/or choking with feeds) [73, 74]. In cases where a motility disorder is suspected as a cause of respiratory symptoms, the addition of impedance to HRM is critical to assess the impact of esophageal clearance on symptoms [74].

Biomarkers: Lipid-Laden Macrophage Index, Bile, and Pepsin

Because it is not clear that measuring esophageal reflux burden reflects the impact of reflux beyond the lung, researchers have sought biomarkers in the oropharynx and lung. In the past, lipid-laden macrophage index was thought to be a useful marker of aspirated refluxate, but more recent studies have called this practice into question. Studies comparing bronchoscopy samples from patients undergoing pH-multichannel impedance testing have shown no significant correlation between lipid-laden macrophage index and the number of acid or nonacid reflux events, and therefore this marker is thought to lack the specificity needed to detect reflux-related lung disease [75, 76].

Measurement of bile acid in the oropharynx or in bronchoalveolar lavage has also been proposed as a marker of reflux-related disease. The idea of using bile stems from the lung transplant literature in which bile in BAL fluid was correlated with weakly acidic reflux by pH-MII testing, and patients with bile in BAL had a worse prognosis in terms of both survival and the presence of bronchiolitis obliterans [77]. There is some pediatric data about bile as a biomarker in the neonatal

population showing that infants with bile aspiration have issues with surfactant and may have more severe bronchopulmonary dysplasia [78]. One of the limitations of bile is that it may not be present in all refluxate and therefore might be less generalizable [40]. Furthermore, measurement of bile is difficult, requiring mass spectrometry for accurate identification and quantification of bile acids.

Several research groups have attempted to validate pepsin, a protein produced solely in the stomach, as a biomarker of extraesophageal reflux disease [40]. Pepsin has been measured in saliva, BAL fluid, middle ear fluid, and sinus washings, and depending on the fluid source, pepsin has been found in 13–88% of extraesophageal sites in symptomatic patients and 0–30% of sites in control subjects [79–81]. In children, pepsin has been found in 35–56% of BAL fluid and in 42–86% of saliva from symptomatic patients [37, 81–83]. Some groups have shown a correlation between bronchoalveolar lavage pepsin and reflux symptoms but not with pH-MII results [79, 81]. However, other studies have shown correlation between nonacid reflux and pepsin positivity, and this pepsin positivity does seem to be correlated with lung inflammation, suggesting that pepsin might be a useful marker of reflux-related lung disease [84]. Research from the intensive care unit has also suggested that a measure of pepsin in tracheal aspirates might be a useful marker of microaspiration in ventilated patients though [16, 80]. Because of the variability of these study results, the sensitivity of BAL pepsin positivity for predicting extraesophageal reflux has been estimated at 57–80% and the specificity has been estimated at 56–100% [81, 84, 85].

More recently, groups have attempted to validate salivary pepsin as a less invasive marker of extraesophageal reflux disease, but studies have shown mixed results, and at this point salivary pepsin remains of unclear clinical utility. In a study of 50 patients undergoing pH-MII for GERD, Dy et al. showed significant difference in the distribution of acid, nonacid, total reflux episodes and full-column reflux between those who were salivary pepsin positive or negative and also no correlation between number of reflux episodes and salivary pepsin concentration [83]. However, Fortunato et al. collected multiple salivary pepsin samples from subjects and found variability in these measurements throughout the day, with the highest correlation found soon after reflux events measured by 24-h impedance, suggesting that perhaps defining a specific regimen for measurement will be needed to validate salivary pepsin as a marker of extraesophageal reflux [82]. Lastly, it is also important to consider that reflux of pepsin into the oropharynx does not always necessarily lead to aspiration and lung disease [86].

The analysis of exhaled breath condensate is another recent approach to measuring pH, pepsin, and other molecules as a means of noninvasively evaluating for reflux disease. Various groups have attempted to correlate condensate values with the occurrence of cough, nocturnal reflux, and response to acid-suppressing medications [17, 87, 88]. This method represents an intriguing and still emerging approach to the diagnosis of reflux disease, but current published studies do not include adequate control and comparison with pH-MII, and a more recent study of children with asthma and reflux based on 24-h pH monitoring concluded that exhaled breath testing did not provide useful information for discriminating between asymptomatic children and those with poorly controlled asthma [89].

Therapies

Potential therapies for reflux-related respiratory symptoms are varied. These include non-pharmacologic therapies such as dietary and lifestyle changes, pharmacologic therapies with the mainstay of pharmacologic therapy being acid suppression, and surgical approaches.

Non-Pharmacologic Therapies

The mainstay for reflux therapy in pediatrics remains dietary and lifestyle changes, especially with the recent publication of multiple studies highlighting the potential risks of anti-reflux medications [90–92]. Non-pharmacologic therapies for reflux include upright positioning, thickening of feeds, change to hypoallergenic formula, and modification of meal frequencies [38]. While these modifications have been studied in the infant population with classical symptoms of reflux such as fussiness, arching, and colic, unfortunately there is limited data to suggest any of these approaches reliably help with the extraesophageal manifestations of reflux [5]. In one study of a potential approach to preventing respiratory symptoms from reflux, Garland et al. evaluated tracheal pepsin samples from intubated neonates and found lower rates of pepsin detection with head-of-bed elevation in this patient population, suggesting that at least this potential marker of extraesophageal reflux can be modulated by position changes [93].

Pharmacologic Therapies

Significant controversy surrounds the use of acid-suppressing medications such as proton pump inhibitors for extraesophageal reflux symptoms [94]. Initial studies of proton pump inhibitor (PPI) for laryngopharyngeal reflux in adults were encouraging but not well-controlled [95, 96]. More recent randomized trials, however, showed no evidence for benefit of PPI for laryngopharyngeal reflux in adults [97, 98]. Both meta-analyses and two randomized controlled trials also showed no benefit in a comparison of PPI vs placebo for chronic cough in adults [99, 100]. A small randomized controlled trial of 38 children randomized to omeprazole or placebo showed no improvement in asthma symptoms, quality of life, lung function, or use of beta-agonists in children with asthma and GERD [101]. A well-powered randomized, placebo-controlled trial of lansoprazole in 306 children aged 6–17 years with poorly controlled asthma also showed absolutely no benefit compared to placebo in improving asthma control or pulmonary function, even when looking at subgroups of patients with pathologic reflux [23]. Another double-blind placebo-controlled study showed no difference in the frequency of cough, hoarseness, or wheezing in infants treated with lansoprazole compared to placebo [102]. There is also good evidence that acid suppression only increases the burden of nonacid

reflux, which may worsen symptoms especially since nonacid reflux might be the primary driver of respiratory symptoms in these patients [52, 92].

Little work has been done to look at any potential role for pro-motility medications in this patient population, but this area needs more investigation. At the present time, the adverse effects of currently available prokinetic medications are thought to outweigh potential benefits in children [103]. Data from studies in adults, however, suggest that a not insignificant proportion of these patients might have esophageal motility disorders that might benefit from manometric testing and therapeutics if motility disorders are diagnosed [104]. Intriguing studies in both animal models and humans have shown that macrolides can play an anti-inflammatory role by way of inactivation of NF-kappaB in a rat model and that azithromycin treatment can decrease both reflux as measured by impedance and also aspiration events in human lung transplant recipients [105–107].

More research is needed regarding potential effective pharmacologic therapies since despite multiple studies showing limited benefit of currently available pharmacologic options, there remains a large clinical and economic burden for patients with extraesophageal symptoms. Prescription costs, primarily in the form of proton pump inhibitors, remain the single largest contributor to the cost of extraesophageal reflux management in adults with expenditures on PPIs constituting 52% of the total cost of care [3]. After such significant expenditure on the evaluation and treatment of their symptoms, only 54% of patients had improvement in their symptoms [3].

An additional consideration in the current use of proton pump inhibitors in these patients is the increased risk of adverse effects, including respiratory tract infections and pharyngitis, which could paradoxically lead to worsened symptoms in children already suffering from respiratory complaints [90]. In a study of children undergoing combined endoscopy and bronchoscopy for cough, we found that patients on acid suppression had increased gastric bacterial overgrowth of both staphylococcus and streptococcus and that full-column nonacid reflux was associated with increased bacteria concentrations in the lung [108]. For these reasons, any potential benefit of acid suppression in this patient population must be weighed carefully against clearly reported risks. At the current time, initiation of pharmacologic therapy for suspected reflux-related lung disease must involve a thorough discussion between clinicians and patient families, and if no benefit is seen, then such therapeutic trials must be time-limited.

Surgical Therapies

If both acid and nonacid reflux are proposed to cause respiratory problems by direct interaction with the pulmonary system, then it would seem reasonable to utilize anti-reflux surgeries to prevent this interaction. Fundoplication has been the primary surgical approach for medically refractory reflux disease in adults and children. The use of anti-reflux surgery has declined in recent years, but there remains a great deal of variability in the utilization of this surgical procedure between institutions throughout the country [109].

A number of studies have evaluated the effectiveness of surgery in treating respiratory tract symptoms, and the results overall have not been encouraging. Tannuri et al. found in a prospective single-center study of 151 children that only 45% had relief from bronchospasm following fundoplication and concluded that the surgical approach had better results for digestive compared to respiratory symptoms with a median follow-up time of 11 months [110]. In contrast, Frongia et al. reported respiratory symptom resolution in 68% of children for a median duration of 3.6 years follow-up after fundoplication [111]. Another study showed that patients had decreased use of anti-reflux medications but either no change or even increased use of asthma medications following anti-reflux surgery [112]. These studies were limited, however, by the lack of a control group, making it difficult to draw firm conclusions from their results.

As another proxy for reflux-related lung disease, several studies have looked at reflux-related hospitalization rates following anti-reflux surgery. Lee et al. retrospectively reviewed the records of 342 pediatric patients and found no improvement in hospital admission rates for aspiration, pneumonia, and respiratory distress following Nissen fundoplication [34]. In an administrative database study of 1142 children who underwent anti-reflux procedures, Goldin et al. showed a modest decline in reflux-related hospitalizations in younger children but less benefit in children above 4 years of age [113]. In contrast, Barnhart found that reflux-related hospitalizations did not differ in the year following surgery in a cohort of neurologically impaired children undergoing gastrostomy tube placement, regardless of whether patients had anti-reflux surgery or not [33].

Therefore, studies of a surgical approach for reflux-related lung disease do not suggest a strong benefit in respiratory outcomes. It is important to note that dysphagia and associated retching can be a frequent side effect of fundoplication [114]. Additionally, children with significant lung disease are necessarily placed at higher risk when undergoing anesthesia, further tipping the calculus of potential options away from the surgical approach. Unfortunately, this leaves limited options for patients with reflux-related lung disease and no strong evidence base for any clear approach.

Economic Impact

Lack of definitive and standardized testing and treatment approaches leads to a great economic burden in caring for patients with suspected extraesophageal manifestations of reflux. Patients with respiratory symptoms suspected of being reflux-related in particular often undergo an extensive workup. Typically, the care of these patients involves multiple subspecialists along with multiple procedures, medication trials, and diagnostic tests, all of which contribute to great expense. A study of the expenditures involved in caring for adults with extraesophageal symptoms revealed that the cost for the first year of workup and treatment was 5.6 times that of adults with typical GERD [3]. The expenditures involved in caring for these patients can

become quite high, but the actual benefits to the patients remain limited, and perhaps these should be taken into account and balanced in the approach to caring for these patients [115].

Conclusions

Respiratory tract symptoms due to gastroesophageal reflux disease represent an important and controversial category of extraesophageal reflux symptoms and an area of active research in pediatric gastroenterology. At this point, multichannel impedance with pH monitoring appears to be the diagnostic test of choice in order to best prove an association between respiratory symptoms and reflux events, but many other diagnostic approaches are currently under active investigation. There are no clear consistent benefits to non-pharmacologic, pharmacologic, and surgical therapies for extraesophageal symptoms, and larger, randomized controlled trials are critically needed in pediatrics. In a field with more questions than answers, a multidisciplinary approach is essential.

References

1. Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. J Pediatr. 1988;112(6):847–58.
2. Lasser MS, Liao JG, Burd RS. National trends in the use of antireflux procedures for children. Pediatrics. 2006;118(5):1828–35.
3. Francis DO, Rymer JA, Slaughter JC, Choksi Y, Jiramongkolchai P, Ogbeide E, et al. High economic burden of caring for patients with suspected extraesophageal reflux. Am J Gastroenterol. 2013;108(6):905–11.
4. Collaco JM, Aherrera AD, Au Yeung KJ, Lefton-Greif MA, Hoch J, Skinner ML. Interdisciplinary pediatric aerodigestive care and reduction in health care costs and burden. JAMA Otolaryngol Head Neck Surg. 2015;141(2):101–5.
5. Tolia V, Vandenplas Y. Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. Aliment Pharmacol Ther. 2009;29(3):258–72.
6. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56(12):1654–64.
7. Gislason T, Janson C, Vermeire P, Plaschke P, Bjornsson E, Gislason D, et al. Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries. Chest. 2002;121(1):158–63.
8. Lightdale JR, Gremse DA. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013;131(5):e1684–95.
9. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--United States, 1980–1999. MMWR Surveil summ. 2002;51(1):1–13.
10. Potter PC. Current guidelines for the management of asthma in young children. Allergy Asthma Immunol Res. 2010;2(1):1–13.
11. Gold BD. Asthma and gastroesophageal reflux disease in children: exploring the relationship. J Pediatr. 2005;146(3, Supplement):S13–20.
12. Thakkar K, Boatright RO, Gilger MA, El-Serag HB. Gastroesophageal reflux and asthma in children: a systematic review. Pediatrics. 2010;125(4):e925–30.
13. Debley JS, Redding GJ, Critchlow CW. Impact of adolescence and gender on asthma hospitalization: a population-based birth cohort study. Pediatr Pulmonol. 2004;38(6):443–50.

14. Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. Chest. 2006;130(5):1520–6.
15. Starosta V, Kitz R, Hartl D, Marcos V, Reinhardt D, Griese M. Bronchoalveolar pepsin, bile acids, oxidation, and inflammation in children with gastroesophageal reflux disease. Chest. 2007;132(5):1557–64.
16. Gopalareddy V, He Z, Soundar S, Bolling L, Shah M, Penfil S, et al. Assessment of the prevalence of microaspiration by gastric pepsin in the airway of ventilated children. Acta Paediatr. 2008;97(1):55–60.
17. Lee AL, Button BM, Denehy L, Roberts S, Bamford T, FT M, et al. Exhaled breath condensate pepsin: potential noninvasive test for gastroesophageal reflux in COPD and bronchiectasis. Respir Care. 2015;60(2):244–50.
18. Banaszkiewicz A, Dembinski L, Zawadzka-Krajewska A, Dziekiewicz M, Albrecht P, Kulus M, et al. Evaluation of laryngopharyngeal reflux in pediatric patients with asthma using a new technique of pharyngeal pH-monitoring. Adv Exp Med Biol. 2013;755:89–95.
19. Kilic M, Ozturk F, Kirmemis O, Atmaca S, Guner SN, Caltepe G, et al. Impact of laryngopharyngeal and gastroesophageal reflux on asthma control in children. Int J Pediatr Otorhinolaryngol. 2013;77(3):341–5.
20. Condino AA, Sondheimer J, Pan Z, Gralla J, Perry D, O'Connor JA. Evaluation of gastroesophageal reflux in pediatric patients with asthma using impedance-pH monitoring. J Pediatr. 2006;149(2):216–9.
21. Chang AB, Connor FL, Petsky HL, Eastburn MM, Lewindon PJ, Hall C, et al. An objective study of acid reflux and cough in children using an ambulatory pHmetry-cough logger. Arch Dis Child. 2011;96(5):468–72.
22. Molle LD, Goldani HA, Fagondes SC, Vieira VG, Barros SG, Silva PS, et al. Nocturnal reflux in children and adolescents with persistent asthma and gastroesophageal reflux. J Asthma. 2009;46(4):347–50.
23. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307(4):373–81.
24. Khoshoo V, Haydel R Jr. Effect of antireflux treatment on asthma exacerbations in nonatopic children. J Pediatr Gastroenterol Nutr. 2007;44(3):331–5.
25. Sopo SM, Radzik D, Calvani M. Does treatment with proton pump inhibitors for gastroesophageal reflux disease (GERD) improve asthma symptoms in children with asthma and GERD? a systematic review. J Investig Allergol Clin Immunol. 2009;19(1):1–5.
26. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: links and risks. Int J Chron Obstruct Pulmon Dis. 2015;10:1935–49.
27. Gadel AA, Mostafa M, Younis A, Haleem M. Esophageal motility pattern and gastroesophageal reflux in chronic obstructive pulmonary disease. Hepato-Gastroenterology. 2012;59(120):2498–502.
28. Sontag SJ, O'Connell S, Khandelwal S, Miller T, Nemchausky B, Schnell TG, et al. Effect of positions, eating, and bronchodilators on gastroesophageal reflux in asthmatics. Dig Dis Sci. 1990;35(7):849–56.
29. Lazenby JP, Guzzo MR, Harding SM, Patterson PE, Johnson LF, Bradley LA. Oral corticosteroids increase esophageal acid contact times in patients with stable asthma. Chest. 2002;121(2):625–34.
30. Berquist WE, Rachelefsky GS, Rowshan N, Siegel S, Katz R, Welch M. Quantitative gastroesophageal reflux and pulmonary function in asthmatic children and normal adults receiving placebo, theophylline, and metaproterenol sulfate therapy. J Allergy Clin Immunol. 1984;73(2):253–8.
31. Berquist WE, Rachelefsky GS, Kadden M, Siegel SC, Katz RM, Mickey MR, et al. Effect of theophylline on gastroesophageal reflux in normal adults. J Allergy Clin Immunol. 1981;67(5):407–11.

32. Danus O, Casar C, Larrain A, Pope CE 2nd. Esophageal reflux--an unrecognized cause of recurrent obstructive bronchitis in children. J Pediatr. 1976;89(2):220–4.
33. Barnhart DC, Hall M, Mahant S, Goldin AB, Berry JG, Faix RG, et al. Effectiveness of fundoplication at the time of gastrostomy in infants with neurological impairment. JAMA Pediatr. 2013;167(10):911–8.
34. Lee SL, Shabatian H, Hsu JW, Applebaum H, Haigh PI. Hospital admissions for respiratory symptoms and failure to thrive before and after Nissen fundoplication. J Pediatr Surg. 2008;43(1):59–63. discussion -5
35. Wong KK, Liu XL. Perioperative and late outcomes of laparoscopic fundoplication for neurologically impaired children with gastro-esophageal reflux disease. Chin Med J. 2012;125(21):3905–8.
36. Livingston MH, Shawyer AC, Rosenbaum PL, Jones SA, Walton JM. Fundoplication and gastrostomy versus percutaneous gastrojejunostomy for gastroesophageal reflux in children with neurologic impairment: a systematic review and meta-analysis. J Pediatr Surg. 2015;50(5):707–14.
37. Duncan DR, Amirault J, Johnston N, Mitchell P, Larson K, Rosen RL. gastroesophageal reflux burden, even in children that aspirate, does not increase pediatric hospitalization. J Pediatr Gastroenterol Nutr. 2016;63(2):210–7.
38. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
39. Rosbe KW, Kenna MA, Auerbach AD. Extraesophageal reflux in pediatric patients with upper respiratory symptoms. Arch Otolaryngol Head Neck Surg. 2003;129(11):1213–20.
40. Johnston N, Ondrey F, Rosen R, Hurley BP, Gould J, Allen J, et al. Airway reflux. Ann N Y Acad Sci. 2016;1381:5–13.
41. Rosen R, Mitchell PD, Amirault J, Amin M, Watters K, Rahbar R. The edematous and erythematous airway does not denote pathological gastroesophageal reflux. J Peds. 2017;183:127–31.
42. Dziekiewicz MA, Banaszkiewicz A, Urzykowska A, Lisowska A, Rachel M, Sands D, et al. Gastroesophageal reflux disease in children with cystic fibrosis. Adv Exp Med Biol. 2015;873:1–7.
43. Woodley FW, Machado RS, Hayes D Jr, Di Lorenzo C, Kaul A, Skaggs B, et al. Children with cystic fibrosis have prolonged chemical clearance of acid reflux compared to symptomatic children without cystic fibrosis. Dig Dis Sci. 2014;59(3):623–30.
44. van der Doef HP, Arets HG, Froeling SP, Westers P, Houwen RH. Gastric acid inhibition for fat malabsorption or gastroesophageal reflux disease in cystic fibrosis: longitudinal effect on bacterial colonization and pulmonary function. J Pediatr. 2009;155(5):629–33.
45. Doumit M, Krishnan U, Jaffe A, Belessis Y. Acid and non-acid reflux during physiotherapy in young children with cystic fibrosis. Pediatr Pulmonol. 2012;47(2):119–24.
46. Button BM, Heine RG, Catto-Smith AG, Phelan PD, Olinsky A. Chest physiotherapy, gastro-oesophageal reflux, and arousal in infants with cystic fibrosis. Arch Dis Child. 2004;89(5):435–9.
47. Button BM, Roberts S, Kotsimbos TC, Levvey BJ, Williams TJ, Bailey M, et al. Gastroesophageal reflux (symptomatic and silent): a potentially significant problem in patients with cystic fibrosis before and after lung transplantation. J Heart Lung Transplant. 2005;24(10):1522–9.
48. Palm K, Sawicki G, Rosen R. The impact of reflux burden on Pseudomonas positivity in children with Cystic Fibrosis. Pediatr Pulmonol. 2011;47:582–7.
49. Boesch RP, Acton JD. Outcomes of fundoplication in children with cystic fibrosis. J Pediatr Surg. 2007;42(8):1341–4.
50. Pegna V, Mickevicius A, Tsang C. How useful is antireflux surgery in lung transplant patients with gastroesophageal reflux? Medicina. 2014;50(6):318–22.

51. Dy FJ, Freiberger D, Liu E, Boyer D, Visner G, Rosen R. The impact of gastroesophageal reflux and delayed gastric emptying on pediatric lung transplant outcomes. J Heart Lung Transplant. 2017; doi:10.1016/j.healun.2017.01.005.
52. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol. 2004;99(12):2452–8.
53. Ghezzi M, Guida E, Ullmann N, Sacco O, Mattioli G, Jasonni V, et al. Weakly acidic gastroesophageal refluxes are frequently triggers in young children with chronic cough. Pediatr Pulmonol. 2012;48:295–302.
54. Rosen R, Amirault J, Johnston N, Haver K, Khatwa U, Rubinstein E, et al. The utility of endoscopy and multichannel intraluminal impedance testing in children with cough and wheezing. Pediatr Pulmonol. 2013;49:1090–6.
55. Jadcherla SR, Gupta A, Fernandez S, Nelin LD, Castile R, Gest AL, et al. Spatiotemporal characteristics of acid refluxate and relationship to symptoms in premature and term infants with chronic lung disease. Am J Gastroenterol. 2008;103(3):720–8.
56. Borrelli O, Battaglia M, Galos F, Aloi M, De Angelis D, Moretti C, et al. Non-acid gastro-oesophageal reflux in children with suspected pulmonary aspiration. Dig Liver Dis. 2010;42(2):115–21.
57. Rosen R, Johnston N, Hart K, Khatwa U, Katz E, Nurko S. Higher rate of bronchoalveolar lavage culture positivity in children with nonacid reflux and respiratory disorders. J Pediatr. 2011;159(3):504–6.
58. Mousa H, Woodley FW, Metheney M, Hayes J. Testing the association between gastroesophageal reflux and apnea in infants. J Pediatr Gastroenterol Nutr. 2005;41(2):169–77.
59. Zimbric G, Bonkowsky JL, Jackson WD, Maloney CG, Srivastava R. Adverse outcomes associated with gastroesophageal reflux disease are rare following an apparent life-threatening event. J Hosp Med. 2012;7(6):476–81.
60. Mittal MK, Donda K, Baren JM. Role of pneumography and esophageal pH monitoring in the evaluation of infants with apparent life-threatening event: a prospective observational study. Clin Pediatr. 2013;52(4):338–43.
61. McMurray JS, Gerber M, Stern Y, Walner D, Rudolph C, Willging JP, et al. Role of laryngoscopy, dual pH probe monitoring, and laryngeal mucosal biopsy in the diagnosis of pharyngoesophageal reflux. Ann Otol Rhinol Laryngol. 2001;110(4):299–304.
62. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54(4):449–54.
63. Blondeau K, Mertens V, Dupont L, Pauwels A, Farre R, Malfroot A, et al. The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings. Pediatr Pulmonol. 2011;46(3):286–94.
64. Rosen R, Amirault J, Giligan E, Khatwa U, Nurko S. Intraesophageal pressure recording improves the detection of cough during multichannel intraluminal impedance testing in children. J Pediatr Gastroenterol Nutr. 2014;58(1):22–6.
65. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope. 2001;111(8):1313–7.
66. van der Pol RJ, Singendonk MM, Konig AM, Hoeve H, Kammeijer Q, Pullens B, et al. Development of the reflux finding score for infants and its observer agreement. J Pediatr. 2014;165(3):479–84.
67. Yuksel ES, Slaughter JC, Mukhtar N, Ochieng M, Sun G, Goutte M, et al. An oropharyngeal pH monitoring device to evaluate patients with chronic laryngitis. Neurogastroenterol Motil. 2013;25(5):e315–23.
68. Andrews TM, Orobello N. Histologic versus pH probe results in pediatric laryngopharyngeal reflux. Int J Pediatr Otorhinolaryngol. 2013;77(5):813–6.
69. Chiou E, Rosen R, Jiang H, Nurko S. Diagnosis of supra-esophageal gastric reflux: correlation of oropharyngeal pH with esophageal impedance monitoring for gastro-esophageal reflux. Neurogastroenterol Motil. 2011;23(8):717–e326.

70. Ummarino D, Vandermeulen L, Roosens B, Urbain D, Hauser B, Vandenplas Y. Gastroesophageal reflux evaluation in patients affected by chronic cough: restech versus multichannel intraluminal impedance/pH metry. Laryngoscope. 2013;123(4):980–4.
71. Patel DA, Harb AH, Vaezi MF. Oropharyngeal reflux monitoring and atypical gastroesophageal reflux disease. Curr Gastroenterol Rep. 2016;18(3):12.
72. Rosen R, Rodriguez L, Nurko S. Pediatric rumination subtypes: a study using high resolution esophageal manometry with impedance. Neurogastroenterol Motil. 2016;29:e12998.
73. Singendonk MM, Smits MJ, Heijting IE, van Wijk MP, Nurko S, Rosen R, et al. Inter- and intrarater reliability of the Chicago Classification in pediatric high-resolution esophageal manometry recordings. Neurogastroenterol Motil. 2015;27(2):269–76.
74. Rommel N, Omari TI, Selleslagh M, Kritas S, Cock C, Rosan R, et al. High-resolution manometry combined with impedance measurements discriminates the cause of dysphagia in children. Eur J Pediatr. 2015;174(12):1629–37.
75. Rosen R, Fritz J, Nurko A, Simon D, Nurko S. Lipid-laden macrophage index is not an indicator of gastroesophageal reflux-related respiratory disease in children. Pediatrics. 2008;121(4):e879–84.
76. Krishnan U, Mitchell JD, Tobias V, Day AS, Bohane TD. Fat laden macrophages in tracheal aspirates as a marker of reflux aspiration: a negative report. J Pediatr Gastroenterol Nutr. 2002;35(3):309–13.
77. Mertens V, Blondeau K, Van Oudenhove L, Vanaudenaerde B, Vos R, Farre R, et al. Bile acids aspiration reduces survival in lung transplant recipients with BOS despite azithromycin. Am J Transplant. 2011;11(2):329–35.
78. De Luca D, Minucci A, Zecca E, Piastra M, Pietrini D, Carnielli VP, et al. Bile acids cause secretory phospholipase A2 activity enhancement, revertible by exogenous surfactant administration. Intensive Care Med. 2009;35(2):321–6.
79. Krishnan U, Mitchell JD, Messina I, Day AS, Bohane TD. Assay of tracheal pepsin as a marker of reflux aspiration. J Pediatr Gastroenterol Nutr. 2002;35(3):303–8.
80. Meert KL, Daphtary KM, Metheny NA. Detection of pepsin and glucose in tracheal secretions as indicators of aspiration in mechanically ventilated children. Pediatr Crit Care Med. 2002;3(1):19–22.
81. Abdallah AF, El-Desoky T, Fathi K, Elkashef WF, Zaki A. Clinical utility of bronchoalveolar lavage pepsin in diagnosis of gastroesophageal reflux among wheezy infants. Can Respir J. 2016;2016:9480843.
82. Fortunato JE, D'Agostino RB Jr, Lively MO. Pepsin in saliva as a biomarker for oropharyngeal reflux compared with 24-hour esophageal impedance/pH monitoring in pediatric patients. Neurogastroenterol Motil. 2016;29:e12936.
83. Dy F, Amirault J, Mitchell PD, Rosen R. Salivary pepsin lacks sensitivity as a diagnostic tool to evaluate extraesophageal reflux disease. J Pediatr. 2016;177:53–8.
84. Rosen R, Johnston N, Hart K, Khatwa U, Nurko S. The presence of pepsin in the lung and its relationship to pathologic gastro-esophageal reflux. Neurogastroenterol Motil. 2012;24(2):129–e85.
85. Farrell S, McMaster C, Gibson D, Shields MD, McCallion WA. Pepsin in bronchoalveolar lavage fluid: a specific and sensitive method of diagnosing gastro-oesophageal reflux-related pulmonary aspiration. J Pediatr Surg. 2006;41(2):289–93.
86. Schallom M, Tricomi SM, Chang YH, Metheny NA. A pilot study of pepsin in tracheal and oral secretions. Am J Crit Care. 2013;22(5):408–11.
87. Emilsson OI, Benediktsdottir B, Olafsson I, Cook E, Juliusson S, Bjornsson ES, et al. Respiratory symptoms, sleep-disordered breathing and biomarkers in nocturnal gastroesophageal reflux. Respir Res. 2016;17(1):115.
88. Hunt J, Yu Y, Burns J, Gaston B, Ngamtrakulpanit L, Bunyan D, et al. Identification of acid reflux cough using serial assays of exhaled breath condensate pH. Cough. 2006;2:3.
89. Fitzpatrick AM, Holbrook JT, Wei CY, Brown MS, Wise RA, Teague WG. Exhaled breath condensate pH does not discriminate asymptomatic gastroesophageal reflux or the response

to lansoprazole treatment in children with poorly controlled asthma. J Allergy Clin Immunol Pract. 2014;2(5):579–86.e7.
90. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006;117(5):e817–20.
91. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics. 2012;129(1):e40–5.
92. Rosen R. Gastroesophageal reflux in infants: more than just a pHenomenon. JAMA Pediatr. 2014;168(1):83–9.
93. Garland JS, Alex CP, Johnston N, Yan JC, Werlin SL. Association between tracheal pepsin, a reliable marker of gastric aspiration, and head of bed elevation among ventilated neonates. J Neonatal-Perinatal Med. 2014;7(3):185–92.
94. Nikaki K, Woodland P, Sifrim D. Adult and paediatric GERD: diagnosis, phenotypes and avoidance of excess treatments. Nat Rev Gastroenterol Hepatol. 2016;13(9):529–42.
95. Garrigues V, Gisbert L, Bastida G, Ortiz V, Bau I, Nos P, et al. Manifestations of gastroesophageal reflux and response to omeprazole therapy in patients with chronic posterior laryngitis: an evaluation based on clinical practice. Dig Dis Sci. 2003;48(11):2117–23.
96. Wo JM, Grist WJ, Gussack G, Delgaudio JM, Waring JP. Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study. Am J Gastroenterol. 1997;92(12):2160–5.
97. Fass R, Noelck N, Willis MR, Navarro-Rodriguez T, Wilson K, Powers J, et al. The effect of esomeprazole 20 mg twice daily on acoustic and perception parameters of the voice in laryngopharyngeal reflux. Neurogastroenterol Motil. 2010;22(2):134–41. e44-5
98. Vaezi MF, Richter JE, Stasney CR, Spiegel JR, Iannuzzi RA, Crawley JA, et al. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope. 2006;116(2):254–60.
99. Faruqi S, Molyneux ID, Fathi H, Wright C, Thompson R, Morice AH. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. Respirology. 2011;16(7):1150–6.
100. Shaheen NJ, Crockett SD, Bright SD, Madanick RD, Buckmire R, Couch M, et al. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011;33(2):225–34.
101. Stordal K, Johannesdottir GB, Bentsen BS, Knudsen PK, Carlsen KC, Closs O, et al. Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. Arch Dis Child. 2005;90(9):956–60.
102. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154(4):514–20. e4
103. Vandenplas Y. Management of paediatric GERD. Nat Rev Gastroenterol Hepatol. 2014;11(3):147–57.
104. Kastelik JA, Redington AE, Aziz I, Buckton GK, Smith CM, Dakkak M, et al. Abnormal oesophageal motility in patients with chronic cough. Thorax. 2003;58(8):699–702.
105. Ou XM, Feng YL, Wen FQ, Wang K, Yang J, Deng ZP, et al. Macrolides attenuate mucus hypersecretion in rat airways through inactivation of NF-kappaB. Respirology. 2008;13(1):63–72.
106. Mertens V, Blondeau K, Pauwels A, Farre R, Vanaudenaerde B, Vos R, et al. Azithromycin reduces gastroesophageal reflux and aspiration in lung transplant recipients. Dig Dis Sci. 2009;54(5):972–9.
107. Solidoro P, Braido F, Boffini M, Corsico AG. New life for macrolides. Minerva Med. 2013;104(6 Suppl 1):7–14.
108. Rosen R, Amirault J, Liu H, Mitchell P, Hu L, Khatwa U, et al. Changes in gastric and lung microflora with Acid suppression: Acid suppression and bacterial growth. JAMA Pediatr. 2014;168(10):932–7.

109. Goldin AB, Garrison M, Christakis D. Variations between hospitals in antireflux procedures in children. Arch Pediatr Adolesc Med. 2009;163(7):658–63.
110. Tannuri AC, Tannuri U, Mathias AL, Velhote MC, Romao RL, Goncalves ME, et al. Gastroesophageal reflux disease in children: efficacy of Nissen fundoplication in treating digestive and respiratory symptoms. Experience of a single center. Dis Esophagus. 2008;21(8):746–50.
111. Frongia G, Ahrens P, Capobianco I, Kossler-Ebs J, Stroh T, Fritsche R, et al. Long-term effects of fundoplication in children with chronic airway diseases. J Pediatr Surg. 2015;50(1):206–10.
112. Lee SL. Short- and long-term antireflux and asthma medication use in children after nissen fundoplication. Perm J. 2009;13(2):4–11.
113. Goldin AB, Sawin R, Seidel KD, Flum DR. Do antireflux operations decrease the rate of reflux-related hospitalizations in children? Pediatrics. 2006;118(6):2326–33.
114. Richards CA, Milla PJ, Andrews PL, Spitz L. Retching and vomiting in neurologically impaired children after fundoplication: predictive preoperative factors. J Pediatr Surg. 2001;36(9):1401–4.
115. Spiegel B. Diagnostic testing in extraesophageal GERD: another case of "furor medicus"? Am J Gastroenterol. 2013;108(6):912–4.

Gastro-oesophageal Reflux and Cow's Milk Allergy

14

Francesco Valitutti, Anna Rybak, and Osvaldo Borrelli

Abstract

Gastro-esophageal reflux disease (GERD) and cow's milk allergy protein (CMPA) and are both common disorders in childhood, mainly infancy, and several studies have hypothesised a causal relationship between them, suggesting that at least in a subgroup of infants GERD is attributable to CMA. In children with CMPA, a neuroimmune interactions provoked by cow's milk challenge might induce gastric motor abnormalities and in turn increase the number of reflux episodes. Studies assessing the relationship between the two conditions have shown an association ranging between 16 and 55%, which is far beyond from that expected from pure coexistence. Therefore, a possible concomitant CMPA, mainly in those infants and children with GERD unresponsive to medical treatment data, should be highly considered. Current ESPGHAN-NASPGHAN guidelines already suggest a short trial cow's milk free diet in those infants with chronic regurgitation unresponsive to medical therapy, vomiting and failure to thrive.

Keywords

Gastroesophageal reflux • Cow's milk protein allergy • pHmetry • pH-impedance

F. Valitutti • A. Rybak • O. Borrelli (✉)
Department of Paediatric Gastroenterology, Division of Neurogastroenterology and Motility, ICH University College of London, Great Ormond Street Hospital for Children, London, UK
e-mail: Osvaldo.Borrelli@gosh.nhs.uk

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_14

Introduction

Allergy is an immune-mediated disorder involving all tissues and organs where immune cells might dwell. Historically, immune-mediated reactions have been distinguished in four major types according to the first classification provided by Coombs and Gell [1]. For the purpose of our chapter, it is only important to mention that allergic reactions can either be immediate, implying an IgE-mediated reaction, or delayed, which are not IgE mediated.

Gastrointestinal (GI) allergies are almost generally mentioned and simplified as "food allergies", since food antigens are the culprits in deranging the physiologic gut immune response in genetically susceptible individuals. However, it is worth mentioning that some foods might cause adverse reaction for immunological, chemical and pseudo-pharmacodynamic interactions, such as in coeliac disease, non-coeliac wheat sensitivity and scombroid fish poisoning.

Allergy-related clinical conditions such as food allergy, rhinitis and eczema have witnessed a constant rise over the last decades, and this trend has not changed [2, 3].

Food allergy prevalence is estimated to be roughly 6–8% in paediatric group. The prevalence is highest in infants and toddlers, with 2.5% of infants suffering from milk allergy and up to 10% of children older than1 year suffering from food allergies, such as cow's milk, egg, nuts, soya, wheat and fish/shellfish [4]. It should be noted that prevalence data are often derived from studies in western populations, which focus on a relatively limited number of foods [5]. Districting patterns of food consumption and allergic sensitization might bias the relevance of specific foods to the public health in different countries [6].

Cow's milk protein allergy (CMPA) is the most common food allergy in infants with prevalence in early childhood of approximately 2–3% in developed countries [7]. CMPA has been identified as a worldwide health problem with high costs and burden for little patients and their families [8, 9]. CMPA has been frequently identified as the underlying cause in common gastrointestinal motility disorders of the childhood such as gastro-oesophageal reflux disease (GORD), recurrent abdominal pain, diarrhoea and constipation. The definitive diagnosis of allergy in these conditions, however, is difficult since CMPA could be non-IgE mediated and thus confirmed only by means of exclusion diet trial and subsequent re-challenge.

This chapter aims to review the putative mechanisms for allergy in GORD and to provide a comprehensive snapshot of available evidence on the topic.

Pathophysiology

In the eighties a clinical study showed that an enteropathy with abundant IgE plasmocytes as well as a rise of intraepithelial lymphocytes could be found in children with GORD attributable to CMPA [10]. The mechanisms by which food allergy causes gastrointestinal motor abnormalities are still a matter of debate. However, it is widely shown that allergic reactions to food proteins, either due to non-IgE or IgE-mediated mechanisms, induce mucosal infiltration and activation of different

type of inflammatory cells, such as eosinophils, mast cells (MCs) and B and T lymphocytes, throughout the gastrointestinal tract [11]. Eosinophils and MCs are considered the key effector cells of both immediate and delayed-type hypersensitivity reactions, and upon activation they release a variety of pro-inflammatory, nociceptive and vasoactive mediators as well as significant number of neurotransmitters. Within the gastrointestinal tract, MCs are in close apposition to nerve endings, and therefore their activation and degranulation are able to evoke different neuromuscular responses, such as activation of muscle contractility and neural reflexes, which might ultimately result in change gastrointestinal motor functions [12, 13].

Several studies in experimental animal models of food hypersensitivity have shown that antigen challenge in vivo is able to induce panenteric motor abnormalities, such as delayed gastric emptying, altered gastric secretion and disruption of both preprandial and postprandial small intestine motor activity with small intestine disappearance of cyclic MMC during fasting period and inability in activating the fed motor activity [14–16]. Moreover, the motor abnormalities induced by antigen challenge parallel the histological evidence of mast cell degranulation in the gastric mucosa as well as the increase in both specific markers for mucosal MC degranulation and intraluminal release of histamine and persist long after the initial challenge [17].

In children, early-onset neuroimmune interactions induced by cow's milk challenge in the gastric mucosa of atopic children could cause prompt imbalance of gastric myoelectrical activity. Ravelli et al. showed that in infants with vomiting induced by CMPA, milk challenge induces delayed gastric emptying and gastric myoelectrical dysrhythmias [18]. Few years later, Schaeppi and coworkers confirm the previous data showing that early-onset neuroimmune interactions induced by cow's milk challenge in the gastric mucosa of atopic children parallel the rapid derangement of gastric myoelectrical activity [19]. Notably, cow's milk exposure of the gastric mucosa induced a rapid degranulation of MCs and eosinophils. Activated MCs migrated in proximity of mucosal nerve fibres; moreover tryptase released from MCs was colocalized with proteinase-activated receptors 2 (PAR-2) on the same fibres. In the interim, there was a swift induction of electrogastrographic myoelectrical abnormalities. Intriguingly in the stomach of animal models, PAR-2 induces neurally mediated motor and secretory response, more specifically a fundic biphasic contractile response which implies relaxation followed by contraction [20]; in addition, a suppression of acid production follows this activity mediated by PAR-2 [21].

Furthermore, it has been identified that episodes of dysrhythmia are possible causes of antral hypo-contractility, which in turn promotes a delay of stomach emptying [22]. A delay in gastric emptying might increase gastro-oesophageal reflux by increasing the availability of material to reflux or by inducing prolonged gastric distention and by increasing the frequency of transient lower oesophageal sphincter relaxations (TLOSRs), which are the main underlying mechanism of gastro-oesophageal reflux [23]. It could be speculated that in a subgroup of infants and children with CMPA neuroimmune activation evoked during milk challenge might derange the gastric motor activity and hence delay the gastric emptying and increase the rate of TLOSRs, resulting in an increase in the number of reflux episodes.

Clinical Picture and Diagnostic Strategies

It is clear that allergy to cow's milk protein may cause symptoms such as irritability, distress and vomiting indistinguishable from GORD, thus complicating the diagnostic pathway in the clinical practice.

Although most studies report a comparable incidence of regurgitation in unselected populations of formula versus breastfed infants, Hegar et al. reported a higher incidence of regurgitation in formula-fed infants [24]. Alongside this consideration, it should be stressed that the prevalence of CMPA is five to ten times higher in formula fed than in breastfed infants [25], thus fashioning the possible epidemiological scenario for two overlapping conditions.

However, studies assessing the relationship between food allergy and GORD show an overall association between 16 and 55% [26], thus far beyond what can be expected from pure coexistence of the two entities. In the mid-1990s, Iacono et al. described that 42% of infants with GORD symptoms and histologic oesophagitis clinically improved on a cow's milk-free diet and then worsened following antigen challenge [27]. Subsequently, Nielsen et al. showed that 56% of children with severe GORD were found to have CMA on double-bind or open challenge [28]. Recently, Yukselen et al. identified food allergy in 65 of 151 children with GORD refractory to medical therapy, of which 89% reacted to cow's milk, whilst a minority (11%) did so towards egg [29]. Notably, only half of those patients with GORD and food allergy had positive oral challenge and skin prick test and/or specific IgE; on the contrary, the other half could merely confirm the diagnosis by means of oral challenge.

In the past, some attempts had been made in order to elucidate the relationship between CMPA and GORD in the clinical setting by means of pH monitoring. However, these pH-only studies have led to conflicting results [25–32]. A particular phasic pH pattern characterized by a slow and progressive decrease in oesophageal pH between two feeds had been previously suggested as an effective tool for identifying patients with CMA-induced GORD by an Italian group [29, 30]. Nielsen et al. performed 48-h pH monitoring in 10 children with a severe GORD and CMA, with CM elimination diet at day 1 and CM challenge at day 2 [31]. Interestingly, they failed to find any difference in the reflux parameters between the two recording days. On the contrary, a Polish study confirmed the findings of the Italian groups showing that amongst the children with CMPA and GORD, pH-metric records showed a pattern of rapid increase of pH value after a meal with its subsequent gradual decrease [33].

However, only the introduction of combined impedance and pH monitoring could shed further light on this topic. Forty-eight-hour multichannel intraluminal impedance-pH monitoring in children with CMPA and suspected GORD has shown a significant increase in weakly acid reflux episodes during cow's milk challenge compared to elemental formula feeding [34]. Nevertheless, it was not possible to ascertain whether the decrease in reflux episodes was attributable to the enhanced gastric emptying because of the elemental formula or to the suppression of an underlining immune mechanism towards cow's milk antigens. This clinical finding, however, relies on the mechanisms addressed in a previous study showing how cow's milk induces severe gastric dysrhythmia and delayed gastric emptying in sensitized infants, thus triggering GORD and inducing reflex vomiting [18].

Albeit oesophageal manometry has no diagnostic yield in this clinical framework, a research study has found that both lower oesophageal sphincter (LOS) resting pressure and LOS length did not differ between children with primary GORD and CMPA-related GORD [35].

Conclusion

In conclusion, CMPA and GORD show an association between 16 and 55% in children. These data should induce paediatricians to screen for possible concomitant CMPA mainly in those infants and children with GORD unresponsive to medical treatment. Current ESPGHAN-NASPGHAN guidelines clearly advice a 2–4 week trial of protein hydrolysate or amino acid–based formula in infants with chronic regurgitation unresponsive to medical therapy, vomiting and failure to thrive [36].

References

1. Rajan TV. The Gell-Coombs classification of hypersensitivity reactions: a re-interpretation. Trends Immunol. 2003;24:376–9.
2. Savage J, et al. Food allergy: epidemiology and natural history. Immunol Allergy Clin N Am. 2015;35:45–59.
3. Kattan I. The prevalence and natural history of food allergy. Curr Allergy Asthma Rep. 2016;16:47.
4. Hill DA, et al. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. BMC Pediatr. 2016;16:133.
5. Burks AW, et al. ICON: food allergy. J Allergy Clin Immunol. 2012;129:906–20.
6. Bjorksten B, et al. Criteria for identifying allergenic foods of public health importance. Regul Toxicol Pharmacol. 2008;51:42–52.
7. Warren CM, et al. The epidemiology of milk allergy in US children. Ann Allergy Asthma Immunol. 2013;110:370–4.
8. Sackesen C, et al. Cow's milk allergy as a global challenge. Curr Opin Allergy Clin Immunol. 2011;11:243–8.
9. Gupta R, et al. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013;167:1026–31.
10. Forget P, et al. Cow's milk protein allergy and gastro-oesophageal reflux. Eur J Pediatr. 1985;144:298–300.
11. Bischoff S, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. Gastroenterology. 2005;128:1089–113.
12. Collins SM. The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. Gastroenterology. 1996;111:1683–99.
13. Barbara G, Stanghellini V, De Giorgio R, et al. Functional gastrointestinal disorders and mast cells: implications for therapy. Neurogastroenterol Motil. 2006;8:6–17.
14. Catto-Smith AG, Patrick MK, Scott RB, et al. Gastric response to mucosal IgE-mediated reactions. Am J Phys. 1989;257:G704–8.
15. Diamant S, Gall D, Scott R. The effect of intestinal anaphylaxis on postprandial motility in the rat. Can J Physiol Pharmacol. 1989;67:1326–30.
16. Scott RB, Diamant SC, Gall DG. Motility effects of intestinal anaphylaxis in the rat. Am J Phys. 1998;255:G505–11.
17. Saavedra Y, Vergara P. Hypersensitivity to ovalbumin induces chronic intestinal dysmotility and increases the number of intestinal mast cells. Neurogastroenterol Motil. 2005;17:112–22.

18. Ravelli AM, Tobanelli P, Volpi S, Ugazio AG. Vomiting and gastric motility in infants with cow's milk allergy. J Pediatr Gastroenterol Nutr. 2001;32:59–64.
19. Schäppi MG, et al. Mast cell-nerve interactions in children with functional dyspepsia. J Pediatr Gastroenterol Nutr. 2008;47:472–80.
20. Cocks TM, et al. Protease-activated receptors mediate apamin-sensitive relaxation of mouse and guinea pig gastrointestinal smooth muscle. Gastroenterology. 1999;116:586–92.
21. Nishikawa H, et al. Suppression by protease activated receptor-2 activation of gastric acid secretion in rats. Eur J Pharmacol. 2002;447:87–90.
22. Chen JZ, et al. Abnormal gastric myoelectrical activity and delayed gastric emptying in patients with symptoms suggestive of gastroparesis. Dig Dis Sci. 1996;8:1538–45.
23. Emerenziani S, et al. Gastroesophageal reflux and gastric emptying, revisited. Curr Gastroenterol Rep. 2005;7:190–5.
24. Hegar B, et al. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009;98:1189–93.
25. Vandenplas Y, et al. Guidelines for the diagnosis and management of cows' milk protein allergy in infants. Arch Dis Child. 2007;92:902–8.
26. Salvatore S, et al. Gastroesophageal reflux and cow's milk allergy: is there a link? Pediatrics. 2002;110:972–98.
27. Iacono G, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol. 1996;97:822–7.
28. Yukselen A, et al. Food allergy in children with refractory gastroesophageal reflux disease. Pediatr Int. 2016;58:254–8.
29. Cavataio F, et al. Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy. Arch Dis Child. 1996;75:51–6.
30. Cavataio F, et al. Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful? Am J Gastroenterol. 1996;91:1215–20.
31. Milocco C, et al. Gastro-oesophageal reflux and cows' milk protein allergy. Arch Dis Child. 1997;77:183–8.
32. Nielsen RG, et al. Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. J Pediatr Gastroenterol Nutr. 2004;39:383–91.
33. Kamer B, et al. Gastroesophageal reflux in infants with food allergy. Med Sci Monit. 2000;6:348–52.
34. Borrelli O, et al. Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease. J Pediatr. 2012;161:476–81.
35. Semeniuk J, et al. Manometric study of lower esophageal sphincter in children with primary acid gastroesophageal reflux and acid gastroesophageal reflux secondary to food allergy. Adv Med Sci. 2008;53:283–92.
36. Vandenplas Y, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.

Gastroesophageal Reflux and Cystic Fibrosis

15

Jernej Brecelj

Abstract

Cystic fibrosis is an autosomal recessive genetic disease characterized by chronic suppurative lung disease, exocrine pancreatic dysfunction, hepatobiliary disease, gastrointestinal disease, and many other clinical manifestations. Gastroesophageal reflux is a primary phenomenon in cystic fibrosis patients and is more prevalent than in general population. Lung aspirations of duodenogastric fluid are an underestimated risk factor for the lung disease progression. Advanced lung disease additionally increases gastroesophageal reflux risk. Many symptoms and signs of cystic fibrosis are overlapping with those of gastroesophageal reflux disease and are not a prognostic factor for its presence or severity level. Despite a lot of evidence, controversies regarding gastroesophageal reflux disease diagnosis and treatment in cystic fibrosis patients still exist. One of diagnostic challenges is lung aspiration detection. Proton pump inhibitors are the mainstay of the treatment employed in half of all patients. Antireflux operation in selected patients probably slows the decline of lung function. In addition, other topics of interest in cystic fibrosis patients interrelated with gastroesophageal reflux are addressed: respiratory physiotherapy, gastrostomy, and lung transplantation. With the prolongation of life expectancy, late complications of gastroesophageal reflux disease will become more prevalent. Gastroesophageal reflux in cystic fibrosis patients is a challenging field for clinical practice and research.

J. Brecelj
Department of Gastroenterology, Hepatology and Nutrition, University Children's Hospital Ljubljana, Bohoričeva ul. 20, SI-1000 Ljubljana, Slovenia

Department of Pediatrics, Faculty of Medicine, University of Ljubljana, Bohoričeva ul. 20, SI-1000 Ljubljana, Slovenia
e-mail: jernej.brecelj@kclj.si

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_15

Keywords
Gastroesophageal reflux disease • Cystic fibrosis • Combined esophageal multichannel intraluminal impedance-pH monitoring • Baseline impedance • Gastric emptying • Proton pump inhibitors • Fundoplication • Respiratory physiotherapy • Gastrostomy • Lung transplantation • Barrett's esophagus

Abbreviations

BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
FEV1	Forced expiratory volume in 1 s
GER(D)	Gastroesophageal reflux (disease)
MII-pH	Combined esophageal multichannel intraluminal impedance-pH monitoring
PPI(s)	Proton pump inhibitor(s)

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by a mutation in a gene for cystic fibrosis transmembrane conductance regulator (CFTR) protein, a transmembrane chloride channel, which also has other functions (e.g., inhibition of sodium transport through the epithelial sodium channel) and is involved in bicarbonate-chloride exchange [1]. A deficiency in bicarbonate secretion leads to poor solubility and aggregations of luminal mucins [2] and due to insufficient neutralization also lowers pH of the intestine [3].

CF leads to chronic suppurative lung disease, exocrine pancreatic dysfunction, hepatobiliary disease, gastrointestinal disease, and many other clinical manifestations, gastroesophageal reflux disease (GERD) being one of them [1]. The relationship between CF and GERD is multifaceted and complex. It was shown that GER is not merely secondary to the lung disease; it is a primary phenomenon and, therefore, more prevalent in CF patients than in the general population. Gastroesophageal reflux (GER) is also an important, but not yet fully evaluated, additional pathogenetic mechanism of lung function deterioration [4].

This chapter provides the epidemiological data and a description of pathogenetic mechanisms of GERD in CF patients. After clinical, diagnostic, and therapeutic considerations, specific situations in CF interrelated with GER are addressed: respiratory physiotherapy, gastrostomy, and lung transplantation. The chapter ends with late esophageal complications of GERD and a comprehensive list of references.

Epidemiology of GERD in CF

The prevalence of GERD in children of all age groups with CF is higher in comparison with the general population. In one of the earliest reports, all ten infants and young children included in a study had GERD measured by esophageal pH monitoring [5]. In another study 19.2% of infants younger than 6 months with CF had pathologic GER defined by the total acid exposure index of more than 10% [6].

In a study of 40 children with CF (1.3–20 years, mean age 10.9 years), 55% had acid GER defined by total exposure index of more than 5%. Upper intestinal endoscopy was performed in 10 patients with the total acid exposure index of more than 10%. Erosive esophagitis was seen on upper gastrointestinal endoscopy in eight of them (80% of a subgroup with a higher total acid exposure index or 20% of the whole group) [7].

In a group of 31 children with CF (4–7 years, mean age 12.6 years) and either typical or atypical GERD symptoms or unexplained progressive lung function decline, combined multichannel esophageal intraluminal impedance-pH monitoring (MII-pH) revealed GERD in 17 (54.8%). Upper gastrointestinal endoscopy was performed in 11 of them and had demonstrated erosive esophagitis in 2 of them (11.8% of the GERD subgroup or 6.5% of the whole group) [8].

In studies above only selected CF patients with GERD symptoms or worsening of lung function were included. Rarely an unselected cohort of CF patients was studied for GERD prevalence as it was in a multicenter study in which 44 consecutive children of median age 10.4 years with CF underwent a MII-pH off the proton pump inhibitor (PPI) treatment. Approximately one third of them had typical GERD symptoms or signs. The pathologic acid reflux was defined as total acid exposure index of more than 6% and according to this criterion GERD was diagnosed in 54.5%. High percentage (43.6%) of GER episodes reached the proximal esophagus [9].

There is less data in adult CF population. In a study of 50 consecutively studied adults with CF, 94% had symptoms of GERD. Unfortunately, further GERD diagnosis was performed in only ten; eight of them had raised DeMeester score; and six had lower value of lower esophageal sphincter pressure [10]. In another, a cross-sectional study at an adult CF center, two thirds of 201 patients had frequent or occasional GERD symptoms as assessed by two different questionnaires. Even in those on acid suppression, the prevalence of heartburn (66%) and acid regurgitation (23%) remained high [11]. In a small prospective study of adults with CF who did not have GERD symptoms, pathological GER was diagnosed in 60% by esophageal pH monitoring [12].

Mechanisms of GER in CF

There are some specificities regarding pathophysiology of GERD in CF patients. They are addressed in this section.

GER is a primary phenomenon in CF and not just a consequence of lung disease; it is prevalent already in infants with CF irrespective of lung disease [13]. The

evidence that GER in CF patients is a primary and not a secondary phenomenon due to cough was confirmed by a study of 24 children with CF, of which 11 had simultaneous measurement of MII-pH and esophageal manometry. In eight, the sequence of reflux-cough was found, and only 3 out of 11 had an inverse sequence of cough-reflux [14].

However, advanced pulmonary disease is a risk factor for GERD as it was shown in patients with terminal lung disease due to various causes. In 78 patients assessed for lung transplantation (only 5 due to CF), 63% had typical symptoms of GERD and 38% had abnormal esophageal pH monitoring [15]. For CF patients with advanced pulmonary disease, this adds to already higher burden of GERD from the CF itself.

The main pathogenetic mechanism for GER is inappropriate lower esophageal sphincter relaxations and not decreased sphincter tone. This was shown in a study of 14 children with CF aged 5 months to 16 years by esophageal manometry [16]. In an adult group of 12 CF patients who underwent esophageal high-resolution manometry impedance, it was shown that not a higher number of transient lower esophageal sphincter relaxations but a higher proportion of them associated with GER was the main pathogenetic event. One possible explanation is a higher pressure difference between thoracic and abdominal cavity because of greater inspiratory negative intrathoracic pressure in CF patients, which consequently provokes also a higher proximal GER extent [17].

Pathogenetic mechanisms of GER specifically present in CF patients are shown in Fig. 15.1.

Tissue Resistance and Local Factors

At the level of esophageal tissue resistance, our research group showed that children with CF had histological changes and lower baseline impedance (recently described esophageal impedance parameter [18, 19]) reflecting epithelial impairment even in the absence of pathologic GER [20]. We hypothesized that this might result from impaired neutralization of acid reflux by impaired bicarbonate secretion from esophageal submucosal glands [21, 22]. This is supported by the finding of prolonged chemical clearance of acid reflux in 16 children with CF and GERD in comparison to 16 children with GERD only, measured by MII-pH [23].

Duodenogastric reflux contributes to the occurrence of esophagitis in patients with GERD. The presence and composition of bile acids in gastric juice was studied in eight adult CF patients and seven control subjects by intragastric perfusion and gastroduodenal manometry. All patients had higher gastric bilirubin levels; bile acids were present in gastric juice in five of them. However, the composition was less toxic with low levels of secondary bile acids, which could result in lower percentage of erosive esophagitis and Barrett's esophagus reported in CF population [24].

Gastric emptying might influence GER in patients with CF. Data vary between different studies, but newer studies showed higher proportion of CF patients with

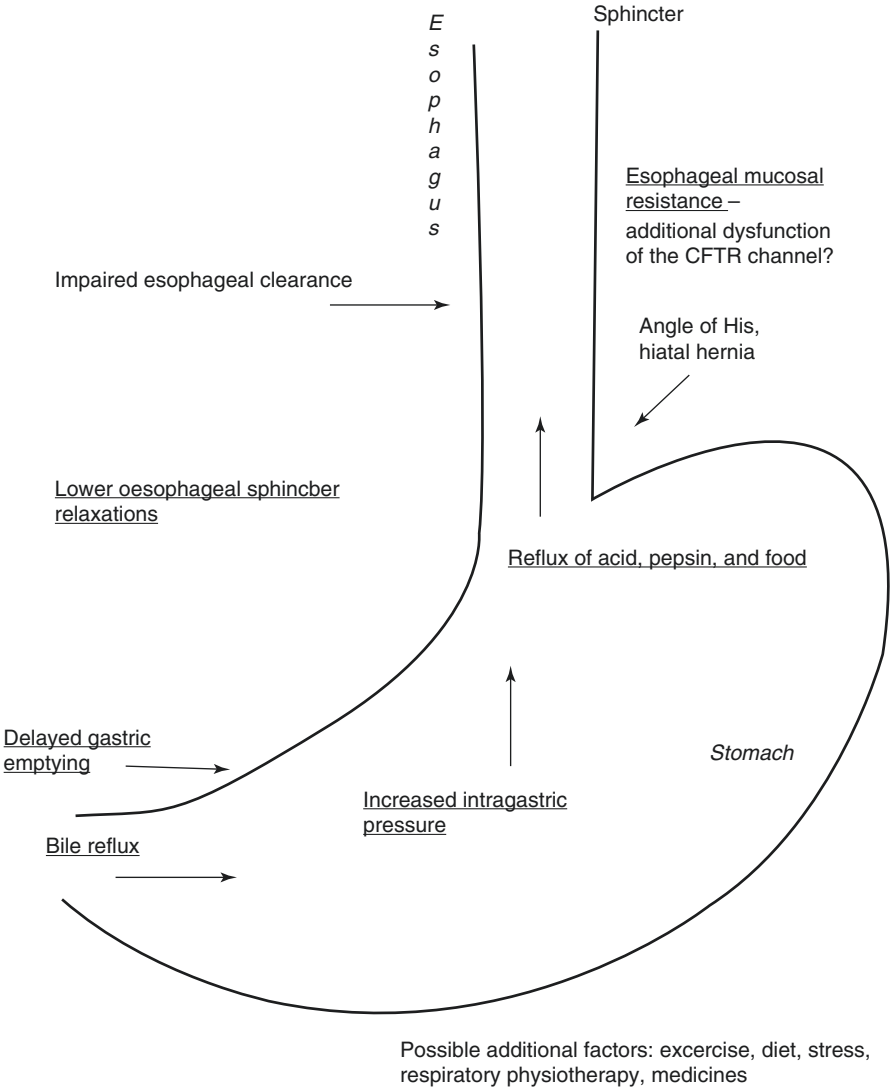


Fig. 15.1 Mechanisms of GER in CF patients

delayed gastric emptying. In a study of 33 adult patients with CF, gastric emptying for solids measured by 13C-octanoic acid breath test was delayed in 33%, predominantly acid reflux was present in 67%, and duodenogastric reflux in 35%. Overall, there was no correlation between gastric emptying and reflux parameters [25]. In a group of 28 children with CF and symptoms suggestive for GERD, 46.4% had increased acid GER, and 21.4% had delayed gastric emptying. They found no correlation between GER and gastric emptying [26].

GER and Lung Disease

The negative impact of GER on lung function has been known since the early 1980s [27, 28]. The interconnection of GER and lung disease in CF was confirmed in a study of 12 children with CF, using different diagnostic techniques for GER assessment, comparing them with lung function tests and chest radiographs. A group of four children without symptoms and signs of GERD and with normal GERD tests had significantly better lung function tests and chest radiographs than those with at least one pathologic GER test result [29].

GERD was associated with 5–10% lower forced expiratory volume in 1 s (FEV1) regardless of age in a large cross-sectional study of 7010 patients older than 6 years (the age at which FEV1 was reliably measured) included in European Epidemiologic Registry of Cystic Fibrosis in 1998 who were analyzed for different factors associated with poor pulmonary function [30].

Recurrent aspirations of duodenogastric content contribute to the lung inflammation in CF patients. In a study of 113 subjects with different diseases (patients with CF, asthma, and chronic cough compared to healthy individuals), bile acids were present in one half of patients with CF in the induced sputum. Inflammatory parameter—neutrophil elastase activity—was also increased. In other study groups, bile acids were present in induced sputum in 13% of healthy individuals, in 14% of patients with chronic cough, and in 28% of patients with asthma [31]. Another study has demonstrated bile acids in saliva of one third of 65 children with CF in contrast to none in the control group of 23 healthy children [14].

Bile was proven to influence pulmonary pathogen adaptation, especially the changes of *Pseudomonas aeruginosa* behavior with increased biofilm formation and other adaptations, all of which leading to the chronic lung infection in CF patients [32].

Gastric juice provoked more proinflammatory interleukin-8 synthesis on the primary bronchial epithelial cell culture from a CF patient in comparison to the healthy donor culture. The synthesis was even higher when the cell culture from CF patient was stimulated by gastric juice from patients treated with proton pump inhibitors due to higher endotoxin levels [33]. Similar finding was confirmed in vivo in a study of 31 children with CF and 7 healthy controls. Higher pepsin levels in bronchoalveolar lavage were found in CF patients with a moderately positive correlation with interleukin-8 levels [34].

The effect of gastric acid inhibition (with proton pump inhibitors or histamine-2 receptor antagonists) on pulmonary function and bacterial colonization was studied in 218 pediatric patients with CF. CF patients treated for GERD had earlier first infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus* and a reduction in lung function (FEV1 and forced vital capacity). Patients with gastric acid inhibition prescribed to improve fat absorption had a similar acquisition rate of *Pseudomonas aeruginosa* and *Staphylococcus aureus* but also a slower lung function decline [35]. Another study of 35 children with CF showed that *Pseudomonas aeruginosa* colonization was more prevalent in those with higher burden of total, acid, and proximal nonacid reflux. Lung function was worse in those with nonacid reflux [36].

A prospective study of seven infants with CF diagnosed by neonatal screening, who had their intestinal and lung microbiome determined every 3 months, showed similarities of both microbiomes [37]. The mode of transmission was not studied, but a possible way could also be GER.

Clinical Presentation and Specificities of GERD in CF Patients

Many symptoms and signs of GERD are overlapping with those of CF and are not a prognostic factor for GERD's presence or severity level [38]. This is especially true for the extraesophageal signs, such as chronic cough, hoarseness, recurrent pneumonias, loss of appetite, and weight loss in all age groups or failure to thrive in children (Fig. 15.2). Absence of typical or atypical symptoms and signs does not exclude GERD in CF patients irrespective of age [38].

In a study of 26 infants with CF younger than 6 months, 46.2% vomited or posseted frequently, 26.9% were irritable, 15.4% had frequent wheeze, 7.7% had feeding difficulties, and 30.8% had a failure to thrive. None of reported presentations was correlated to acid reflux parameters, with the exception of frequent vomiting, which had a negative predictive value of 92.9% [6]. Another study of 40 children with CF between 1 and 20 years revealed that 67.5% had signs and symptoms suggesting GERD: heartburn, abdominal or retrosternal pain, belching, and vomiting. Esophageal pH monitoring proved GERD in 55% of them, but there was no statistically significant difference regarding reported symptoms between the groups [7].

In a cross-sectional study of 201 adults with CF assessed by 2 validated questionnaires, 24% of patients had weekly GERD symptoms and 39% had them occasionally. The most common were heartburn (53%), acid regurgitation (33%), and

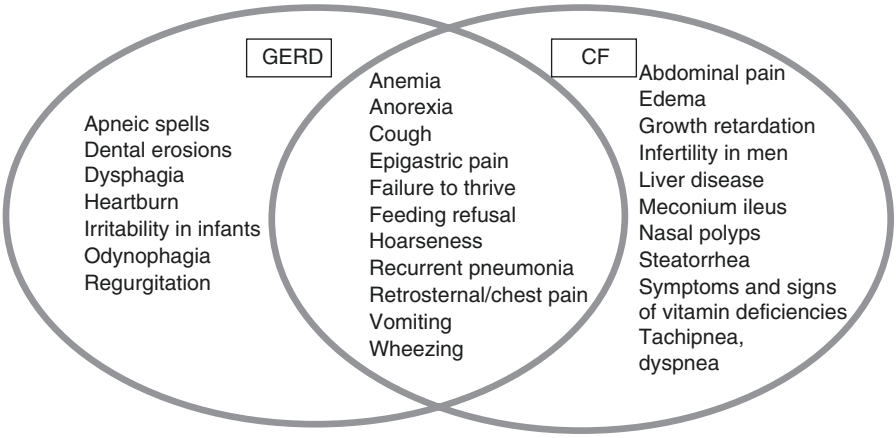


Fig. 15.2 Symptoms and signs of GERD, CF, and those common in both diseases

dysphagia (18%). However, 61% of patients were taking proton pump inhibitors or histamine-2 receptor antagonists, and questionnaires were not compared to other standardized diagnostic tests [11].

Diagnosis of GERD in CF Patients

Pediatric guidelines draw attention to CF as predisposing factor for GERD in children [39]. Due to many open questions regarding GERD in CF patients, no specific algorithm for the diagnosis and treatment of GERD in CF patients has been developed yet.

The clinical presentation of GERD in CF patients is in most cases nondiagnostic; therefore, it is mandatory to actively search for the presence of GERD in this patient group. On the other hand, CF patients are highly burdened with numerous medical investigations; many patients are also on acid suppressive treatment due to different indications [38]. Considering all these, until evidence-based guidelines for the diagnosis and treatment of GERD in CF patients are developed, patients should be managed on the individual basis.

According to recent publications and clinical experience MII-pH is probably the single most informative investigation for the diagnosis of GER in CF patients. MII-pH gives data on acid, weakly acid, and nonacid reflux and also about the upper extent of refluxes in contrast to the data on acid reflux with pH monitoring alone [40]. In addition, it offers the possibility of the measurement of bolus clearance and chemical clearance [23] and might add an information on epithelial integrity if the concept of baseline impedance is adopted in practice [19]. The combination of MII-pH and esophageal manometry provides further insights in the pathophysiology of GERB in CF [17] and offers many research possibilities.

Indications for upper gastrointestinal endoscopy and barium contrast studies do not differ from other patients [39]. Esophageal high-resolution manometry has its role in CF patients for the evaluation of esophageal motility before antireflux surgery [41].

There is no single diagnostic tool to prove pulmonary aspiration of refluxate. Nuclear scintigraphy is not reliable due to the low sensitivity and poor standardization [39]. Measurement of pepsin and bile acids in bronchoalveolar lavage is one possibility employed in some studies [42]. Lipid laden (macrophage) index (LL(M)I) is calculated from counting 100 consecutive macrophages from bronchoalveolar lavage fluid after centrifugation and the staining for lipids with Sudan 4. The LL(M)I index correlates well with lung aspirations, but is not pathognomonic [43]. In a study of 17 CF patients with GERD after lung transplantation, 12 underwent antireflux surgery and 5 refused it. LL(M)I reduced significantly after laparoscopic Nissen fundoplication and correlated with the resolution of clinical symptoms [44].

Treatment of GERD in CF Patients

Treatment of GERD in CF patients does not differ from other patients, but according to CF specificities, the proportion of various treatment options differs from the patients without CF.

Lifestyle modifications for the treatment of GERD can be very challenging in CF patients as there are not many possibilities to comply with the recommendations to eat more small meals and to avoid them before physical exercises and before sleep [39] due to the requirements for higher caloric intake in the majority of children with CF which usually ranges from 110 to 200% of the recommended daily intake for age- and sex-matched individuals [45].

In patients with erosive esophagitis, aggressive treatment with PPIs is the most effective [46]. In CF patients, however, some concerns exist. As it was already mentioned above, gastric juice of GERD patients treated with PPIs provokes more synthesis of proinflammatory cytokine interleukin-8 in vitro due to higher endotoxin levels. As gastric juice might provoke more inflammation in the lungs when aspirated, in the case of CF patients who have high prevalence of GERD and aspirations, alternative antireflux treatments should be considered [33]. In a small randomized control study of 15 CF patients, those treated with esomeprazole had more frequent pulmonary exacerbation than in the placebo group [12]. PPI treatment is not very efficient in symptom improvement in CF patients. In a cross-sectional study of 201 CF patients, of these 122 on acid suppression, 66% reported heartburn and 23% had acid regurgitation [11].

Despite all the concerns, PPIs are regularly prescribed in approximately half of the patients with CF [12, 47]. PPIs are effective also in improving the bioavailability of pancreatic enzyme supplements in patients with failure to thrive, steatorrhea, or other signs of ineffective pancrelipase treatment [48].

H2 blockers are less frequently prescribed (16.3% of the US CF population), probably due to the inferior efficiency in comparison to PPIs and the development of tachyphylaxis with prolonged use [47].

Treatment with cisapride was effective in terms of pH monitoring normalization in a small nonrandomized study in infants and small children [5], but cisapride is no longer available for routine treatment. Other prokinetics, metoclopramide, domperidone, and erythromycin, have unfavorable safety profile. Azithromycin, which is on the other hand commonly used in CF patients to treat lung infection, has not been studied yet as a prokinetic in CF population, but is sometimes prescribed due to its prokinetic properties in patients with gastroparesis [4].

The role of new drugs for CF, CFTR modifiers, has not yet been evaluated in esophageal disease in CF patients. Two medicines are approved at present, a potentiator ivacaftor for the treatment of patients with the specific mutation G551D [49] and a combination of CFTR activator lumacaftor and the aforementioned ivacaftor for the treatment of patients homozygous for F508del mutation, with varying results of treatment in different organs [50]. There are no reports on their effectiveness in

GERD in CF patients, but one study reported overall improvement of different parameters in patients with G551D mutation treated with ivacaftor, including an increase in body weight [49]. A clinical study proving the concept of better bicarbonate secretion is a study of 11 patients with CF and G551D mutation (of 151 patients included) which, among other parameters, reported significant improvement in early ability for the neutralization of gastric acid in duodenum after 1 month treatment with ivacaftor [51].

In patients with lung aspiration of refluxate and in those with intractable GERD, surgical treatment with fundoplication is at present the best choice [52–54]. In undernourished patients, which is often the case in CF patients, the gastrostomy tube can be inserted at the same time [55]. For more data on fundoplication, see "GER and Lung Transplantation."

Special Issues Regarding GER and CF

Physiotherapy and GER

There are some controversies regarding GER in CF patients during chest physiotherapy, which is an important part of everyday treatment of the majority CF patients from the very early age.

A large study of 63 infants aged 1–4 months who had pH monitoring for different indications compared to the healthy control group clearly showed higher incidence of acid reflux during 30-min physiotherapy of postural drainage, percussion, and gentle vibrations despite performing it not earlier than 180 min after the previous feeding [56]. Postural drainage physiotherapy with head-down tilt was shown to increase acid GER in 20 infants with CF as determined by the number of acid reflux episodes and total acid exposure index in comparison to the modified physiotherapy without head-down tilt [57]. This finding was not confirmed in a similar study with 21 infants and young children aged 1–27 months with respiratory disorders (half of them having cystic fibrosis) [58]. A prospective study of 20 infants with newly diagnosed CF tried to answer the question regarding head-down tilt. Their results showed that children with CF who had modified chest physiotherapy without head-down tilt had fewer respiratory complication and better chest X-ray and lung function measured by FEV1 than the group with classical respiratory physiotherapy during 5-year follow-up [59]. Another study which assessed GER during physiotherapy with the MII-pH could not prove that head-down position exacerbates GER, but a long-term follow-up regarding pulmonary complications and lung function has not been performed [60].

Positive expiratory pressure physiotherapy was found superior to the conventional postural drainage and percussion physiotherapy [61]. Respiratory physiotherapy has evolved over the time and forced expiration technique and autogenic drainage replaced modified postural drainage and percussion in children older than 1.5–4 years [62]. The superiority of positive expiratory pressure physiotherapy in

comparison to other techniques was supported by the 2015 Cochrane review [63]. The impact of these physiotherapy techniques on GER has not yet been studied.

The dilemma about the influence of physiotherapy on GER has not been resolved by two systematic reviews published in 2015 [64, 65]. The majority of included studies were not comparable due to various techniques of respiratory physiotherapy and heterogeneous children groups [64].

GER and Lung Transplantation

End-stage lung disease in CF patients is a third most common indication for lung transplantation with the best long-term survival comparing to the patients with more common indications for lung transplantation which are chronic obstructive pulmonary disease and pulmonary fibrosis [66]. According to the 2013 European Cystic Fibrosis Society Patient Registry report with the data from 27 countries (not all patients were included), 5.3% of the total 38,985 CF patients from the registry lived with transplanted lungs, among children 0.5% [67].

GERD is common in end-stage respiratory disease patients and is an important pathogenic factor leading to a bronchiolitis obliterans and the resultant graft dysfunction after lung transplantation [68]. In a study of 29 lung transplant patients compared to 23 patients with GERD only, the lung transplant group had a lower incidence of hiatus hernia and a higher incidence of proximal acid reflux [69]. In a study of ten children after lung or heart-lung transplantation, nine of them having CF, 90% had GERD as assessed by pH monitoring. The only one without GERD had antireflux operation performed before transplantation [70].

Bronchiolitis obliterans is common after lung transplantation, reported in approximately half of lung transplant patients after 5 years. It appears to be related to repeated episodes of acute graft rejection and possibly also due to various nonimmunologic factors, such as infection, ischemic injury, and GER [70]. Its clinical correlate is bronchiolitis obliterans syndrome which is defined by a persistent decline in FEV1 [71].

Lung transplant patients with CF had a higher prevalence of GERD than did other lung transplant recipients as it was shown in a study of 88 consecutive predominately adult lung transplant patients assessed by two-channel pH monitoring. In a group of ten CF patients, 90% had pathologic acid reflux with a higher prevalence of proximal reflux (70%) in comparison to lung transplant patients for other indications that had acid reflux in 54% with the proximal extent of reflux in 29% [72].

MII-pH enables to measure all kinds of reflux, including weakly acid and nonacid reflux, which are believed to be important additional pathogenetic factors for bronchiolitis obliterans. In a study of 63 adult patients after lung transplantation for different indications, 49% had GERD measured by MII-pH, of which 27% had isolated nonacid reflux. Prevalence was the highest among CF patients. Pepsin, the marker of lung aspirations, was found in all with GERD; bile acids, which are more

specific for lung aspirations, were found in contrary, in only half of them. Authors concluded that bile acids are a possible trigger of bronchiolitis obliterans [42].

With the PPI treatment, the pH of refluxate is less acidic, without affecting the amount of it. Higher gastric pH enables bacterial growth. CF patients treated with PPIs have more weakly acid and nonacid reflux, both playing a role in the development of bronchiolitis obliterans [68, 73].

In the case of surgical treatment, the majority of studies report performing total laparoscopic Nissen fundoplication. If esophageal motility is disordered, then partial Toupet fundoplication is preferred. In case of gastroparesis, pyloroplasty should be considered [68, 69].

Laparoscopic antireflux surgery was safe before and after lung transplantation as it was shown in a group of 35 patients (15 before and 20 after lung transplantation). In addition, authors draw an attention to the high proportion of delayed gastric emptying in both groups [71].

Fundoplication improves lung function in lung transplant recipients with GERD as it was shown in a study of 128 patients (23% with CF), of which 73% had pathologic acid reflux. After antireflux surgery which was performed in 43 patients, FEV1 significantly improved after at least 6 months. The majority of those with lower stages of bronchiolitis obliterans improved, so that they no longer met the criteria for it, and 3- and 5-year survival was significantly better than in overall series of 353 lung transplant patients [74]. In a study which involved 25 pediatric patients after lung or heart-lung transplantation, 11 had consecutively performed laparoscopic Nissen fundoplication. There was no mortality and morbidity was not significant. Due to the small sample and unreliable spirometry results in younger patients, the conclusions regarding an effect on posttransplant lung function could not be made [75].

According to the published evidence above, it is necessary to actively search for GERD in CF patients before or at least after lung transplantation, even in patients with atypical and infrequent symptoms and signs.

GER and Gastrostomy

Adequate nutrition is one of mainstays of CF patients' treatment. Normal body weight is an important predictor of survival [76]. Nutritional needs of CF patients are increased due to inflammation, increased work of breathing, fat maldigestion, and, over the years, also glucosuria. On the other hand, food intake is inadequate in many patients due to nasal polyps, GERD, and other gastrointestinal problems, psychological issues, and others [76, 77]. All issues must be individually addressed in a specific patient, but gastrostomy insertion for additional feeding is often needed when nutritional goals are not met [78].

Gastrostomy must be inserted timely to enable the child achieving a body mass index (BMI) above at least 25th percentile or preferably around 50th percentile [79]. There is no doubt in the advantage of this intervention for the improvement of BMI and lung function in the majority of studies [77, 80–82]. However, there is a controversy regarding GERD and antireflux operation simultaneously with gastrostomy insertion in CF patients.

In a retrospective study of 170 patients after percutaneous gastrostomy insertion (29 of them with CF), GERD symptoms worsened in six patients, who already had GERD preoperatively, and in two patients they developed following gastrostomy insertion. In only two of these eight patients, antireflux surgery was needed. The majority of patients were treated with different antisecretory medicines already before, as GERD was diagnosed in nearly half of them [83].

Guidelines do not recommend upper gastrointestinal series or other diagnostics before gastrostomy insertion routinely, but in the risk groups for GERD and lung aspirations, including patients with CF, after detailed history and physical examination, the decision regarding concurrent antireflux surgery at the time of gastrostomy insertion should be made [84]. Evidence that MII-pH or other studies will predict the development of GERD and complications, such as lung aspirations is limited [84]. But it is believed that in patients with cystic fibrosis, this practice might change as the evidence accumulates that GER aspirations deteriorate lung function.

Complications of GER in CF

In CF patients late complications of GER are expected to be more frequent due to the high proportion of GERD among them.

In older patient's series, before the widespread use of PPIs, esophageal strictures in CF patients were more common. In a series of seven CF patients (all but one were children) with upper gastrointestinal symptoms, esophageal stricture was diagnosed in three; the youngest had 8 years. They were treated with periodic balloon dilatations, and later two of them underwent the Nissen fundoplication [27].

Abnormal mucosal secretions and impaired innate mucosal defense are leading to the mucosal inflammation. The consequence is increased cell injury and turnover, which might lead to dysplasia and metaplasia [85, 86]. There are no prevalence studies of esophageal metaplasia (Barrett's esophagus) and adenocarcinoma in CF patients. A case series of children with Barrett's esophagus draws attention to this often relatively silent and presumably underreported condition in CF patients [87]. Two case reports of esophageal adenocarcinoma in adult CF patients have been published by now [86, 88].

Conclusions

Data on the importance of the diagnosis and treatment of GERD in CF patients exist and should be routinely implemented at least in CF patients with:

- Symptoms or signs of GERD
- Worsening of lung function disproportionately to the decline provoked by a lung infection or a natural course of the disease
- A lung disease poorly responsive to the treatment
- Advanced lung disease or after lung transplantation
- Failure to thrive or weight loss

The role of PPIs, although widely used, is still controversial. It seems that antireflux operation has many advantages over conservative treatment in CF patients with GERD, but high-quality randomized controlled trials are needed before the development of clinical practice guidelines for better management of GERD in CF patients with the goal of the preservation of lung function and the increase of survival.

References

1. Elborn JS. Cystic fibrosis. Lancet. 2016;388:2519–31.
2. Quinton PM. Cystic fibrosis: impaired bicarbonate secretion and mucoviscidosis. Lancet. 2008;372:415–7.
3. Gregory PC. Gastrointestinal pH, motility/transit and permeability in cystic fibrosis. J Pediatr Gastroenterol Nutr. 1996;23:513–23.
4. Demeyer S, De Boeck K, Witters P, Cosaert K. Beyond pancreatic insufficiency and liver disease in cystic fibrosis. Eur J Pediatr. 2016;175:881–94.
5. Dab I, Malfroot A. Gastroesophageal reflux: a primary defect in cystic fibrosis? Scand J Gastroenterol Suppl. 1988;143:125–31.
6. Heine RG, Button BM, Olinsky A, Phelan PD, Catto-Smith AG. Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. Arch Dis Child. 1998;78:44–8.
7. Brodzicki J, Trawinska-Bartnicka M, Korzon M. Frequency, consequences and pharmacological treatment of gastroesophageal reflux in children with cystic fibrosis. Med Sci Monit. 2002;8:529–37.
8. Caldaro T, Alghisi F, De Angelis P, Garganese MC, Rea F, Pizzoferro M, et al. Cystic fibrosis: a surgical matter? J Pediatr Surg. 2014;49:753–8.
9. Dziekiewicz MA, Banaszkiewicz A, Urzykowska A, Lisowska A, Rachel M, Sands D, et al. Gastroesophageal reflux disease in children with cystic fibrosis. Adv Exp Med Biol. 2015;873:1–7.
10. Ledson MJ, Tran J, Walshaw MJ. Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients. J R Soc Med. 1998;91:7–9.
11. Sabati AA, Kempainen RR, Milla CE, Ireland M, Schwarzenberg SJ, Dunitz JM, et al. Characteristics of gastroesophageal reflux in adults with cystic fibrosis. J Cyst Fibros. 2010;9:365–70.
12. Dimango E, Walker P, Keating C, Berdella M, Robinson N, Langfelder-Schwind E, et al. Effect of esomeprazole versus placebo on pulmonary exacerbations in cystic fibrosis. BMC Pulm Med. 2014;14:21.
13. Mousa HM, Woodley FW. Gastroesophageal reflux in cystic fibrosis: current understandings of mechanisms and management. Curr Gastroenterol Rep. 2012;14:226–35.
14. Blondeau K, Pauwels A, Dupont L, Mertens V, Proesmans M, Orel R, et al. Characteristics of gastroesophageal reflux and potential risk of gastric content aspiration in children with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2010;50:161–6.
15. D'Ovidio F, Singer LG, Hadjiliadis D, Pierre A, Waddell TK, de Perrot M, et al. Prevalence of gastroesophageal reflux in end-stage lung disease candidates for lung transplant. Ann Thorac Surg. 2005;80:1254–60.
16. Cucchiara S, Santamaria F, Andreotti MR, Minella R, Ercolini P, Oggero V, et al. Mechanisms of gastro-oesophageal reflux in cystic fibrosis. Arch Dis Child. 1991;66:617–22.
17. Pauwels A, Blondeau K, Dupont LJ, Sifrim D. Mechanisms of increased gastroesophageal reflux in patients with cystic fibrosis. Am J Gastroenterol. 2012;107:1346–53.
18. Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJ, Loots CM, Smout AJ. Esophageal acid exposure decreases intraluminal baseline impedance levels. Am J Gastroenterol. 2011;106:2093–7.

19. Farre R, Blondeau K, Clement D, Vicario M, Cardozo L, Vieth M, et al. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. Gut. 2011;60:885–92.
20. Brecelj J, Zidar N, Jeruc J, Orel R. Morphological and functional assessment of oesophageal mucosa integrity in children with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2016;62:757–64.
21. Quinton PM. Role of epithelial HCO_3^- transport in mucin secretion: lessons from cystic fibrosis. Am J Physiol Cell Physiol. 2010;299:1222–33.
22. Abdulnour-Nakhoul S, Nakhoul HN, Kalliny MI, Gyftopoulos A, Rabon E, Doetjes R, et al. Ion transport mechanisms linked to bicarbonate secretion in the esophageal submucosal glands. Am J Physiol Regul Integr Comp Physiol. 2011;301:83–96.
23. Woodley FW, Machado RS, Hayes D Jr, Di Lorenzo C, Kaul A, Skaggs B, et al. Children with cystic fibrosis have prolonged chemical clearance of acid reflux compared to symptomatic children without cystic fibrosis. Dig Dis Sci. 2014;59:623–30.
24. Hallberg K, Fandriks L, Strandvik B. Duodenogastric bile reflux is common in cystic fibrosis. J Pediatr Gastroenterol Nutr. 2004;38:312–6.
25. Pauwels A, Blondeau K, Mertens V, Farre R, Verbeke K, Dupont LJ, et al. Gastric emptying and different types of reflux in adult patients with cystic fibrosis. Aliment Pharmacol Ther. 2011;34:799–807.
26. Hauser B, De Schepper J, Malfroot A, De Wachter E, De Schutter I, Keymolen K, et al. Gastric emptying and gastro-oesophageal reflux in children with cystic fibrosis. J Cyst Fibros. 2016;15:540–7.
27. Bendig DW, Seilheimer DK, Wagner ML, Ferry GD, Barrison GM. Complications of gastroesophageal reflux in patients with cystic fibrosis. J Pediatr. 1982;100:536–40.
28. Vinocur CD, Marmon L, Schidlow DV, Weintraub WH. Gastroesophageal reflux in the infant with cystic fibrosis. Am J Surg. 1985;149:182–6.
29. Gustafsson PM, Fransson SG, Kjellman NI, Tibbling L. Gastro-oesophageal reflux and severity of pulmonary disease in cystic fibrosis. Scand J Gastroenterol. 1991;26:449–56.
30. Navarro J, Rainisio M, Harms HK, Hodson ME, Koch C, Mastella G, et al. Factors associated with poor pulmonary function: cross-sectional analysis of data from the ERCF. European Epidemiologic Registry of Cystic Fibrosis. Eur Respir J. 2001;18:298–305.
31. Pauwels A, Decraene A, Blondeau K, Mertens V, Farre R, Proesmans M, et al. Bile acids in sputum and increased airway inflammation in patients with cystic fibrosis. Chest. 2012;141:1568–74.
32. Reen FJ, Woods DF, Mooij MJ, Adams C, O'Gara F. Respiratory pathogens adopt a chronic lifestyle in response to bile. PLoS One. 2012;7:e45978.
33. Pauwels A, Verleden S, Farre R, Vanaudenaerde BM, Van Raemdonck D, Verleden G, et al. The effect of gastric juice on interleukin-8 production by cystic fibrosis primary bronchial epithelial cells. J Cyst Fibros. 2013;12:700–5.
34. McNally P, Ervine E, Shields MD, Dimitrov BD, El Nazir B, Taggart CC, et al. High concentrations of pepsin in bronchoalveolar lavage fluid from children with cystic fibrosis are associated with high interleukin-8 concentrations. Thorax. 2011;66:140–3.
35. van der Doef HP, Arets HG, Froeling SP, Westers P, Houwen RH. Gastric acid inhibition for fat malabsorption or gastroesophageal reflux disease in cystic fibrosis: longitudinal effect on bacterial colonization and pulmonary function. J Pediatr. 2009;155:629–33.
36. Palm K, Sawicki G, Rosen R. The impact of reflux burden on pseudomonas positivity in children with cystic fibrosis. Pediatr Pulmonol. 2012;47:582–7.
37. Madan JC, Koestler DC, Stanton BA, Davidson L, Moulton LA, Housman ML, et al. Serial analysis of the gut and respiratory microbiome in cystic fibrosis in infancy: interaction between intestinal and respiratory tracts and impact of nutritional exposures. MBio. 2012;3:e00251-12.
38. Robinson NB, DiMango E. Prevalence of gastroesophageal reflux in cystic fibrosis and implications for lung disease. Ann Am Thorac Soc. 2014;11:964–8.
39. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
40. Wenzl TG, Benninga MA, Loots CM, Salvatore S, Vandenplas Y. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. J Pediatr Gastroenterol Nutr. 2012;55:230–4.
41. Shaker A, Stoikes N, Drapekin J, Kushnir V, Brunt LM, Gyawali CP. Multiple rapid swallow responses during esophageal high-resolution manometry reflect esophageal body peristaltic reserve. Am J Gastroenterol. 2013;108:1706–12.
42. Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, Sifrim D, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Respir J. 2008;31:707–13.
43. Kazachkov MY, Muhlebach MS, Livasy CA, Noah TL. Lipid-laden macrophage index and inflammation in bronchoalveolar lavage fluids in children. Eur Respir J. 2001;18:790–5.
44. Hayes D Jr, Kirkby S, KS MC, Mansour HM, Khosravi M, Strawbridge H, et al. Reduction of lipid-laden macrophage index after laparoscopic Nissen fundoplication in cystic fibrosis patients after lung transplantation. Clin Transpl. 2013;27:121–5.
45. Munck A. Nutritional considerations in patients with cystic fibrosis. Expert Rev Respir Med. 2010;4:47–56.
46. Colletti RB, Di Lorenzo C. Overview of pediatric gastroesophageal reflux disease and proton pump inhibitor therapy. J Pediatr Gastroenterol Nutr. 2003;37(Suppl 1):S7–S11.
47. 2014 Annual Data Report. Bethesda: Cystic Fibrosis Foundation Patient Registry; 2015.
48. Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Spear SL, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009;155(Suppl):S73–93.
49. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365:1663–72.
50. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med. 2015;373:220–31.
51. Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. Am J Respir Crit Care Med. 2014;190:175–84.
52. Boesch RP, Acton JD. Outcomes of fundoplication in children with cystic fibrosis. J Pediatr Surg. 2007;42:1341–4.
53. Sheikh SI, Ryan-Wenger NA, McCoy KS. Outcomes of surgical management of severe GERD in patients with cystic fibrosis. Pediatr Pulmonol. 2013;48:556–62.
54. Rinsma NF, Farre R, Bouvy ND, Masclee AA, Conchillo JM. The effect of endoscopic fundoplication and proton pump inhibitors on baseline impedance and heartburn severity in GERD patients. Neurogastroenterol Motil. 2015;27:220–8.
55. Tovar JA, Olivares P, Diaz M, Pace RA, Prieto G, Molina M. Functional results of laparoscopic fundoplication in children. J Pediatr Gastroenterol Nutr. 1998;26:429–31.
56. Vandenplas Y, Diericx A, Blecker U, Lanciers S, Deneyer M. Esophageal pH monitoring data during chest physiotherapy. J Pediatr Gastroenterol Nutr. 1991;13:23–6.
57. Button BM, Heine RG, Catto-Smith AG, Phelan PD, Olinsky A. Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis. Arch Dis Child. 1997;76:148–50.
58. Phillips GE, Pike SE, Rosenthal M, Bush A. Holding the baby: head downwards positioning for physiotherapy does not cause gastro-oesophageal reflux. Eur Respir J. 1998;12:954–7.
59. Button BM, Heine RG, Catto-Smith AG, Olinsky A, Phelan PD, Ditchfield MR, et al. Chest physiotherapy in infants with cystic fibrosis: to tip or not? A five-year study. Pediatr Pulmonol. 2003;35:208–13.
60. Doumit M, Krishnan U, Jaffe A, Belessis Y. Acid and non-acid reflux during physiotherapy in young children with cystic fibrosis. Pediatr Pulmonol. 2012;47:119–24.

61. McIlwaine PM, Wong LT, Peacock D, Davidson AG. Long-term comparative trial of conventional postural drainage and percussion versus positive expiratory pressure physiotherapy in the treatment of cystic fibrosis. J Pediatr. 1997;131:570–4.
62. McIlwaine M. Chest physical therapy, breathing techniques and exercise in children with CF. Paediatr Respir Rev. 2007;8:8–16.
63. McIlwaine M, Button B, Dwan K. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev. 2015;6:CD003147.
64. Van Ginderdeuren F, Kerckhofs E, Deneyer M, Vanlaethem S, Vandenplas Y. Influence of respiratory physiotherapy on gastro-oesophageal reflux in infants: a systematic review. Pediatr Pulmonol. 2015;50:936–44.
65. Freitas DA, Dias FA, Chaves GS, Ferreira GM, Ribeiro CT, Guerra RO, et al. Standard (head-down tilt) versus modified (without head-down tilt) postural drainage in infants and young children with cystic fibrosis. Cochrane Database Syst Rev. 2015;3:CD010297.
66. Rosenblatt RL. Lung transplantation in cystic fibrosis. Respir Care. 2009;54:777–86.
67. Zolin A, McKone E, van Rens J, Fox A, Iansa P, Pypops U, et al. ECFSPR annual report 2013. Karup: European Cystic Fibrosis Society; 2016.
68. Vaquero Barrios JM, Redel Montero J, Santos LF. Comorbidities impacting on prognosis after lung transplant. Arch Bronconeumol. 2014;50:25–33.
69. Fisichella PM, Davis CS, Gagermeier J, Dilling D, Alex CG, Dorfmeister JA, et al. Laparoscopic antireflux surgery for gastroesophageal reflux disease after lung transplantation. J Surg Res. 2011;170:e279–86.
70. Benden C, Aurora P, Curry J, Whitmore P, Priestley L, Elliott MJ. High prevalence of gastroesophageal reflux in children after lung transplantation. Pediatr Pulmonol. 2005;40:68–71.
71. Gasper WJ, Sweet MP, Hoopes C, Leard LE, Kleinhenz ME, Hays SR, et al. Antireflux surgery for patients with end-stage lung disease before and after lung transplantation. Surg Endosc. 2008;22:495–500.
72. Mendez BM, Davis CS, Weber C, Joehl RJ, Fisichella PM. Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis. Am J Surg. 2012;204:e21–6.
73. Braun AT, Merlo CA. Cystic fibrosis lung transplantation. Curr Opin Pulm Med. 2011;17:467–72.
74. Davis RD Jr, Lau CL, Eubanks S, Messier RH, Hadjiliadis D, Steele MP, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. J Thorac Cardiovasc Surg. 2003;125:533–42.
75. Zheng C, Kane TD, Kurland G, Irlano K, Spahr J, Potoka DA, et al. Feasibility of laparoscopic Nissen fundoplication after pediatric lung or heart-lung transplantation: should this be the standard? Surg Endosc. 2011;25:249–54.
76. Culhane S, George C, Pearo B, Spoede E. Malnutrition in cystic fibrosis: a review. Nutr Clin Pract. 2013;28:676–83.
77. Woestenenk JW, Castelijns SJ, van der Ent CK, Houwen RH. Nutritional intervention in patients with cystic fibrosis: a systematic review. J Cyst Fibros. 2013;12:102–15.
78. Oliver MR, Heine RG, Ng CH, Volders E, Olinsky A. Factors affecting clinical outcome in gastrostomy-fed children with cystic fibrosis. Pediatr Pulmonol. 2004;37:324–9.
79. Grime CJ, Greenaway C, Clarke S, Balfour-Lynn IM. Critical timing of gastrostomy insertion in a child with cystic fibrosis. Paediatr Respir Rev. 2015;16(Suppl 1):19–21.
80. Ledder O, Oliver MR, Heine RG, Graham J, Volders E, Robinson PJ. Clinical audit results in earlier nutritional intervention in malnourished children with cystic fibrosis with improved outcome. J Paediatr Child Health. 2015;51:988–93.
81. Morton A, Wolfe S. Enteral tube feeding for cystic fibrosis. Cochrane Database Syst Rev. 2015;4:CD001198.
82. Best C, Brearley A, Gaillard P, Regelmann W, Billings J, Dunitz J, et al. A pre-post retrospective study of patients with cystic fibrosis and gastrostomy tubes. J Pediatr Gastroenterol Nutr. 2011;53:453–8.
83. Kakade M, Coyle D, McDowell DT, Gillick J. Percutaneous endoscopic gastrostomy (PEG) does not worsen vomiting in children. Pediatr Surg Int. 2015;31:557–62.

84. Heuschkel RB, Gottrand F, Devarajan K, Poole H, Callan J, Dias JA, et al. ESPGHAN position paper on management of percutaneous endoscopic gastrostomy in children and adolescents. J Pediatr Gastroenterol Nutr. 2015;60:131–41.
85. Munck A. Cystic fibrosis: evidence for gut inflammation. Int J Biochem Cell Biol. 2014;52:180–3.
86. Holt EW, Yimam KK, Liberman MS. Esophageal adenocarcinoma in a 40-year-old man with cystic fibrosis: coincidence or not? Ochsner J. 2013;13:252–5.
87. Hassall E, Israel DM, Davidson AG, Wong LT. Barrett's esophagus in children with cystic fibrosis: not a coincidental association. Am J Gastroenterol. 1993;88:1934–8.
88. Miller R, Bourke S, Immanuel A, Metcalfe S. Subtotal esophagectomy for carcinoma in a patient with cystic fibrosis. A A Case Rep. 2016;6:394–6.

GERD and Eosinophilic Esophagitis

16

Jorge Amil Dias

Abstract

GERD and EoE cause chronic esophageal inflammation sharing some common characteristics. Distinction between them requires 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. The current diagnostic tests may not provide clear-cut differences in diagnosis. Combined clinical, endoscopic, and histologic data may provide the best diagnostic criteria to identify the exact diagnosis and take appropriate therapeutic options.

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 10 pediatric patients with previous diagnosis of gastro-esophageal reflux disease (GERD) that failed to improve on treatment (including fundoplication in 6)

J.A. Dias
Pediatric Gastroenterology, Department of Pediatrics, Centro Hospitalar S. João, 4202-451 Porto, Portugal
e-mail: jamildias@zonmail.pt

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_16

but had considerable improvement on amino acid formula. All of these patients showed a considerable decrease in the number of eosinophils in the esophageal mucosa and subsequent reports confirmed that this new entity was different from typical cases with acid reflux [2–4].

The new disease was termed Eosinophilic Esophagitis 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 marked increase in recent years, has male predominance, frequent relation with atopy or food sensitization and high family association. Genome-wide microarray expression analysis revealed a consistent pattern of upregulated genes related to the production of Eotaxin-3 and Th2 related cytokines [5, 6].

EoE typically presents as food impaction, dysphagia, or heartburn but these symptoms are more common in adolescents or adults. Infants and younger children may have signs of abdominal pain, food aversion, or failure to thrive. In many patients, involving all age groups symptoms may also be identical to GERD [7–9].

Functional and morphologic tests may help clarify which is the diagnosis although the two conditions may overlap in some cases. Esophageal pH and impedance monitoring were considered to be usually abnormal in GERD but not in EoE. However, studies have found that pH study is frequently abnormal in patients with EoE that respond to PPI treatment as discussed below. 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 [10]. 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 typical longitudinal furrows in the lumen (Fig. 16.1). Other aspects common in

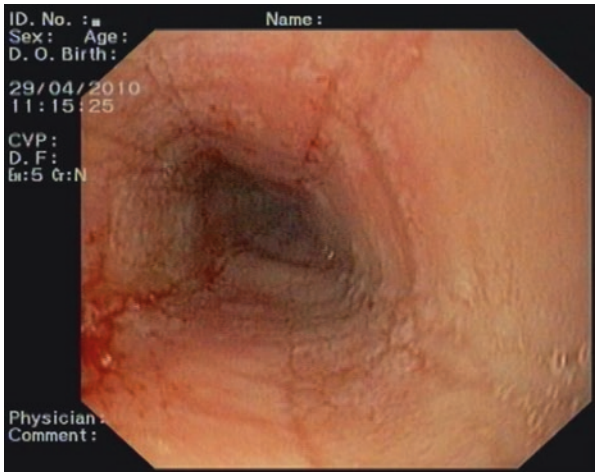


Fig. 16.1 Endoscopic image showing linear furrows from edema of the esophageal wall and friability of the mucosa with easy bleeding

EoE are concentric rings that give a trachea-like appearance of the esophagus (Fig. 16.2). 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. However, the morphologic endoscopic features of EoE may be subtle or even absent, especially in younger patients. One study revealed that approximately 30% of pediatric cases of EoE had normal appearing mucosa [11]. The abnormalities of the esophageal lumen may occur throughout the whole esophagus while in GERD they 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 diseases depending on multiple factors, including local epidemiology [12, 13].

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 is typical of EoE (Figs. 16.3 and 16.4). However if density of eosinophils is

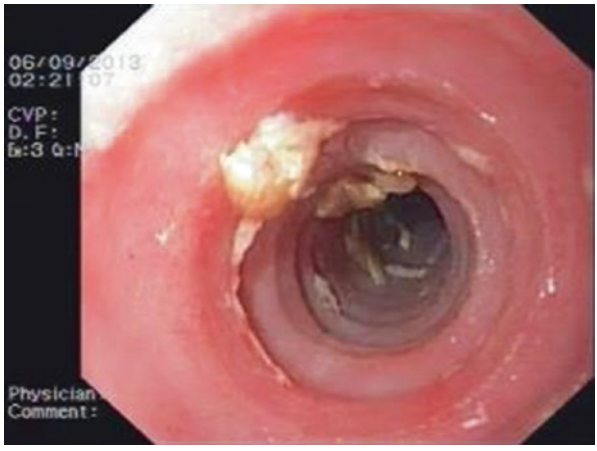


Fig. 16.2 Trachealization of the esophageal wall with remains from food impaction

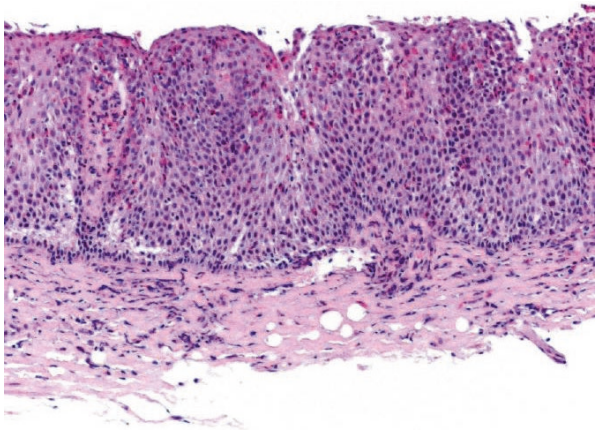


Fig. 16.3 Histology of the esophagus revealing elongation of the papillae and dense eosinophilic infiltrate (courtesy of F. Carneiro)

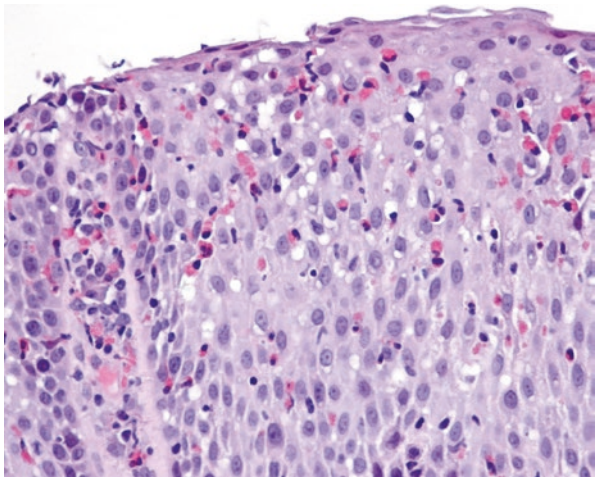


Fig. 16.4 Histology with higher magnification showing diffuse infiltrate of eosinophils and abundant granules (courtesy of F. Carneiro)

Table 16.1 Histological features of EoE

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

Adapted from Collins [14]

considerably higher (>30/hpf) in a single biopsy, it may also be accepted as strongly in favor of EoE [9]. The mere presence of increased number of eosinophils may not be enough and other features related to eosinophil-related inflammation are usually seen: degranulation, micro-abscesses of eosinophils or dilated intercellular spaces (Table 16.1) [14]. Features of inflammation and quantification of eosinophils in the mucosa are therefore important for accurate diagnosis. Peak count should be registered.

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 [15]. For this reason histological diagnosis of EoE requires multiple samples. Current guidelines recommend that multiple biopsies are obtained at three different levels of the esophagus [16].

Clinical features, endoscopy, and histology are the usual tools used in daily practice to establish the diagnosis of EoE [17]. However there are additional important features like subepithelial fibrosis, increased angiogenesis, and mast cell infiltration [18–21]. Experimental models have shown that mast cells may have a relevant role in esophageal muscle cell hyperplasia and dysmotility [22–24]. Basal cell hyperplasia is seen more frequently in EoE than in GERD [25]. High resolution endoscopic ultrasound also reveals thickening of the esophageal wall in EoE [26].

Table 16.2 Possible explanations for the association of GERD and eosinophilic esophagitis

1. GERD causes esophageal injury that results in a mild eosinophilic infiltration
a. Acid exposure induces endothelial cells to express adhesion molecules recognized *by ligands on the eosinophil*
b. Acid exposure induces esophageal epithelium to release chemokines that attract eosinophils
c. Acid exposure increases esophageal blood flow, thereby enhancing the delivery of eosinophils
2. GERD and eosinophilic esophagitis coexist but are unrelated
3. Eosinophilic esophagitis contributes to or causes GERD
a. Eosinophil secretory products alter esophageal motility so as to favor gastroesophageal reflux
b. Eosinophil secretory products alter esophageal motility so as to delay the clearance of refluxed material
c. Eosinophilic esophagitis causes structural esophageal changes (mural thickening, fibrosis) that might affect LES function and esophageal clearance
d. Eosinophil secretory products render the esophageal mucosa more susceptible to injury by refluxed gastric juice
4. GERD contributes to or causes eosinophilic esophagitis
a. Acid-peptic damage to epithelial cells and their tight junctions increases epithelial permeability, thereby exposing deep layers of the epithelium to antigens
b. Acid-peptic injury recruits immune cells to the esophageal epithelium

Reproduced with permission from Spechler [30]

The possible relation between GERD and EoE is difficult to establish and results suggest that 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 [27–29]. On the other hand, the consistency and accuracy of pH-probe studies in inflamed esophagus infiltrated by eosinophils is also matter for some debate [30]. Not only various chemical products from eosinophil metabolism (Table 16.2) but also acid may cause some damage to the esophageal epithelium rendering it more susceptible to penetration of acid or antigens [30]. Therefore the causality relation is difficult to establish and possibly not uniform in all patients.

It is therefore 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 [29, 31]. However differential diagnosis is not always easy and these two conditions are not mutually exclusive [32]. Occasionally patients may have both and cases have been reported where initial GERD treated with gastric-acid suppression evolved to a clear pattern of EoE [33]. This may be a rare circumstance but illustrates that the relation and distinction between the two diagnosis may be difficult [8].

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 [34].

Taking into account the much higher prevalence of GERD than EoE it is not surprising that there may be a considerable overlap of cases. In view of this, experts have recommended that a trial of PPI treatment for 8 weeks should be prescribed before a firm diagnosis of EoE would be accepted, even in the presence of high eosinophil count [16, 35].

Following this diagnostic protocol there emerged a group of patients with consistent features of EoE that indeed responded to PPI treatment, which supported the concept that EoE might derive from GERD [7]. Subsequent research showed that PPIs also have therapeutic effect in EoE-related inflammation by decreasing eotaxin-3 levels [36–38]. This group of patients with typical features of EoE that respond to PPI treatment (two daily doses) was then named "PPI-responsive esophageal eosinophilia" (PPI-REE) [39]. 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 the good outcome [40]. Accumulated evidence shows that one third to half of the patients with initial diagnosis of EoE would be classified as having PPI-REE [41, 42]. Response 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. Furthermore it revealed that the response in PPI-REE patients was apparently better when PPIs were given twice daily, therefore not dose-dependent but rather related to sustained therapeutic drug levels [43]. 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 [44].

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 [45]. This supports the concept that inflammation leads to impaired epithelial integrity although acid exposure may also evoke cytokine stimulation [46].

The subgroup of patients classified as PPI-REE has been intensively studied and the concept that it would represent a separate category from both GERD and EoE is now changing into the notion that it very likely represents a subgroup of EoE with similar immune expression (Th2, elevated expression of Eotaxin 3, IL-13, and IL-5) in whom PPIs are a valuable therapeutic option (Fig. 16.5 and Table 16.3) [41, 47]. In fact, PPI-REE adults have downregulation of cytokine signaling (Eotaxin-3, IL-13, and IL-5) which is similar to EoE patients treated with topical steroids [48]. Following these findings that confirm previous studies it has been suggested that the term "PPI-REE" may be replaced by "PPI-responsive EoE," acknowledging that PPIs may be a first line therapy that may need intensification or other treatments if it fails or loses response [49].

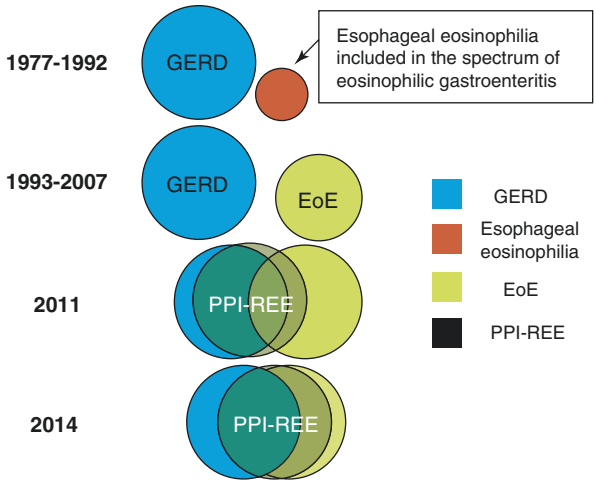


Fig. 16.5 Evolution of concepts over 40 years regarding the responsiveness to PPI therapy (with permission from Molina-Infante et al. [41])

Table 16.3 Currently accepted similarities and differences between GERD, PPI-REE, and EoE

	GERD	PPI-REE	EoE
Etiology	Gastric content reflux	Unknown	Food/airborne allergens
EoE diagnostic panel expression	Different from PPI-REE and EoE	Similar to EoE	Similar to PPI-REE
Symptoms	Heartburn, regurgitation, less often dysphagia	Dysphagia, food bolus impaction, less often heartburn	Dysphagia, food bolus impaction, less often heartburn
Esophageal involvement	Distal	Distal > proximal	Proximal > distal
Esophageal pH monitoring	Erosive GERD	70% increased acid exposure	50–70% normal acid exposure
	80% increased acid exposure	30% normal acid exposure	30–50% increased acid exposure
	Nonerosive GERD		
	50% normal acid exposure		
Type of immune response/involved chemo/cytokines	Th1	Th2	Th2
	IL-8, MCP-1, RANTES	Eotaxin-3, IL-13, IL-5	Eotaxin-3, IL-13, IL-5
Inflammatory cells	Neutrophils, lymphocytes, low-grade eosinophilia	Eosinophils and mast cells	Eosinophils and mast cells
Treatment	PPI therapy effective in most patients: fundoplication	PPI therapy effective in all patients	PPI therapy not effective:Steroids/ Diet

Reproduced with permission from Molina-Infante [47]

Conclusion

Several clinical features and diagnostic tests may help distinguish typical cases of pure GERD and EoE but 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 endoscopic evaluation of reflux-like symptoms, multiple biopsies should be obtained from proximal, mid, and distal esophagus. Diagnosis of GERD and EoE is 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 inflamed 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 is still under intense investigation and knowledge is rapidly evolving.

References

1. Winter HS, et al. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. Gastroenterology. 1982;83(4):818–23.
2. Kelly KJ, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109(5):1503–12.
3. Straumann A, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. Schweiz Med Wochenschr. 1994;124(33):1419–29.
4. Attwood SE, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci. 1993;38(1):109–16.
5. Blanchard C, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest. 2006;116(2):536–47.
6. Blanchard C, et al. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. J Allergy Clin Immunol. 2011;127(1):208–17.
7. Ngo P, et al. Eosinophils in the esophagus–peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. Am J Gastroenterol. 2006;101(7):1666–70.
8. Molina-Infante J, et al. Overlap of reflux and eosinophilic esophagitis in two patients requiring different therapies: a review of the literature. World J Gastroenterol. 2008;14(9):1463–6.
9. Parfitt JR, et al. Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. Mod Pathol. 2006;19(1):90–6.
10. van Rhijn BD, et al. Oesophageal baseline impedance values are decreased in patients with eosinophilic oesophagitis. United Eur Gastroenterol J. 2013;1(4):242–8.
11. Liacouras CA, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005;3(12):1198–206.
12. Al-Subu A, et al. The accuracy of endoscopic features in eosinophilic esophagitis: the experience in children from rural West Virginia. J Clin Gastroenterol. 2012;46(10):e83–6.
13. Gill RK, et al. Prevalence and characteristics of eosinophilic esophagitis in 2 ethnically distinct pediatric populations. J Allergy Clin Immunol. 2013;133:576–7.
14. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin N Am. 2014;43(2):257–68.
15. Saffari H, et al. Patchy eosinophil distributions in an esophagectomy specimen from a patient with eosinophilic esophagitis: implications for endoscopic biopsy. JAllergy ClinImmunol. 2012;130(3):798–800.

16. Papadopoulou A, et al. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr. 2014;58(1):107–18.
17. Mulder DJ, et al. Clinical features distinguish eosinophilic and reflux-induced esophagitis. J Pediatr Gastroenterol Nutr. 2013;56(3):263–70.
18. Abonia JP, Franciosi JP, Rothenberg ME. TGF-beta1: Mediator of a feedback loop in eosinophilic esophagitis–or should we really say mastocytic esophagitis? J Allergy Clin Immunol. 2010;126(6):1205–7.
19. Dellon ES, et al. Tryptase staining of mast cells may differentiate eosinophilic esophagitis from gastroesophageal reflux disease. Am J Gastroenterol. 2011;106(2):264–71.
20. Kirsch R, et al. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2007;44(1):20–6.
21. Aceves SS, et al. Esophageal remodeling in pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2007;119(1):206–12.
22. Aceves SS, et al. Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-beta1, and increase esophageal smooth muscle contraction. J Allergy Clin Immunol. 2010;126(6):1198–204.e4.
23. Niranjan R, et al. Pathogenic role of mast cells in experimental eosinophilic esophagitis. Am J Physiol Gastrointest Liver Physiol. 2013;304(12):G1087–94.
24. Cheng E, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. Am J Physiol Gastrointest Liver Physiol. 2012;303(11):G1175–87.
25. Steiner SJ, Kernek KM, Fitzgerald JF. Severity of basal cell hyperplasia differs in reflux versus eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2006;42(5):506–9.
26. Fox VL, et al. High-resolution EUS in children with eosinophilic “allergic” esophagitis. Gastrointest Endosc. 2003;57(1):30–6.
27. Remedios M, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. Gastrointest Endosc. 2006;63(1):3–12.
28. Sant'Anna AM, et al. Eosinophilic esophagitis in children: symptoms, histology and pH probe results. J Pediatr Gastroenterol Nutr. 2004;39(4):373–7.
29. Steiner SJ, et al. Correlation between number of eosinophils and reflux index on same day esophageal biopsy and 24 hour esophageal pH monitoring. Am J Gastroenterol. 2004;99(5):801–5.
30. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. Am J Gastroenterol. 2007;102(6):1301–6.
31. Ruchelli E, et al. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. Pediatr Dev Pathol. 1999;2(1):15–8.
32. Shah A, et al. Histopathologic variability in children with eosinophilic esophagitis. Am J Gastroenterol. 2009;104(3):716–21.
33. Orel R, et al. Eosinophilic esophagitis that develops during therapy with proton pump inhibitors : case series and possible mechanisms. Acta Gastroenterol Belg. 2016;79(2):245–50.
34. Dellon ES, et al. Diagnosis of eosinophilic esophagitis after fundoplication for 'refractory reflux': implications for preoperative evaluation. Dis Esophagus. 2010;23(3):191–5.
35. Furuta GT, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2007;133(4):1342–63.
36. Cheng E, Souza RF, Spechler SJ. Eosinophilic esophagitis: interactions with gastroesophageal reflux disease. Gastroenterol Clin N Am. 2014;43(2):243–56.
37. Cheng E, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013;62(6):824–32.
38. Zhang X, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. PLoS One. 2012;7(11):e50037.
39. Hirano I. Editorial: should patients with suspected eosinophilic esophagitis undergo a therapeutic trial of proton pump inhibition? Am J Gastroenterol. 2013;108(3):373–5.
40. Molina-Infante J, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. Clin Gastroenterol Hepatol. 2011;9(2):110–7.
41. Molina-Infante J, Katzka DA, Dellon ES. Proton pump inhibitor-responsive esophageal eosinophilia: a historical perspective on a novel and evolving entity. Rev Esp Enferm Dig. 2015;107(1):29–36.

42. Molina-Infante J, Katzka DA, Gisbert JP. Review article: proton pump inhibitor therapy for suspected eosinophilic oesophagitis. Aliment Pharmacol Ther. 2013;37(12):1157–64.
43. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2015;14:13–22.e1.
44. Krarup AL, et al. Acid hypersensitivity in patients with eosinophilic oesophagitis. Scand J Gastroenterol. 2010;45(3):273–81.
45. Sherrill JD, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. Mucosal Immunol. 2014;7(3):718–29.
46. Souza RF, et al. Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. Gastroenterology. 2009;137(5):1776–84.
47. Molina-Infante J, van Rhijn BD. Interactions between gastro-oesophageal reflux disease and eosinophilic oesophagitis. Best Pract Res Clin Gastroenterol. 2015;29(5):749–58.
48. Molina-Infante J, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. Aliment Pharmacol Ther. 2014;40(8):955–65.
49. Molina-Infante J, et al. Long-term loss of response in proton pump inhibitor-responsive esophageal eosinophilia is uncommon and influenced by CYP2C19 genotype and rhinoconjunctivitis. Am J Gastroenterol. 2015;110:1567–75.

Duodenogastroesophageal Reflux

17

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 lesions. Gastroesophageal reflux symptoms are more related to acid reflux events than to non-acid 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, surgery, and mucosal protective agents.

Keywords

Bile reflux • Non-acid 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

Abbreviations

DGER	Duodenogastroesophageal reflux
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal

I. Hoffman
University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium
e-mail: ilse.hoffman@uzleuven.be

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_17

PPI Proton pump inhibitor
ROS Reactive oxygen species
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. In adults, 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 bilirubins are the constituents used most often as markers of the reflux [1–8].

Measurement of Duodenogastroesophageal Reflux

Methodologies employed for measuring DGER including endoscopy, aspiration studies (both gastric and esophageal), scintigraphy, and pH-monitoring/impedance have technical difficulties and do not measure adequately DGER (Table 17.1).

The observation of bile in the esophagus or stomach is a poor indicator of DGER. Stein found poor sensitivity (37%), specificity (70%), and positive predictive value (55%) for endoscopy in diagnosing excessive DGER [10]. Scintigraphic studies using radiolabeled products found no difference in DGER between patients with esophagitis and healthy adults. Patients with Barrett's esophagus had more frequently DGER detected by ^{99m}Tc DISIDA scintigraphy compared to healthy adults. Aspiration techniques allow direct detection of duodenal contents and the possibility of bile measurements, but are unpleasant and time consuming. Reports using this technique have been conflicting and this technique cannot characterize DGER through the circadian cycle [4, 9–13].

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 17.1

Method	Advantages	Disadvantages
Endoscopy	Easy visualization	Poor sensitivity/specificity of bile
		Positive predictive value
		Requires sedation
		High costs
Aspiration studies	Less invasive than endoscopy	Short duration of study
	No sedation	Requires familiarity with enzymatic assay for bile acids
	Low cost	
Scintigraphy	Noninvasive	Semi-quantitative
		Radiation exposure
		High costs
pH monitoring/impedance	Easy to perform	pH > 7 not a marker for DGER
	Relatively noninvasive	Not specific for DGER
	Prolonged monitoring	
	Ambulatory	
Bilirubin monitoring	Easy to perform	Underestimates DGER in acidic medium
	Relatively noninvasive	Requires modified diet
	Prolonged monitoring	
	Ambulatory	
	Good correlation with bile acids	

Adapted from: Vaezi and Richter [9]

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 [14]. 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 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 non-acid reflux detected by impedance monitoring represent the same event, but studies have shown that the DGER component usually accompanies acid reflex events and that the non-acid component is not equivalent to bile reflux. The pH monitoring/impedance certainly lacks in determining the composition of the refluxate [3–6, 9, 15–19].

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. [20] 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 on 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 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. Tack has shown that a liquid meal (Nutridrink 200 ml, 300 kcal) does not interfere with the measurements [21]. 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. The bilitec probe was developed as a useful tool for detection of bilirubin in bile, but the technology had his limitations. No other technology is available for the moment [2–5, 9, 13–28].

Mechanism of Bile Injury

The interaction of gastric acid, bile acids and the development of mucosal damage have been studied extensively in vivo and 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, 28].

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 [28, 29].

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 [29]. Therefore, this

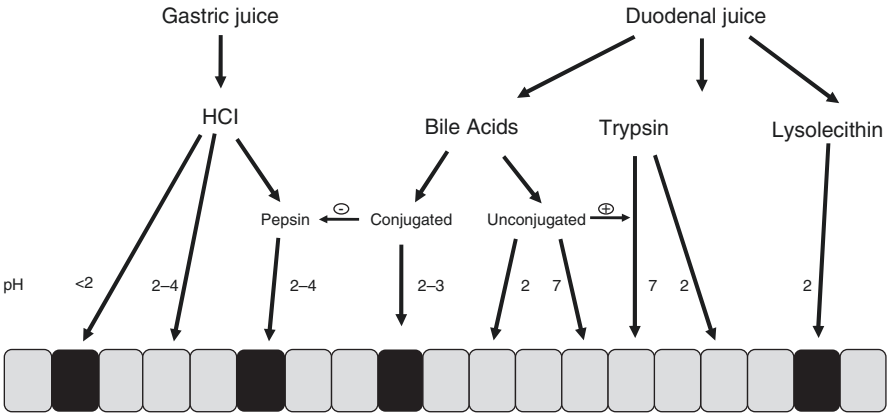


Fig. 17.1 Adapted from: Vaezi and Richter [9]

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. Batzri makes support for this presumption. Bile acids, once penetrating the mucosal barrier, are trapped inside the cells by intracellular ionization, explaining the increase in intracellular concentrations of bile acids [30]. Studies by Schweitzer have correlated bile acid entry and mucosal accumulation with bile acid-mediated mucosal damage [29]. 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 [28–30] (Fig. 17.1).

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 [10, 31–37].

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 of 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 [37]. 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. [35] 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 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 [32, 33]. In the study by Hoffman, it was demonstrated that DGER might play a role in the pathophysiology of PPI refractory GERD and esophagitis [31]. The results of these studies are supportive of a 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 [10, 31–37].

Role of Duodenogastroesophageal Reflux in Esophageal 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 the most symptom episodes were associated with acid reflux alone or mixed reflux, while <10% were associated with bile reflux alone. [37].

When symptomatic patients are studied while on PPI therapy, a high proportion of symptomatic episodes are related to non-acid reflux, as measured with the esophageal impedance meting. The prevalence of a positive symptom index for non-acid reflux (defined as weakly acidic (pH > 7) or alkaline reflux is 25–27% in adults, and in these patients, non-acidic reflux seems to trigger refractory GERD (Table 17.2). So, DGER without excessive acid reflux can cause symptoms but not usually produce esophagitis [37, 39] (Fig. 17.2).

Table 17.2

Symptom association (SI and SAP) in patients with typical GERD			Symptoms on PPI		
Study (*n*; total patients on PPi therapy)	Assessment method	Patients with pathological acid exposure	Patients with positive SI for acid reflux	Patients with positive SI for non-acid reflux	Other patient populations (positive SAP for acid or non-acid reflux)
Katzka et al. (1996) *n* = 45	pH	4	–	–	–
Charbel et al. (2005) *n* = 250	pH	42	44	–	–
Bautista et al. (2005) *n* = 69	pH	25	21	–	–
Zerbib et al. (2006) *n* = 71	pH/impedance	5	6	23	12* 19‡
Mainie et al. (2006) *n* = 168	pH/impedance	–	16	53	–
Tutuian et al. (2006) *n* = 50	pH/impedance	1	–	13	–
Anandasabapathy et al. (2006) *n* = 33	pH/impedance	–	3	4	–
Pace et al. (2007) *n* = 13	pH/impedance Bilitec®	2	–	–	–
Becker et al. (2007) *n* = 143	pH/impedance	20	–	–	–
Sharma et al. (2008) *n* = 200	pH/impedance	–	14	77	–
Karamanolis et al. (2008) *n* = 347	pH/Bilitec®	105	18	–	–
Hemmink et al. (2008) *n* = 30	pH/impedance	10	–	–	–
Tutuian et al. (2006) *n* = 120	pH/impedance	–	–	–	–
Blonski et al. (2009) *n* = 70	pH/impedance	10	–	–	–
Pritchett et al. (2009) *n* = 39	Bravo® pH impedance	0	–	–	–
Khan, A. et al. (2010) *n* = 51	pH/impedance	13	–	–	–
Iwakiri et al. (2010) *n* = 10	pH/impedance	–	3	7	–
Frazzoni et al. (2011) *n* = 20	pH/impedance	–	4	–	–

(continued)

Table 17.2 (continued)

Symptom association (SI and SAP) in patients with typical GERD			Symptoms on PPI		
Study (*n*; total patients on PPi therapy)	Assessment method	Patients with pathological acid exposure	Patients with positive SI for acid reflux	Patients with positive SI for non-acid reflux	Other patient populations (positive SAP for acid or non-acid reflux)
Karamanolis et al. (2011) *n* = 71	pH/impedance	–	12	13	–
Kohata et al. (2012) *n* = 29	pH/impedance	–	1	2	–
Kunsch et al. (2012) *n* = 47	pH/Bilitec®	9	–	–	–
Yamashita et al. (2012) *n* = 25	pH/impedance	2	4	5	–
Frazzoni et al. (2012) *n* = 80	pH/impedance	7	–	–	–
Overall *n* = 1981		255/1985 (16%)	146/1099 (13%)	197/788 (25%)	12/71 (17%)* 19/71 (28%)‡

Adapted from: Scarpellini et al. [38]
– not available, *SAP* symptom association probability, *SI* symptom index, *Patients with positive SAP and acid reflux, ‡Patients with positive SAP and non-acid reflux

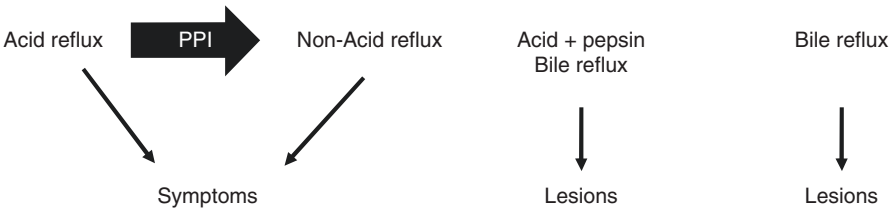


Fig. 17.2 Adapted from: Tack [4]

Luminal Factors Responsible of Impaired Mucosal Integrity

Cell-to-cell adhesions proteins are in charge to maintain the integrity of the esophageal epithelium. Comparing to other parts of the gastrointestinal tract, the esophageal mucosa is not composed by 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:

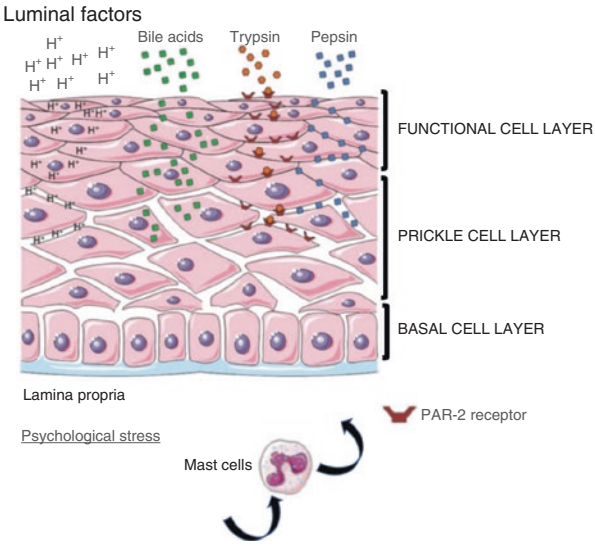


Fig. 17.3 Adapted from: Farré [40]

zonula occludens or tight junctions, adherence junction, and macula adherens or desmosomes [7, 40–43] (Fig. 17.3).

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 the1980s in rabbit tissue. The 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. 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. [43].

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 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. [40] Further studies

in humans are needed. Bile acids may also induce release of intracellular mediators and induce mast cell degranulation and release of histamine and prostaglandins [7, 40–45] (Fig. 17.3).

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 process and in the development of a Barrett esophagus, intestinal-type epithelium replaces the reflux-damaged squamous epithelium. Although the mechanisms of the development of a Barrett 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 into the esophagus compared with age and sex matched healthy controls [46–48].

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 maintain 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. Further research is necessary to study the effect of bile acids on the proliferation and apoptosis in esophageal cells [46–49] (Fig. 17.4).

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 [49–54]. Acid suppressant therapy prevents esophageal exposure to duodenal contents by reducing intragastric volume as a consequence of 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% [49–54]. In recent studies this reduction is less pronounced from 22% to 12%. [49] Important is that

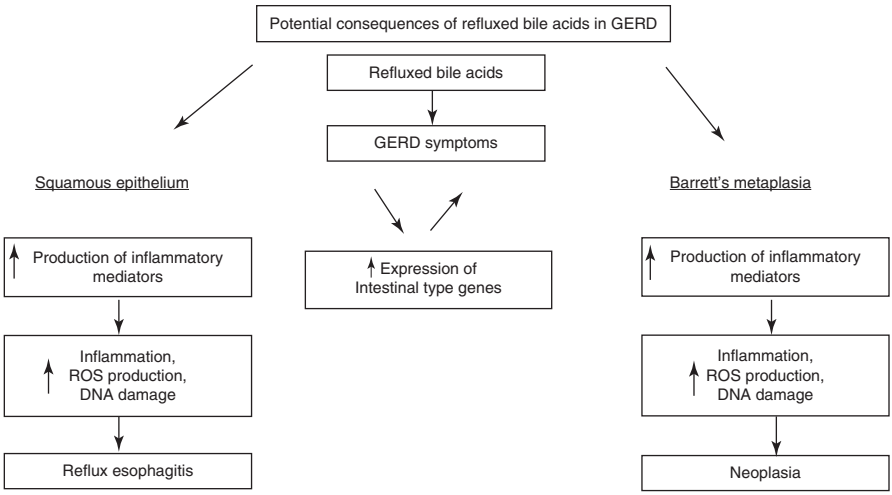


Fig. 17.4 Adapted from: McQuaid et al. [47]

60% of the patients had still pathological bile exposure time. Studies evaluating DGER before and after a 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 [49–51].

It seems logical that prokinetics may improve DGER, by accelerating esophageal clearance and gastric emptying, but this has only been demonstrated in partial gastrectomy patients using high doses of cisapride, which is no longer available because of cardiac adverse events. 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 an add-on therapy, but due to adverse effect the development and evaluation of newer GABA-B agonist is driven [54].

In view of the involvement of toxic radicals and cellular membrane degeneration, there is a role for locally acting mucosal protective therapy. Alginates decrease the 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 [52]. Anti-reflux 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 [47–54].

References

1. Vandenplas Y, Hassall E. Mechanism of gastroesophageal reflux and gastroesophageal reflux disease. JPGN. 2002;35:117–24.
2. Cuomo R, Koek G, et al. Analysis of ambulatory duodenogastroesophageal reflux monitoring. Dig Dis Sci. 2000;45:2463–9.
3. Vaezi MF, Singh S, et al. Role of acid and duodenogastric reflux in esophageal injury: a review of animal and human studies. Gastroenterology. 1995;108:1897–907.
4. Tack J. 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):10–6.
5. Koek G, Vos R, et al. Mechanisms underlying duodeno-gastric reflux in man. Neurogastroenterol Motil. 2005;17:191–9.
6. Kavilaakso E, Fromm D, et al. Effect of bile salts and related compounds on isolated mucosa. Surgery. 1980;87:280–5.
7. Harmon JW, Johnson LF, et al. Effects of acid and bile salts on the rabbit esophageal mucosa. Dig Dis Sci. 1981;26:65–71.
8. Mearin F, Azpiroz F, et al. Antroduodenal resistance to flow in the control of duodenogastric bile reflux during fasting. Gastroenterology. 1987;93:1026–33.
9. Vaezi M, Richter J. Duodenogastroesophageal reflux and methods to monitor nonacidic reflux. Am J Med. 2001;111(8A):160S–8S.
10. Stein HJ, Smyrk TC, et al. Clinical value of endoscopy and histology in the diagnosis of duodenogastroesophageal reflux disease. Surgery. 1992;112:796–804.
11. Nehra D. Bile in the esophagus–model for a bile acid biosensor. J Gastrointest Surg. 2010;14(suppl 1):S6–8.
12. Kauer W, Stein H. Bile reflux in the constellation of gastroesophageal reflux disease. Thorac Surg Clin. 2005;15:335–40.
13. Todd J, De Caestecker J, et al. Gastro-esophageal reflux disease and bile acids. JPGN. 2013;36:172–4.
14. Gotley DC, Appleton GV, et al. Bile acids and trypsin are unimportant in alkaline esophageal reflux. J Clin Gastoenterol. 1992;14:2–7.
15. Hirano I, Richter J, et al. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol. 2007;102:668–85.
16. Koek G, Vos R, et al. Oesophageal clearance of acid and bile: a combined radionuclide, pH and Bilitec study. Gut. 2004;53:21–6.
17. Karamanolis G, Vanuytsel T, et al. Yield of 24-hour esophageal pH and Bilitec monitoring in patients with persisting symptoms on PPI therapy. Dig Dis Sci. 2008;53:2387–93.
18. Iftikhar SY, Ledingham S, et al. Alkaline gastro-esophageal reflux: dual probe pH-monitoring. Gut. 1995;37:465–70.
19. Vandenplas Y, Working group of the European Society of Pediatric Gastroenterology and Nutrition. A standardized protocol for the methodology of esophageal pH monitoring and interpretation of the data for the diagnosis of gastroesophageal reflux. JPGN. 1992;14:467–71.
20. Vaezi M, Lacamera R, et al. Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system. Am Physiol Soc. 1994;267(6 Pt 1):G1050–7.
21. Tack J, Bisschops R, et al. Dietary restrictions during ambulatory monitoring of duodenogastroesophageal reflux. Dig Dis Sci. 2003;48:1213–20.
22. Barrett MW, Myers JC, Watson DI. Detection of bile reflux: in vivo validation of the bilitec fiberoptic system. Dis Esophagus. 2000;13:44–50.
23. Bechi P, Falciai R, et al. A new fiber optic sensor for ambulatory entero-gastric reflux detection. In: Katzir A, editor. Fiber optic medical and fluorescent sensors and applications, vol. 1648. Bellingham, Washington: SPIE; 1992. p. 130–5.
24. Bechi P, Cianchi F. Technical aspects and clinical indications of 24-hour intragastric bile monitoring. Hepato-Gastroenterology. 1999;46:54–9.
25. Byre J, Romagnoli R, et al. Duodenogastric reflux of bile in health: the normal range. Physiol Meas. 1999;20:149–58.

26. Champion G, Richter JE, et al. Duodenogastroesophageal reflux relationship to pH and importance of Barrett's. Gastroenterology. 1994;107:747–54.
27. Johnsson F, Joelsson B, et al. Bile salts in the esophagus of patients with esophagitis. Scand J Gastroenterol. 1988;23:712–6.
28. Kauer W, Burdiles P, et al. Does duodenal juice reflux into the esophagus of patients with complicated GERD? Evaluation of a fiberoptic sensor for bilirubin. Am J Surg. 1995;170:310–2.
29. Schweitzer EJ, Bass BL. Lipid solubilization during bile salt-induced esophageal mucosal barrier disruption in rabbit. J Lab Clin Med. 1987;110:172–9.
30. Batzei S, Harmon JW, et al. Bile acid accumulation in gastric mucosal cells. Exp Biol Med. 1991;197:393–9.
31. Hoffman I, Tertychnyy A, et al. Duodenogastro-esophageal reflux in children with refractory gastro-esophageal reflux disease. J Pediatr. 2007:307–11.
32. Orel R, Markovic S. Bile in the esophagus in children: a factor in the pathogenesis of reflux esophagitis. JPGN. 2002;36:266–73.
33. GadEl-Hak NA, El-Hemaly M, et al. Bile reflux measurement and its contribution to the severity of reflux esophagitis. Saudi J Gastroenterol. 2007;13(4):180–6.
34. Jiang M, Chen J, et al. Bile and acid reflux in the pathogenesis of reflux esophagitis in children. J Pediatr Health. 2009;45:64–7.
35. Wilmer A, Tack J, et al. Duodenogastroesophageal reflux and esophageal mucosal injury in mechanically ventilated patients. Gastroenterology. 1999;116:1293–9.
36. Boeckxstaens V, Bisschops R, et al. Modulation of the postprandial acid and bile pockets at the gastro-esophageal junction by drugs that affect gastric motility. Aliment Pharmacol Ther. 2011;33:1370–7.
37. Koek G, Tack J, et al. The role of acid and duodenal gastroesophageal reflux in symptomatic GERD. Am J Gastroenterol. 2001;96(7):2033–40.
38. Scarpellini E, Ang D, et al. Management of refractory typical GERD symptoms. Nat Rev. 2016;13:281–94.
39. Siddiqui A, Rodriguez-Stanley S, et al. Esophageal visceral sensitivity to bile salts in patients with functional heartburn and in healthy control subjects. Dig Dis Sci. 2005;50:81–5.
40. Farré R. Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? Neurogastroenterol Motil. 2013;25:783–99.
41. Farré R, Van Malenstein H, et al. Short exposure of esophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intracellular spaces. Gut. 2008;57:1366–74.
42. Pardon N, Vicario M, et al. A weakly acidic solution containing deoxycholic acid induces esophageal epithelial apoptosis and impairs integrity in an in vivo perfusion rabbit model. Am J Physiol Gastrointest Liver Physiol. 2016;310:G487–96.
43. Chen X, Oshima T, et al. Bile salts disrupt human esophageal squamous epithelial barrier function by modulating tight junctions proteins. Am J Physiol Gastrointest Liver Physiol. 2012;303:G199–208.
44. Ghatak S, Reveiller M, et al. Bile salts at low pH cause dilatation of intercellular spaces in in vitro stratified primary esophageal cells, possibly by modulating Wnt signaling. J Gastrointest Surg. 2016;20:500–9.
45. Nakos A, Kouklakis G, et al. The histological and immunohistochemical aspects of bile reflux in patients with gastroesophageal reflux disease. Gastroenterol Res Pract. 2011;2011:9.
46. Bani-Hani KE, Bani-Hani BK. Pathogenesis of columnar-lined esophagus. World Gastroenterol. 2006;12:1521–8.
47. 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;34:146–65.
48. Wolfgarten E, Pütz B, et al. Duodenogastroesophageal reflux–what is pathologic? Comparison of patients with Barrett's esophagus and age-matched volunteers. J Gastrointest Surg. 2007;11:479–86.

49. Turcotte S, Duranceau A, et al. Gastroesophageal reflux and cancer. Thorac Surg Clin. 2005;15:341–52.
50. Woodland P, Batista-Lima F, et al. Topical protection of human esophageal mucosal integrity. Am J Physiol Gastrointest Liver Physiol. 2015;308:G975–80.
51. Orel R, Brecelj J, Homan M. Treatment of oesophageal bile reflux in children: the results of a prospective study with omeprazole. JPGN. 2006;42:376–83.
52. Rohof W, Bennink R, et al. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clin Gasterenterol Hepatol. 2013;11:1585–91.
53. Stein HJ, Kauer WK, et al. Bile reflux in benign and malignant Barrett's esophagus: effect on medical acid suppression and Nissen fundoplication. J Gastrointest Surg. 1998;2:333–41.
54. Koek GH, Sifrim D, et al. The effect of the GABA b agonist baclofen in patients with symptoms and duodenogastroesophageal reflux refractory to proton pump inhibitors. Gut. 2003;10:1397–402.

Gastroesophageal Reflux Disease and *Helicobacter pylori* in Children

18

Nicolas Kalach

Abstract

There is a complex relationship among *H. pylori*, gastric acid production, and the development of reflux symptoms and disease. Studies that fail to address this complexity will not provide clear information on which to base clinical decisions and still not well understood in adults as well as in children.

The implications of *H. pylori* infection for the acquisition of GERD are a matter of current controversy. Some studies suggest a causative association between *H. pylori* infection and GERD, whereas others postulate a protective role for *H. pylori* infection. On balance and based on the pediatric published data, we consider that *H. pylori* eradication more likely to provide benefits than harm in children with GERD.

Frequency of GERD and clinical manifestations of *H. pylori* infection; relationship of *H. pylori* and erosive reflux disease; relationship of GERD and *H. pylori* CagA and VacA and other genes' status; effect of *H. pylori* and type of gastritis on gastrin, ghrelin, motilin, and GERD; influence of *H. pylori* eradication on GERD symptoms; and, finally, influence of *H. pylori* on the development of EoE in children were all summarized in this chapter.

Keywords

GER • *H. pylori* • Child • Esophagitis

N. Kalach
Clinique Pédiatrique St Antoine, Hôpital St Vincent de Paul, Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), Catholic University of Lille, BD de Belfort, 59020 Lille Cedex, France
e-mail: kalach.nicolas@ghicl.net

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_18

Abbreviations

CagA	Cytotoxin-associated gene A
DU	Duodenal ulcers
EoE	Eosinophilic esophagitis
ENT	Ear nose throat
eos/HPF	Eosinophils per high-power field
GERD	Gastroesophageal reflux disease
GER	Gastroesophageal reflux
H. pylori	*Helicobacter pylori*
IgE	Immunoglobulin E
LESP	Lower esophageal sphincter pressure
NUD	Non-ulcer dyspepsia
NERD	Nonerosive reflux disease
RUT	Rapid urease test
RAP	Recurrent abdominal pain
RE	Reflux esophagitis
PCR	Polymerase chain reaction
PPI	Proton pump inhibitor
upper GI endoscopy	Upper gastrointestinal endoscopy

Introduction

Helicobacter pylori (H. pylori) is a Gram-negative spiral bacterium that colonizes the gastric mucosa in the infected host. Antral gastritis and duodenal ulcer have been described as common presenting features in children. Acquisition of the infection is often before the age of 5 years by oro-fecal, oro-oral, or gastro-oral transmission. Children with symptomatic *H. pylori* infection associated with peptic ulcer, lymphoma, or rarely atrophic gastritis with intestinal metaplasia require treatment to eradicate the bacterium [1].

Gastroesophageal reflux disease (GERD) frequently affected infants before the acquisition of walking age, but it could also affect to less extent old children that could impair the health-related quality of life. The prevalence of GERD in childhood varies by age; 85% of premature infants, 100% of infants aged less than 3 months based on clinical manifestations, and by 6 months of age 20–40% of infants have GERD, and less than 20% of infants have GERD by ≥12 months of age [2].

Given the high prevalence of *H. pylori* infection and GERD in the community and their serious, although relatively rare, consequences, any relationship of these conditions is likely to be important [3]. The relationship between *H. pylori* infection and GER is very complex and still not well understood in adults as well as in children. Small prospective studies address specific issues in selected pediatric population but do not have sufficient power to describe [3]. The implications of *H. pylori*

infection for the acquisition of GERD are a matter of current controversy. Some studies suggest a causative association between *H. pylori* infection and GERD, whereas others postulate a protective role for *H. pylori* infection [2].

The frequency and the relationship of GERD and *H. pylori* infection in children were rarely published, and there are no well-designed published prospective multicenter, randomized, double-blind, placebo-controlled studies. Most of the published studies are open and monocentric ones.

This chapter summarizes mainly the pediatric literature studies in this field about this controversial and complex relationship between *H. pylori* infection and GERD.

Gastroesophageal Reflux Disease (GERD) and Clinical Manifestations of *Helicobacter pylori* (*H. pylori)* Infection in Children

GERD in children could be presented either with digestive or extra-digestive manifestations, i.e., ear nose throat (ENT) manifestations, recurrent bronchitis or bronchiolitis, or asthma [2].

Frequency and Relationship of GERD in the Course of *H. pylori* Infection in Children

Digestive Manifestations

GERD in children could be presented by digestive manifestations mainly as regurgitations and sometimes by dysphagia and crying in infants, as well as nausea, vomiting, recurrent abdominal pain (RAP) or epigastric pain and tenderness, heartburns, and weight stagnation or failure to thrive in older children. Those clinical manifestations are also common in the course of *H. pylori* infection in children. However, those gastrointestinal manifestations are not specific of *H. pylori* infection in children [1], and the primary goal of clinical investigation of gastrointestinal symptoms should be to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection [1].

There is a complex relationship among *H. pylori*, gastric acid production, esophageal acid exposure, esophagitis, and the development of reflux symptoms and disease. This is because GERD is not the only cause of RAP that could be linked to *H. pylori*. In adults meta-analysis suggests that the prevalence of *H. pylori* is higher in patients with non-ulcer dyspepsia (NUD) than in healthy controls (55% vs 40%). Another separate adult's meta-analysis demonstrated a symptomatic benefit from *H. pylori* eradication (9% relative risk reduction) in patients with NUD. It is well known that the presentation of GERD and NUD overlaps, so treatment for GERD may appear to improve dyspeptic as well as reflux symptoms [3].

Another possibility is that *H. pylori* gastritis may affect the pathogenesis by inducing visceral hypersensitivity, a process considered important in NUD and the subgroup of patients with GERD and nonerosive reflux disease (NERD). Evidences that support this hypothesis are based on the first; compared with controls with no

symptoms and patients with reflux esophagitis (RE), patients with NERD and NUD have a relatively high prevalence of *H. pylori* infection (40% and 36% vs 62% and 55%, respectively). Second, in patients with GERD, the symptomatic remission after a course of acid suppression is significantly longer in patients in whom *H. pylori* has been eradicated than in those in whom infection persists (100 vs 54 days) [3].

Arguments Against This Association

Xinias et al. [4] investigate the association between *H. pylori* infection and GERD in 64 patients with symptoms suggestive for GERD, of which 40 *H. pylori* positive (group A) and 24 *H. pylori* negative (group B) underwent upper gastrointestinal endoscopy (upper GI endoscopy) biopsy, esophageal manometry, and 24-h pH-metry. At inclusion, there were no significant differences between the two groups regarding sex, age, grade of endoscopic esophagitis, and manometric and pH-metric findings. All *H. pylori*-positive patients had an antral predominant gastritis. They conclude that in children and young adults with GER symptoms and GERD, the presence or absence of *H. pylori* has no impact on manometric and pH-metric findings. [4].

Abdollahi et al. [5] carried out another cross-sectional study to determine the role of *H. pylori* infection and GERD in children living in a region which is endemic for *H. pylori* infection (Iran). The study was undertaken in 263 children aged 3–18 years, all of whom had symptoms of GERD and underwent upper GI endoscopy. *H. pylori* status was determined by conventional rapid urease test (RUT) and Giemsa staining of antral and cardiac biopsies. Of the 263 patients, 81 (31%) had GERD and 162 (61%) had gastritis. There were 59 *H. pylori*-infected patients (22%) and 204 were uninfected. *H. pylori* infection was detected in 52 (88%) of the antral and 10 (2%) of the cardiac biopsies. Three (5%) of the biopsies revealed infection of both antrum and cardia and in seven (12%) only the cardia was infected. The prevalence of *H. pylori* infection among patients with GERD (13/83, 15%) was significantly lower than in those without GERD (46/180, 26%) (OR 0.54, CI 0.27–0.93, $p < 0.05$). The prevalence of *H. pylori* infection among those with gastritis (48/162, 30%) was significantly higher than in those without gastritis (11/101, 10.8%) (OR 3.44, CI 1.69–7.015, $p < 0.001$). The authors conclude that *H. pylori* infection might protect against GERD in children [5].

Brazowski et al. [6] carried out a study in 160 children (75 girls and 85 boys between 12 months old and 18 years old with a mean age 8.47) to assess *H. pylori* prevalence in children with acid GERD. Acid GERD was diagnosed in all patients according to their clinical features and the results of 24-h continuous esophageal pH-metry. During routine diagnostic procedures of RAP, vomiting, nausea, and other nonspecific symptoms, upper GI endoscopy tract was simultaneously performed. *H. pylori* infection was diagnosed according to histology and positive RUT. *H. pylori* infection was detected in 29/160 patients (18.1%). Endoscopic esophagitis was presented in 28/160 (17%) of all patients, where *H. pylori* infection was only detected in 4 patients (14%). The authors conclude that *H. pylori* infection was lower in children with acid GERD than the general population and that this infection does not influence the prevalence of esophagitis [6].

Arguments Support This Association

Rintala et al. [7] evaluated the prevalence of *H. pylori* colonization in 266 children who underwent upper GI endoscopy during a 12-m period. The indications for endoscopy were follow-up of esophagitis related to gastroesophageal reflux (GER) ($n = 17$), suspicion of GER ($n = 51$), RAP ($n = 28$), vomiting ($n = 30$), follow-up of esophageal atresia ($n = 46$) and duodenal atresia ($n = 28$), inflammatory bowel disease ($n = 28$), and miscellaneous ($n = 38$). *H. pylori* colonization was demonstrated in 31 (11.6%) of the 266 patients. In two patient groups, a high prevalence of colonization was identified. In patients with an operated duodenal atresia, 36% (10 of 28) had *H. pylori* on the gastric mucosa. The organism was demonstrated on the gastric mucosa in 47% (8 of 17) of the patients with GERD-esophagitis; five of the eight patients had neurological impairment. In the other patient groups, the prevalence of *H. pylori* infection ranged from 2 to 14%. The present study suggests that, in children, the disturbed esophago-gastroduodenal motility, which is commonly associated with GERD and duodenal atresia, predisposes to *H. pylori* infection [7].

Daugule et al. [8] investigate the link between *H. pylori* infection and dyspepsia in children and association with reflux esophagitis (RE). *H. pylori* status was detected by RUT and/or culture in 130 consecutive symptomatic children coming for upper GI endoscopy: 40, aged 8–12 years (55% boys), and 90, aged 13–18 years (21% boys). *H. pylori* prevalence in the age group 8–12 years was compared to the prevalence among 55 asymptomatic children, aged 7–12 years (13C-urea breath test). The prevalence of *H. pylori* infection among patients with gastrointestinal symptoms was 54%. It was significantly higher among patients with RE compared to patients with hyperemic gastropathy: OR = 5.5; $p = 0.03$, 95% CI, 1.15–26.3. In logistic regression analysis, no significant difference between the prevalence of *H. pylori* infection between asymptomatic and symptomatic children could be demonstrated. They conclude that *H. pylori* prevalence was significantly higher among patients with RE compared to patients with hyperemic gastropathy alone. Adjusting for age the prevalence of *H. pylori* infection was not higher among symptomatic children compared to asymptomatic children of the same age [8].

Extra-digestive Manifestations (ENT)

Ear Nose Throat Manifestations

There is growing interest in studying the presence of *H. pylori* in the upper aerodigestive tract. It was shown in several pilot studies that it colonizes the area, while other authors found no evidence of its presence there and a third group of authors believed that it had only a transient presence there.

Arguments Against This Association

The authors [9] investigated a possible role for *H. pylori* in middle ear disease in children. Consecutive patients undergoing myringotomy and adenoidectomy for chronic otitis media with effusion or recurrent otitis media were enrolled. Middle ear fluids were cultured on three types of agar plate and a double polymerase chain reaction (PCR) was run to detect urease-C and adhesion subunit genes. RUT and

PCR were used on the adenoid specimens. Children were interviewed regarding symptoms suggestive of GERD. Eighteen patients were enrolled in the study (mean age 4.4 years, age range 3–8 years). All 28 middle ear fluid cultures were negative in all media. Twenty-one of the 28 samples contained DNA, yet PCR revealed that none of them belonged to *H. pylori*. Ten of the 13 adenoid specimens obtained were positive on RUT but none on PCR. Seven of the 18 patients had at least one symptom suggestive of GERD during the 6 months preceding the study, but this did not have an impact on any of the results. Thus, they conclude that there was no evidence from this study that *H. pylori* colonizes the nasopharynx of children with middle ear disease, whether dyspeptic or not. There is also no apparent role for this bacterium in middle ear pathology [9].

Arguments Support This Association

Katra et al. [10] carried out a pilot study to investigate an association between laryngopharyngeal reflux detected by combined multiple intraluminal impedance and pH monitoring and *H. pylori* in adenoid hyperplasia detected with PCR. The study group consisted of 30 children (median age 5.34 years) with extraesophageal symptoms of GERD with adenoid hyperplasia. All children underwent adenoidectomy with subsequent PCR detection of *H. pylori* DNA in the tissue and multiple intraluminal impedance and pH monitoring. They found significant differences in the number of reflux episodes among patients with PCR positivity (median 35) and negativity (median 0) of *H. pylori* ($p < 0.0056$). Patients with PCR positivity of *H. pylori* had significantly more reflux episodes reaching the upper esophageal sphincter (p 0.023). The absence of reflux episode was the only independent factor for PCR negativity of *H. pylori* in the multiple logistic regression model. These results support the hypothesis that reflux episodes reaching the upper esophageal sphincter may play an important role in the transmission of *H. pylori* into lymphoid tissue of the nasopharynx and thus may contribute to adenoid hyperplasia in children [10].

Another prospective study [11] was carried out in 32 patients who underwent adenoidectomy, in which age ranges between 4 and 13 were included. All children with adenoid hypertrophy underwent 24-h pH monitoring with a dual probe. Proximal probe was placed in the nasopharynx. The presence of nasopharyngeal reflux and GERD was investigated by 24-h pH monitoring. The presence of *H. pylori* was investigated in adenoidectomy samples by *H. pylori* fast test. Of the 32 patients who underwent adenoidectomy, 5 had nasopharyngeal reflux positivity, while 27 patients did not show nasopharyngeal reflux positivity with pH monitorization. *H. pylori* could not be detected in 5 nasopharyngeal reflux-positive children, while 3 of 27 nasopharyngeal reflux-negative children showed *H. pylori* positivity, one of them in the mucosa and others in the core. This study demonstrated the high incidence of nasopharyngeal reflux and GERD in adenoid hypertrophy and the possible colonization of *H. pylori* in the adenoid tissue. This may change the assessment of children with adenotonsillar hypertrophy in the near future. However, more placebo-controlled and double-blind studies and larger series are still needed to support this hypothesis [11].

Respiratory Manifestations

The authors [12] investigate the prevalence of *H. pylori* infection, frequency of GERD, existence of atopy, and levels of serum immunoglobulin E (IgE) in children with bronchial asthma. About 137 children who were diagnosed as bronchial asthma and/or wheezy child aged between 1 and 17 years were enrolled into the study. Peripheral venous blood samples were obtained to determine the total IgE and *H. pylori* IgG antibody levels. GER was evaluated by the scintigraphic method and the presence of atopy was investigated by skin prick test. *H. pylori* IgG antibody levels were found negative in 125 (91.2%) and positive in only 12 (8.8%) cases. GERD was detected in 73 (53.7%) of the children and 41 (37.3%) of atopic children. A significant difference could not be determined related to GERD, atopy frequency, and serum IgE levels between the cases with and without *H. pylori* antibody positivity. The present findings suggest that the rate of *H. pylori* antibody positivity is low in patients with bronchial asthma and a significant difference could not be determined in GER and atopy between patients with positive and negative *H. pylori* antibodies. High atopy frequency found in our patient group raises the question of whether allergic diseases can be protective against fecal-oral infectious diseases [12].

RE is uncommon in countries in which most people are colonized by *H. pylori* infection and is extremely rare in persons with RE, although esophagitis is detected in almost 50% of children with recurrent lower respiratory tract symptoms. The authors' [13] hypothesis was that failure to acquire *H. pylori* can enhance esophagitis risk in children with chronic asthma. Forty-two pediatric outpatients with chronic asthma (mean age 13.2 ± 1.18 years, range 12–15 years, 23 boys and 19 girls) were included in the study. They had undergone upper GI endoscopy with gastric and esophageal biopsies for upper dyspeptic complaints. *H. pylori* positivity was confirmed by positive Giemsa staining. Esophagitis was diagnosed by standard histologic procedure (updated Sydney classification). *H. pylori* colonization was detected histologically in 22 of 42 patients (52.4%) enrolled in the study. Histology demonstrated that in asthmatic children with evidence of *H. pylori* infection esophagitis was a dramatically rare finding than in the patients without the infection ($p < 0.001$). It was an unexpected finding that lung function parameters (FEF50, FEF75) were significantly lower in asthmatics infected with *H. pylori* ($p < 0.05$). They conclude that the present findings suggest inverse association between esophagitis and *H. pylori* in the course of asthma in pediatric patients [13].

Relationship of *H. pylori* and Erosive Reflux Disease in Children

Arguments Against This Association

The relationship between gastric *H. pylori* colonization and esophagitis was determined in 457 children undergoing upper GI endoscopic evaluation of RAP and/or vomiting. The incidence of biopsy-proven esophagitis was similar in *H. pylori*-positive (15/56 patients, 26.7%) and *H. pylori*-negative (94/401, 23.4%; p = NS) groups. They conclude to the absence of relationship between *H. pylori* and RE [14].

Pollet et al. [15] carried out a retrospective study to assess the relationship between *H. pylori* infection and GERD in a high-risk population of children. Forty-three neurologically impaired pediatric patients with *H. pylori* had upper GI endoscopy between 1990 and 2000. Infection was confirmed by positive *H. pylori* culture or by identification of organisms in gastric biopsy specimens (fundus, $n = 2$; antrum, $n = 3$). RE was diagnosed by ulceration of the esophageal mucosa at upper GI endoscopy. At the first endoscopy, esophagitis was noted in only 14 of 43 (32.5%) patients. They also conclude to the absence of relationship between *H. pylori* and RE [15].

Emiroglu et al. [16] carried out a study in 206 children [mean age 8.4 ± 4.9 (0.16–18) years]. Children who underwent diagnostic upper GI endoscopy were tested for *H. pylori* infection, and the relationship between *H. pylori* infection and GERD (endoscopic features and histopathological findings) was investigated retrospectively. The patients diagnosed with GERD were divided into two groups: those with macroscopic erosions or ulceration constituted the erosive esophagitis GERD group, and those without constituted the nonerosive GERD group. Prevalence of *H. pylori* infection was 31.3% in the patients with GERD and 36.7% in the control group ($p > 0.05$, NS). Prevalence of erosive esophagitis GERD was found to be 23.8% in the patients with *H. pylori* infection and 41.3% in those without ($p > 0.05$, NS). They conclude that there was no negative significant association between the prevalence of *H. pylori* infection and erosive esophagitis GERD. The presence of *H. pylori* infection did not influence the severity of esophagitis either [16].

In a recent study, Lupu et al. [17], in order to show the possible protective role of *H. pylori* infection for GERD, explored a group of 72 children with GERD confirmed by 24-h continuous esophageal pH monitoring, who underwent upper GI endoscopy with gastric biopsy specimens to detect *H. pylori* infection. They found that only 19 children (26.39%) had *H. pylori* infection, whereas 53 (73.61%) did not. According to the Los Angeles classification system of esophagitis, *H. pylori* infection was significantly detected in 16/47 (34.04%) children with esophagitis A vs only 3/25 (12%) children with esophagitis B, $p < 0.05$. Furthermore, regarding the value of the Boix-Ochoa score, it appears that the presence of the *H. pylori* determines significant lower pH-metry scores ($F = 8.13$, $P = 0.0015$, 95% CI). Thus, the presence of *H. pylori* infection was not an important factor in GERD, but on the other hand, its relationship with esophagitis appears to be inverse ratio. They conclude that *H. pylori* infection could confirm the hypothesis that the bacteria would slow down the development of the endoscopic esophagitis in the course of GERD [17].

Zagorskii et al. [18] carried out a study in 300 children and adolescents 12–18 years old with GERD-esophagitis to determine clinical-epidemic correlations between GERD-esophagitis and *H. pylori*. *H. pylori* infection was diagnosed by histology according to the updated Sydney classification and RUT. Subjective symptoms of GERD-esophagitis, i.e., heartburn, RAP, and other dyspeptic complaints, were analyzed by questionnaire. *H. pylori* infection was found in 45% of children and adolescents with GERD-esophagitis, and there was no significant

association between clinical symptoms of GERD-esophagitis and *H. pylori* infection. They conclude that the development of GERD-esophagitis does not associate *H. pylori* infection in children [18].

Eltisur et al. [19] investigate retrospectively, before *H. pylori* eradication treatment, a total of 150 charts, mean age 11.8 ± 3.5 years, where *H. pylori* infection was confirmed by upper GI endoscopy with positive gastric biopsy specimen on histology and RUT in 50 *H. pylori*-positive children (the test group) vs 100 *H. pylori*-negative children (the control group) with negative gastric biopsy specimen on histology and RUT. There was no significant difference between endoscopic esophagitis in the test group 10% vs the control one 18%. Similarly, there was no significant difference between histological inflammations of the esophagus detected at any level (mild, moderate, and severe) between the test and control groups. Thus, they conclude that these findings demonstrated the lack of significant interaction between *H. pylori* infection and histological and endoscopic esophagitis in children before eradication treatment [19].

Arguments Support This Association

Adult studies suggested that *H. pylori* infection may protect against GERD by causing atrophic gastritis, which leads to reduced gastric acid secretion. The objective of this study was to determine the role of *H. pylori* infection in the development of GERD in a pediatric population [20]. A retrospective analysis of 420 patients (M:F = 214:206) who underwent upper GI endoscopy with biopsies between January 2000 and April 2006 was conducted. Patient demographics, clinical indications for upper GI endoscopy, and the prevalence of RE, the biomarker for GERD, in two groups, *H. pylori* positive and *H. pylori* negative, were reviewed. The prevalence of RE in the *H. pylori*-positive and *H. pylori*-negative groups was further analyzed on the basis of sex and age (<1 year, 1–10 years, >10 years). The clinical indications for upper GI endoscopy were as follows: RAP (n = 186, 44%), malabsorption (n = 80, 19%), persistent vomiting (n = 80, 19%), suspected eosinophilic gastrointestinal disorders (n = 63, 15%), and others such as upper gastrointestinal bleeding or inflammatory bowel disease surveillance (n = 11, 3%). Among the 420 patients, 16 patients (3.8%) were positive for *H. pylori* and 167 patients (39.8%) were found to have RE. Thirteen patients with *H. pylori* were found to have histologic evidence of RE. The prevalence of RE in the *H. pylori*-positive population was 81.3% compared with 38.1% in the *H. pylori*-negative population ($p \leq 0.05$). There were no patients with *H. pylori* in the youngest age group. In the second age group (1–10 years), 100% of the *H. pylori*-positive patients had RE, whereas 44.6% of the *H. pylori*-negative patients had RE ($p \leq 0.05$). On a multivariate logistical regression, for the overall study cohort, *H. pylori*-positive patients had an odds ratio of 5.79 of developing RE compared with *H. pylori*-negative patients, $p \leq 0.05$. They conclude that there is a significantly higher prevalence of RE in an *H. pylori*-infected cohort independent of age or sex. The findings suggest that *H. pylori* infection in children is positively associated with RE [20].

Influence of *H. pylori* Eradication on Gastroesophageal Reflux Symptoms

Conflicting reports have noted a possible association linking eradication of *H. pylori* with aggravation of GERD.

Levine et al. [21] prospectively evaluated the effect of eradication of *H. pylori* on GERD symptoms and epigastric pain and the association among these three parameters in a pediatric cohort. Patients who were referred for upper GI endoscopy were evaluated for frequency, severity, and nocturnal presence of symptoms related to GERD as well as epigastric pain. Patients who were positive for *H. pylori* received proton pump inhibitor (PPI)-based triple antibiotic therapy. The patients were followed for at least 6 months after therapy. Patients with successful eradication had symptoms compared with their pre-eradication state and were compared with a cohort of patients without *H. pylori* or those with persistent *H. pylori*. Of 119 children and adolescents who were recruited, 95 patients completed the study, with a mean follow-up of 11.2 months. The distribution of outcomes for each GERD symptom (better, worse, unchanged) was similar before and after eradication and did not depend on prior *H. pylori* status. Among patients with GERD and epigastric pain, improvement in epigastric pain was significantly correlated with the improvement in GERD symptoms but not with eradication of *H. pylori*. They conclude that eradication of *H. pylori* is not associated with increased symptoms of GERD in children and adolescents. Improvement in epigastric pain in children is significantly correlated with the improvement in GERD symptoms but not with eradication of *H. pylori* [21].

In another study carried out in 457 children undergoing upper GI endoscopy evaluation of RAP and/or vomiting [14], they found that clinical improvement, after 2 months of antisecretory therapy with H2 receptor antagonists, was independent of *H. pylori* status (11/15 vs 68/94 responders; p = NS). All 26 *H. pylori*-negative nonresponders became asymptomatic with a second course of H2 blockers. The 4/15 *H. pylori*-positive patients (all of whom had associated gastritis/duodenitis) who failed antisecretory therapy responded clinically to treatment with amoxicillin plus bismuth subsalicylate. These data indicate that primary treatment of biopsy-confirmed esophagitis in children should include antisecretory agents, regardless of *H. pylori* status. A small percentage of *H. pylori*-positive patients with esophagitis and concomitant gastroduodenal inflammation may require additional antibacterial therapy [14].

Poulet et al. [15] reported that after treatment, *H. pylori* infection was eradicated in all 14 patients with esophagitis but in only 19 of 29 (66%) of those with normal esophagus ($p = 0.01$). Esophagitis was still present in 4 of 14 (29%) patients who had esophagitis at the first endoscopy. Persistent esophagitis was only related to the presence of esophagitis before treatment ($p = 0.02$). In 29 patients with a normal esophagus at the first endoscopy, only one case of esophagitis was observed after *H. pylori* eradication. They conclude that treatment of *H. pylori* infection should be considered in children with concomitant GERD, and such treatment is unlikely to either induce or exacerbate peptic esophagitis [15].

Xinias et al. [4] investigate the impact of *H. pylori* eradication on esophageal acid exposure and motility in adolescents and young adults with *H. pylori* gastritis and GERD. Sixty-four patients with symptoms suggestive for GERD, of which 40 are *H. pylori* positive (group A) and 24 are *H. pylori* negative (group B), underwent upper GI endoscopy biopsy, esophageal manometry, and 24-h pH-metry. All group A patients received eradication treatment and were reevaluated 6 months later again with 24-h pH-metry, esophageal manometry, endoscopy biopsy, and clinical assessment. Eradication of *H. pylori* was successful in all patients, and gastritis and esophagitis were healed in all patients. The mean lower esophageal sphincter pressure (LESP) increased significantly from 11.25 mmHg before to 11.71 mmHg after eradication ($p < 0.05$). A significant decrease in reflux index was observed (mean RI 6.02% before versus 4.96% after eradication ($p < 0.05$)). However clinical symptoms of GER improved not significantly after 6 months of follow-up. Eradication of *H. pylori* infection results in increase in LESP with a consequent decrease in esophageal acid exposure but not significant clinical improvement. These data suggest that the presence of *H. pylori* infection has no impact on the pH-metric and manometric findings in patients with GERD, and thus in case that *H. pylori* infection is identified, an eradication treatment should be offered to prevent peptic ulcer disease and gastric cancer, but also it could have a beneficial effect on esophageal function. However, clinical improvement of GERD seems to be not significant after *H. pylori* eradication in those patients [4].

In conclusion, on balance and based on the pediatric published data, we consider that *H. pylori* eradication more likely to provide benefits than harm in children with GERD.

Gastroesophageal Reflux and CagA, VacA (+) and CagA, VacA (−) *H. pylori* Infection in Children

Cytotoxin-associated gene A (CagA) product is a bacterial virulence factor contributing to the pathogenicity of *H. pylori* infection in humans. Host factors, which vary in different countries, interact with bacterial factors to determine the disease state. The gastritis location could play a role in the induction of GERD, and genotypic differences in *H. pylori* could play an important role in the genesis of clinical manifestation of GERD in the course of this infection in children [22]. The relationship of different *H. pylori* genotype and GERD had been studies in different pediatric studies with conflicting results.

Arguments Against This Association

Sokucu et al. [23] carried out to investigate the frequency of CagA-positive *H. pylori* strains and evaluate the contribution of CagA positivity to symptoms and development of mucosal lesions in *H. pylori*-infected Turkish children. The study was a prospective clinical trial in 240 consecutive children undergoing upper GI endoscopy (110 girls, 130 boys; mean age, 8.7 ± 4.3 years). *H. pylori* infection was diagnosed on the basis of a positive rapid urease test and histology of the mucosal specimens. *H. pylori* IgG and CagA IgG antibodies were measured by enzyme-linked immunosorbent assay in *H. pylori*-positive children. The *H. pylori* positivity

rate was 50.4% in our study group. CagA was positive in 74.4%. *H. pylori* infection was less common in children with vomiting (25.9%, $p < 0.05$). CagA positivity was not associated with any clinical symptom. *H. pylori* positivity was higher in children with DU (80% vs 49.1%, $p = 0.05$), while CagA positivity was similar. Antral nodularity was strongly associated with *H. pylori* positivity and CagA positivity (30.6% vs 3.4% and 36.7% vs 12.9%, respectively, $p < 0.05$). A negative association between CagA positivity and esophagitis was observed (20% vs 76.7%, $p < 0.05$). They conclude that CagA positivity is common in *H. pylori*-infected Turkish children. Esophageal lesions are less common in children infected with CagA-positive strains. Although *H. pylori* is associated with DU disease, CagA positivity does not seem to contribute to development of ulcers in children [23].

Arguments Support This Association

Mendoza-Elizalde et al. [24] characterized the diversity of the cagA, cagE, babA2, and vacA genes in *H. pylori* strains isolated from pediatric patients and the relationship between these genes and clinical disease. Of 93 patients analyzed, 32 were positive for infection. A total of 160 *H. pylori* strains (5 isolates per positive patient) were analyzed. A total of 91% and 83% of strains possessed the cagA and cagE genes, respectively. For the vacA gene, 84% of strains possessed the s1 allele, 15% the s2 allele, 81% the m1 allele, and 13.8% the m2 allele. The babA2 gene was present in 79% of strains. Infection with *H. pylori* strains with the vacA (s1m1) genotype was associated with risk of esophagitis and gastritis ($p = 0.0001$). The combination of cagA and vacA (s1m1) was significantly associated with RAP ($p = 0.002$); however, EPIYA type was not significantly associated with RAP. A total of 16 different genotypes were identified; the most common genotype was vacAs1m1cagA+cagE+babA2+ (47.5%). A total of 84% of pediatric patients were infected by at least two and up to five different genotypes. The presence of multiple paths in the network suggests that reticulate events, such as recombination or reinfection, have contributed to the observed genotypic diversity [24].

The authors carried out a study to assess the prevalence of GERD symptoms in 403 adolescents (14–17 years old) according to their *H. pylori* status in a 2-year prospective school-based survey. Initially the *H. pylori* infection was revealed in 55.3%. GERD was reported by 16.1% vs 17.3% of *H. pylori*-negative vs *H. pylori*-positive subjects where 30.3% of them being CagA positive, NS. Over 2 years later, among 275 subjects without initial GERD, symptoms appeared in 43 (15.6%), GERD was reported by 10.8% vs 18.8% of *H. pylori*-negative vs *H. pylori*-positive subjects where 21% of them being CagA positive. They conclude that *H. pylori* CagA-positive strains in older children result in GERD symptoms, explained by the development of antral gastritis inducing an increase of acid secretion [25].

The authors [26] analyzed the relationship between the occurrence of selected genes such as cagA, vacA, iceA, and babA2 determining pathogenicity of *H. pylori* strains and clinical outcome in children. The study was performed on *H. pylori* strains isolated from biopsies taken from 130 children and adolescents with NUD, gastric and DU, and GERD. The cagA gene was detected in 79/130 (60.8%) *H. pylori* isolates. The presence of the cagA gene was significantly associated with DU

($p < 0.05$). The vacAs1/m1 genotype as more frequent in children with ulcers than in other groups, whereas the vacAs2/m2 genotype was more frequent in patients with gastritis and GERD. The iceA1, iceA2, and babA2 genes were present in 59/130 (45.4%), 27/130 (21%), and 30/130 (23.1%) of the strains, respectively. The vacAs1/cagA+ genotype was most frequently observed in strains isolated from children with PUD. The predominant genotype in children with NUD and GERD was vacAs2/cagA-/iceA1+/babA2-. The study showed a high incidence of strains with increased virulence, possessing cagA, vacAs1, and iceA1 genes in symptomatic children with *H. pylori* infection [28].

Effect of *H. pylori* and Type of Gastritis on Gastrin, Ghrelin, Motilin, and Gastroesophageal Reflux

The possible role of *H. pylori* infection in GERD has recently become a topic of major interest. Some studies have suggested a protective role of *H. pylori* and exacerbation of GERD after eradication [27], although other authors did not confirm this. These controversial results used to be explained with the anatomic location of *H. pylori* infection and the consequent hypo- or hyperacidity.

The distribution of *H. pylori* within the stomach affects the risk of disease development. Antral gastritis is associated with an increase in gastric acid production. Corpus gastritis with atrophy of mucosa is associated with decreased gastric acid production. The GERD severity is related to esophageal acid load, which in turn is affected by acid production in the stomach. Thus, children with antral gastritis have an increased risk, not only of DU but also of GERD; eradication of *H. pylori* in this population reduces acid production and improves reflux and ulcer-related symptoms. Conversely, patients with atrophic gastritis have a decreased risk of GERD; eradication of the bacterium in this group leads to an increase in acid production and an increased risk of the development of reflux symptoms and esophagitis [3].

Within the context of these hypotheses, gastrin, which is the main regulatory hormone in acid secretion, gains importance. *H. pylori* infection may lead to changes on various motility-regulating gastric hormones such as ghrelin and motilin.

Motilin, an endogenous prokinetic hormone, is secreted by gastrointestinal endocrine cells [28, 29]. Besides initiating gastric contraction that distally propagates in the gastrointestinal tract, motilin increases LESP acting both via the enteric nervous system and directly on the LESP muscle.

Another peptide that is influenced by *H. pylori* infection is ghrelin. It is an appetite-increasing peptide that is structurally related to motilin and is produced by the enteroendocrine cells of gastric mucosa. It stimulates gastric acid secretion, gastrointestinal motility, gastric emptying via the vagus nerve, and histamine release [28, 29]. The effect of *H. pylori* infection on ghrelin concentration has been evaluated in a few studies. Nwokolo et al. [30] demonstrated that ghrelin increases after *H. pylori* eradication.

Eren et al. [28] carried out a pediatric study; symptoms of *H. pylori*-infected children, their total GER episodes, acid exposure percentage, and gastrin, ghrelin,

and motilin levels were evaluated before and after *H. pylori* eradication. Forty-two *H. pylori*-infected children were eligible for this study. Acid exposure percentage and total reflux episodes before and after *H. pylori* eradication were 10.2% ± 14.8% vs 7.71% ± 5.0% and 94.7% ± 102.1% vs 64.6% ± 55.0%, respectively ($p = 0.28$, $p = 0.082$). There was an insignificant change in the serum gastrin (93.4 ± 153.8 pmol/L vs 1.28 ± 149.4 pmol/L, $p = 0.67$), ghrelin (7.69 ± 197.5 pg/mL vs 8.36 ± 299.5 pg/mL, $p = 0.274$), and motilin (75.1 ± 81.2 pg/mL vs 97.2 ± 80.5 pg/mL, $p = 0.206$) levels after eradication. Gastrin and ghrelin levels were negatively correlated after *H. pylori* eradication ($r = -0.38$, $p = 0.031$). There was no association between GER episodes and gastrin, ghrelin, and motilin levels ($r = 0.25$ and $p = 0.11$; $r = 0.24$ and $p = 0.13$; $r = -0.23$ and $p = 0.14$, respectively). The authors conclude that, *H. pylori* infection is neither protective nor harmful in the GERD. Neither ghrelin nor motilin levels was associated with GERD. None of gastrin, ghrelin, and motilin levels was affected by *H. pylori* infection. There is an inverse association between gastrin and ghrelin levels after *H. pylori* eradication [28].

Although the prevalence of *H. pylori* infection is not different between patients with GERD and healthy subjects, a significant proportion of patients with GERD also have *H. pylori* infection [31]. Eren et al. [28] demonstrated that over half of the *H. pylori*-infected patients also had GERD. In contrast to studies demonstrating an inverse relation between *H. pylori* infection and GERD development, they could not demonstrate an increase in GERD after *H. pylori* infection eradication [31]. Neither the amount of reflux episode nor the acid exposure time changed after eradication. Those patients who had GERD in the infected state continued to have GERD in noninfected state.

Most of the studies evaluating the association of GERD and *H. pylori* infection have been conducted with adult patients. In these studies, the proposed primary mechanism by which *H. pylori* influences the pathogenesis of GERD depends on the modification of gastrin and gastric acid secretion. Gastrin is released by antral G cells, and it is often increased in *H. pylori*-infected adults [32]. Depending on the anatomical region and the consequence of infection, the serum level of gastrin and its effect may vary. According to the current proposed mechanism, the protective effect is mediated by *H. pylori*-induced corpus-limited gastritis, which results in hypoacidity as a consequence of parietal cell destruction. This resulting hypoacidity leads to increased gastrin release that ends up with rebound hyperacidity and GERD development after eradication. On the contrary, in antrum-limited *H. pylori* infection, because of the destruction of somatostatin secreting cells, an unopposed hypergastrinemia occurs during infection. Consequently, acid secretion increases from the intact corpal parietal cells, resulting in increased occurrence of GERD in the *H. pylori*-infected state. However, if the nature of gastritis is atrophic, then the opposite occurs. Gastrin level decreases because of the antral G cell atrophy, and the resulting hypoacidity provides protects from GERD development [29]. Eren et al. [28] observed neither a change in the gastrin level nor in GERD occurrence between *H. pylori*-infected and noninfected state. In contrast to these hypotheses, Eren et al. [28] in their study could not demonstrate any relationship between gastrin and GERD, which was comparable with a few studies in the literature [33]. One of the

reasons for this difference can be the predominant corpoantral infection in the pediatric patients. Another reason can be the nature of the infection that *H. pylori* causes in children. Atrophic gastritis, which may be encounter to the hypogastrinemia and hypoacidity in adults, is rare in children [34]. In a study, atrophic gastritis was detected only in 6% of the children. Gastric atrophy has been reported to exert an 80% decrease in GERD symptoms, and a decrease in gastrin level has been proposed as a predictor of atrophic gastritis. In the study of Eren et al. [28], none of the patients had atrophic gastritis, and gastrin level did not change between pre- and post-eradication state. May be because of this, most of the children had GERD even though they were infected with *H. pylori*, and we could not observe any change in GERD occurrence after eradication.

Influence of *H. pylori* on the Development of Eosinophilic Esophagitis

We realized a study [35] to measure the number of eosinophils per high-power field (eos/HPF) according to age, organs, and clinical symptoms and to compare the results to histological characteristics of the upper digestive tract mucosa in children.

A systematic prospective assessment of 284 esophagus, 342 antrum, 453 corpus, and 167 duodenum biopsies was carried out in 316 girls and 366 boys referred for endoscopy (median age 9 months), eos/HPF, and histological analysis. Counts (mean-max SD) were as follows: esophagus 1.73 to 50 eos/HPF (5.35), antrum 3.27 to 40 (4.7), corpus 2.11 to 38 (3.76), and duodenum 4.80 to 46 (7.7). Counts >15 eos/HPF were found in 2.8% esophagi, 3.5% corpora, 4.9% antra, and 10.7% duodena. Duodenal eos/HPF were significantly higher than those of esophageal, corporeal, and antral. Mucosal eos/HPF increased with age in esophagus and antrum. The highest esophageal eos/HPF were significantly associated with recurrent abdominal pain and with anemia in the antrum, corpus, and duodenum. Major and/or minor histological features of eosinophilic esophagitis (EoE) were seen in 9 of 10 esophagi with 5–15 eos/HPF and 7 of 8 esophagi with >15 eos/HPF. Eosinophils per high-power field were significantly correlated with histological antral and corporeal gastric inflammation. *H. pylori*-positive children had higher eos/HPF than *H. pylori*-negative ones both in the esophagus and in the antrum.

The present study shows that in a Western European country, mucosal hypereosinophilia is rare. Mucosal eosinophil counts increase from the esophagus to the duodenum and also with age in the esophagus and antrum. The highest eos/HPF in the esophagus are associated with recurrent abdominal pain and in the corpus, antrum, and duodenum with anemia. Features of eosinophilic esophagitis are rare but detectable in association with counts as low as 6 eos/HPF [35].

H. pylori infection and EoE in children seem to have a reversed association with socioeconomic status (hygienic condition) and allergy conditions. While *H. pylori* infection is highly associated with poor hygiene and/or poor socioeconomic status, but not with allergic conditions (asthma, rhinitis, etc.), EoE has the opposite epidemiological relationship (high association with allergy but low with low hygienic conditions).

Elitur et al. [36] carried out a study to investigate the association between *H. pylori* infection and EoE in children**.** A retrospective chart review of all children who undergo the first upper GI endoscopy procedure in the gastroenterology clinic, between 2007 and 2012, was performed. Demographic, endoscopic, and histological data were collected. The data was divided into four diagnostic groups: *H. pylori* infection, EoE, RE, and children who had normal histology. The relationship between *H. pylori*-positive children and the other groups was performed.

A total of 966 charts were available for review. Esophagitis, idiopathic gastritis, EoE, and *H. pylori* infection were detected in 268 (28%), 480 (49%), 62 (6%), and 31 (3%) children, respectively. The mean age of the EoE group was significantly lower compared to all reference groups ($p < 0.002$), but no significant different was detected among the reference groups (gastritis, GERD, and *H. pylori* infection). Simple logistic regression analysis using *H. pylori* infection as a predictor for EoE did not find a significant relationship between these two variables. However, multivariable logistic regression analysis between EoE and the reference groups indicated a significant negative relationship between *H. pylori* infection and EoE. Neither gastritis nor GERD showed significant relationship with EoE. The authors conclude a reversed association between *H. pylori* and EoE was found in a cohort of West Virginia children [36]. The possible explanations for these findings will be discussed. However, prospective multicenter, randomized, double-blind, placebo-controlled clinical trials are needed in the future to elucidate the real relationship between *H. pylori* and EoE in children.

Conclusion

The relationship between *H. pylori* infection and GER is very complex and still not well understood in adults as well as in children. Some studies suggest a causative association between *H. pylori* infection and GERD, whereas others postulate a protective role for *H. pylori* infection. Few studies have investigated the role of *H. pylori* eradication in children with GERD. On balance and based on the pediatric published data, we consider that *H. pylori* eradication more likely to provide benefits than harm in children with GERD. Moreover, in the long term, this treatment is likely to provide cost-effective prevention, in particular in children who require long-term maintenance therapy with PPI, of morbidity and mortality from DU and gastric cancer.

References

1. Koletzko S, Jones NL, Goodman K, Rowland M, Cadranel S, Chong S, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011;53:230–43.
2. Gold B. Outcome of pediatric gastroesophageal reflux disease: in the first year of life, in childhood, and in adults…oh, and should we really leave *Helicobacter pylori* alone? J Pediatr Gastroenterol Nutr. 2003;37(Suppl 1):S33–9.
3. Schwizer W, Fox M. *Helicobacter pylori* and gastro-esophageal reflux disease: a complex organism in a complex host. J Pediatr Gastroenterol Nutr. 2004;38:12–5.

4. Xinias I, Maris T, Mavroudi A, Panteliadis C, Vandenplas Y. *Helicobacter pylori* infection has no impact on manometric and pH-metric findings in adolescents and young adults with gastro-esophageal reflux and antral gastritis: eradication results to no significant clinical improvement. Pediatr Rep. 2013;5(e3):13–6.
5. Abdollahi A, Morteza A, Khalilzadeh O, Zandieh A, Asgarshirazi M. The role of *Helicobacter pylori* infection in gastro-esophageal reflux in Iranian children. Ann Trop Paediatr. 2011;31:53–7.
6. Brazowski J, Nowak A, Szaflarska-Poptawska A. Prevalence of *Helicobacter pylori* infection among children and youth with acid gastro-esophageal reflux. Przegl Lek. 2006;63:128–30. [Article in Polish]
7. Rintala R, Kokkonen ML, Lindahi H, Sariola H. Does disordered upper gastrointestinal motility predispose to *Helicobacter pylori* colonization of the stomach in children? J Pediatr Surg. 1994;29:734–7.
8. Daugule I, Rumba I, Alksnis J, Ejderhamn J. *Helicobacter pylori* infection among children with gastrointestinal symptoms: a high prevalence of infection among patients with reflux oesophagitis. Acta Paediatr. 2007;96:1047–9.
9. Bitar M, Mahfouz R, Soweid A, Racoubian E, Ghasham M, Zaatari G, et al. Does *Helicobacter pylori* colonize the nasopharynx of children and contribute to their middle ear disease? Acta Otolaryngol. 2006;126:154–9.
10. Katra R, Kabelka Z, Jurovcik M, Hradsky O, Kraus J, Pavlik E, et al. Pilot study: association between *Helicobacter pylori* in adenoid hyperplasia and reflux episodes detected by multiple intraluminal impedance in children. Int J Pediatr Otorhinolaryngol. 2014;78:1243–9.
11. Aydin E, Aydogan F, Tastan E, Arslan M, Karaca G. Does *Helicobacter pylori* have a role in the etiology of adenoid hypertrophy? Indian J Otolaryngol Head Neck Surg. 2014;66(Suppl 1):S65–70.
12. Asilsoy S, Babayigit A, Olmez D, Uzuner N, Karaman O, Oren O, et al. *Helicobacter pylori* infection and gastro-esophageal reflux in asthmatic children. J Trop Pediatr. 2008;54:129–32.
13. Nijevitch AA, Loguinovskaya VV, Tyrtyshnaya LV, Sataev VU, Ogorodnikova IN, Nuriakhmetova AN. *Helicobacter pylori* infection and reflux esophagitis in children with chronic asthma. J Clin Gastroenterol. 2004;38:14–8.
14. Rosioru C, Glassman MS, Halata MS, Schwarz SM. Esophagitis and *Helicobacter pylori* in children: incidence and therapeutic implications. Am J Gastroenterol. 1993;88:510–3.
15. Pollet S, Gottrand F, Vincent P, Kalach N, Michaud L, Guimber D, et al. Gastroesophageal reflux disease and *Helicobacter pylori* Infection In neurologically impaired children: interrelation and therapeutic Implication. J Pediatr Gastroenterol Nutr. 2004;38:70–4.
16. Emiroglu HH, Sokucu S, Suoglu OD, Gulluoglu M, Gokce S. Is there a relationship between *Helicobacter pylori* infection and erosive reflux disease in children. Acta Paediatr. 2010;99:121–5.
17. Lupu VV, Ignat A, Ciubotariu G, Ciubara A, Moscalu M, Burlea M. *Helicobacter pylori* infection and gastro-esophageal reflux in children. Dis Esophagus. 2015; doi:10.1111/dote.12429. [Epub ahead of print]
18. Zagorskï SE, Voïtovich TN. Clinical epidemic interaction of reflux esophagitis and *Helicobacter pylori* infection in children and adolescents. Eksp Klin Gastroenterol. 2012;5:29–33. [Article in Russian]
19. Elitsur Y, Paul D, Zandra L, Mary R. Does *Helicobacter pylori* protect children from reflux disease? J Clin Gastroenterol. 2008;42:215–6.
20. Moon A, Solomon A, Beneck D, Cunningham-Rundles S. Positive association between *Helicobacter pylori* and gastro-esophageal reflux disease in children. J Pediatr Gastroenterol Nutr. 2009;49:283–8.
21. Levine A, Milo T, Broide E, Wine E, Dalal I, Boaz M, et al. Influence of *Helicobacter pylori* eradication on gastro-esophageal reflux symptoms and epigastric pain in children and adolescents. Pediatrics. 2004;113:54–8.
22. Canbakan B, Dobrucali A, Celik A, Canbakan M, Bal K, Erzin Y, et al. Gastritis localization and GERD incidence in patients with Cag A (+) and Cag A (-) *Helicobacter pylori* infection. Wien Med Wochenschr. 2000;150:91–3. [Article in German]

23. Sökücü S, Ozden AT, Süoglu OD, Elkabes B, Demir F, Cevikbas U, et al. CagA positivity and its association with gastro-duodenal disease in Turkish children undergoing endoscopic investigation. J Gastroenterol. 2006;41:533–9.
24. Mendoza-Elizalde S, Cortés-Marquez AC, Giono-Cerezo S, Zuniga G, Consuelo-Sanchez A, Valencia-Mayoral P, et al. Analysis of the genotypic diversity of strains of *Helicobacter pylori* isolated from pediatric patients in Mexico. Infect Genet Evol. 2015;29:68–74.
25. Reshetnikov OV, Kurilovich SA, Krotova VA, Krotov SA. *Helicobacter pylori* and symptoms of gastro-esophageal reflux in adolescents: role of cagA-comprising strains. Eksp Klin Gastroenterol. 2006;115:25–7. [Article in Russian]
26. Biernat MM, Gosciniak G, Iwanczak B. Prevalence of *Helicobacter pylori* cagA, VacA, iceA, babA2 genotypes in Polish children and adolescents with gastroduodenal disease. Postepy Hig Med Dosw. 2014;68:1015–21.
27. Nordenstedt H, Nilsson M, Johnsen R, Lagergren J, Hveem K. *Helicobacter pylori* infection and gastroesophageal reflux in a population-based study (The HUNT Study). Helicobacter. 2007;12:16–22.
28. Eren M, Colak O, Isiksoy S, Yavuz A. Effect of *Helicobacter pylori* infection on gastrin, ghrelin, motilin, and gastro-esophageal reflux. Turk J Gastroenterol. 2015;26:367–72.
29. Zullo A, Hassan C, Repici A, Bruzzese V. *Helicobacter pylori* eradication and reflux disease onset: did gastric acid get "crazy"? World J Gastroenterol. 2013;19:786–9.
30. Nwokolo CU, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of *Helicobacter pylori*. Gut. 2003;52:637–40.
31. JC W, Sung JJ, Ng EK, et al. Prevalence and distribution of *Helicobacter pylori* in gastro-oesophageal reflux disease: a study from the East. Am J Gastroenterol. 1999;94:1790–4.
32. Peitz U, Wex T, Vieth M, et al. Correlation of serum pepsinogens and gastrin-17 with atrophic gastritis in gastroesophageal reflux patients: a matched-pairs study. J Gastroenterol Hepatol. 2011;26:82–9.
33. JC W, Sung JJ, Chan FK, et al. *Helicobacter pylori* infection is associated with milder gastro-esophageal reflux disease. Aliment Pharmacol Ther. 2000;14:427–32.
34. Cam S. Risk of gastric cancer in children with *H. Pylori* infection. APJCP. 2014;15:9905–8.
35. Kalach N, Huvenne H, Gosset P, Papadopoulos S, Dehecq E, Decoster A, et al. Eosinophils counts in upper digestive mucosa of West European children: variations with age, organs, symptoms, *Helicobacter pylori* status and pathologic findings. J Pediatr Gastroenterol Nutr. 2011;52:175–82.
36. Elitsur Y, Alrazzak BA, Preston D, Demetieva Y. Does *Helicobacter pylori* protect against eosinophilic esophagitis in children? Helicobacter. 2014;19:367–71.

The Management of Infant Regurgitation

19

S. Salvatore, M.M. Tabbers, M.M.J. Singendonk, F. Savino, A. Staiano, M.A. Benninga, K. Huysentruyt, and Y. Vandenplas

Abstract

Regurgitation is a frequent manifestation in infants and, in most cases, a self-limiting physiological condition. However, it is a frequent cause of parental anxiety, feeding problems, change of milk formula, and medical referral.

Regurgitation is not a reason to stop breastfeeding. A thickened anti-regurgitation formula is indicated in formula-fed infants with frequent, persistent, or troublesome regurgitation. Several agents have been used to thicken infant formula including rice and cornstarch and nondigestible carbohydrates such as carob bean gum, guar gum, and soybean polysaccharides.

Data suggest that thickened formula reduces regurgitation, increases weight gain, and may improve reflux-associated symptoms. Clinical efficacy and effect on gastroesophageal reflux are related to different variables such as origin and concentration of thickener, viscosity, kind of protein, hydrolysis, osmolarity, frequency and volume of the meal, gastric accommodation, gastric emptying, and

S. Salvatore (✉) • M.A. Benninga
Clinical Pediatrica di Varese, Universita dell'Insubria, Varese, Italy
e-mail: silvia.salvatore@uninsubria.it

M.M Tabbers • M.M.J. Singendonk
Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, The Netherlands

F. Savino
Ospedale Infantile Regina Margherita, Città della Salute e della Scienza di Torino, Torino, Italy

A. Staiano
Department of Translation Medical Science, Section of Pediatrics, University of Naples, Federico II, Naples, Italy

K. Huysentruyt • Y. Vandenplas (✉)
Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium
e-mail: Yvan.Vandenplas@uzbrussel.be

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_19

position of the infant. Parental reassurance and dietary guidance for appropriate volume and frequency of feeding remain the cornerstone of the management. Commercial thickened formulas offer a preferable composition with better viscosity, digestibility, and nutritional balance compared to adding thickeners to standard formula. Positional treatment (side sleeping or elevated supine position) cannot be recommended in sleeping infants as there are insufficient data regarding both efficacy and safety.

Conclusion: If reassurance and appropriate dietary intake are not sufficient to reassure parents, or in case of poor weight gain due to the regurgitation and infant distress, anti-regurgitation formula should be considered. Commercial thickened formulas reduce regurgitation frequency and severity and parental anxiety and prevent unneeded referral and drug overuse.

Keywords

Anti-regurgitation milk formula • Thickened formula • Thickening agents • Positional treatment • Regurgitation • Gastroesophageal reflux • Positional treatment • Reassurance • Vomiting

Introduction

Infantile regurgitation is a common condition occurring in at least half of the infants around the age of 4 months of life, in 20% at 8 months, and in 5–10% at 1 year of age [1–3].

The distinction between physiological regurgitation and regurgitation related to gastroesophageal reflux disease (GERD) is challenging even for expert physicians, because regurgitation is neither sufficient nor necessary for the diagnosis of GERD, as it is a nonsensitive and nonspecific manifestation [4–6]. GERD implies the presence of troublesome symptoms or complications, but parental coping determines whether regurgitation and infant distress are considered as troublesome or not [4–6]. Recent guidelines on GER recommend non-pharmacologic treatment such as parental reassurance and dietary management, as an appropriate first approach in regurgitating infants without alarm symptoms and signs [4, 5]. Since almost 20 years, anti-regurgitation formulas are commercially available for formula-fed infants [7].

Why Is Management Recommended?

Although reviews on the natural evolution of regurgitation in infants are available [3], there are only limited to no data on the natural history of GERD in infants and children because most patients do receive treatment at some point. Traditionally, the impact of regurgitation on the long-term quality of life is trivialized since regurgitation is transitory in the vast majority of infants. However, there are data that suggest a decreased quality of life in parents of infants presenting with frequent regurgitation, even if the regurgitation has disappeared [8]. Infants spilling during 90 days or more

during the first 2 years of life are at a greater risk for GER later on during childhood [1]. In the absence of treatment, histologic esophagitis does persist (at least 1 year after the initial diagnosis), although symptoms improve in more than half of the patients [9]. But it is still unclear if treatment of regurgitation, GER, and GERD during infancy changes the incidence, symptoms, and outcome of GER(D) in adults. There are no data to suggest that early intervention during infancy would change the course GER(D) in adults, because it has not been studied. However, although there are no data indicating that early intervention is beneficial on the long term, there are a few data to suggest that non-intervention results in chronic conditions such as persisting histologic esophagitis or persisting decreased quality of life [9].

Reassurance and Anticipatory Guidance

At common reason for parents to seek medical help is frequent troublesome regurgitation and infant distress. Because infants with physiologic but troublesome regurgitation are difficult to distinguish from infants with mild to moderate GERD symptoms, non-pharmacologic treatment (reassurance, dietary management) is recommended as an appropriate first approach. Physiologic and pathologic GER has no clear clinical delineation and is a continuum where "at some point" "normal" stops and "disease" begins. Parental coping determines whether regurgitation and infant distress are considered as troublesome or not.

In many situations, reassurance means observation of feeding and handling of the child during and after feeding. A "reduction of the ingested volume" per feed is a classic recommendation that can be found in all overviews and guidelines or recommendations [4, 5, 10]. However, there are no data that relate ingested volume to frequency and volume of regurgitation, although it seems logic to hypothesize that feeding of large volumes favors regurgitations since it will increase TLESRs. Therefore, a normal feeding pattern avoiding overfeeding, with feeding frequency and volume adjusted for age and weight, is recommended. Reassurance while showing compassion for the impaired quality of life is of importance [4, 5, 10, 11].

In general, regurgitation is not a reason to stop breastfeeding. If mothers have decided to pump milk, expert opinion suggests that thickener can be added to the pumped milk. However, there are no data endorsing this approach as this kind of trial has not been performed.

Recent data suggest that parental reports during a first consultation may be inaccurate and overestimate the incidence of regurgitation [11], similar to what is well known regarding crying infants or infant colic. Therefore, a "prospective 3-day diary" may contribute to bring reassurance.

The Reasons Behind Anti-regurgitation Formula

In most infants, regurgitation is a self-limiting phenomenon. However the presence of persistent, frequent, and voluminous regurgitation is a main reason for parental distress and concern, for formula changes, and for medical referral [12, 13]. Frequent

(≥4 episodes per day) regurgitation is a cause of concern in around 20% of parents, particularly in 1–4-month-old infants. An Indonesian study highlighted that the frequency of regurgitation is perceived by mothers as "the main problem," much more than crying/irritability, food refusal, arching back, or volume of regurgitation (66% vs. 57%, 26%, 20%, and 9%, respectively) [14]. In an Italian observational report based on 2879 infants followed from birth to 6 months, 55% of the infants presented with at least one gastrointestinal (GI) symptom: regurgitation occurred in 23%, 3% were hospitalized, and formula was changed in 60% [15]. Parents of 200 infants (6–18 months old) reported at least one formula change in the first 6 months of life in almost half of all infants, with regurgitation or vomiting as the main reason for switching formula and use of commercial anti-regurgitation formula in 7% of them. The main reasons indicated by parents for thickening the infant formula were to improve night sleep (45%), restlessness (14%), regurgitation or vomiting (12%), and failure to thrive (11%) [12].

Remission of regurgitation occurs in most infants before the age of 1 year [1–3]. However, even thereafter, feeding refusal, prolonged duration of a meal, and parental feeding-related distress have been reported to be significantly higher in the group with (previous) regurgitation compared to a control group [2]. Moreover, infants spitting at least 90 days during their first 2 years of life present an increased risk to develop GER symptoms at 9 years of age [1].

Parental reassurance and guidance and overfeeding avoidance are strongly recommended as the first step in the therapeutic approach of regurgitation in infants [4, 16]. A thickened or commercial anti-regurgitation (AR) formula is indicated in formula-fed infants with both persistent regurgitation and poor weight gain [4, 5]. Breastfeeding should be further encouraged in the vast majority of infants. If a mother decided to pump milk, this can be thickened. This advice is based on expert opinion as there are no data to endorse this recommendation. In contrast, in the last 20 years, over- and misuse of acid inhibitors have been worldwide reported in infants with the (erroneous) intention of reducing regurgitation and associated symptoms [17–19].

The Rationale of Anti-regurgitation Formula

The principle of AR formula is adding a thickening agent to an infant formula to increase its viscosity, a quantitative rheological measurement of frictional resistance to shear in a fluid, and thus to visibly reduce the number and volume of episodes of regurgitation. Rice, corn, or potato starch, carob (locust) bean gum (prepared from St. John's bread, a galactomannan) or flours, and carboxymethyl cellulose have all been used as thickening agents in formula [16, 20]. These thickening agents are legally allowed and different maximum concentrations have been established for each group (European Parliament and Council 1995) (European Parliament and Council 2006). According to the European legislation, modified starches may be added to infant formula up to either 30% of total carbohydrate or 2.0 g/100 mL [21]. The maximum accepted level of locust bean gum differs worldwide. In Europe it may be added to infant formula up to 1 g/100 mL when prescribed under medical supervision to treat GER [22, 23]. Rice cereal may contain significant levels of arsenic (see below).

Decreasing regurgitation and consequently decreasing nutrient losses can be particularly advantageous for infants who fail to thrive. Thickening agents may be associated with delayed esophageal clearance and gastric emptying, increased intestinal fermentation, modification of bowel movements, and nutrient absorption.

Viscosity of Anti-regurgitation Formula

In vitro models demonstrated that carob seed flour is the thickening agent with the highest viscosity [24, 25]. Using a rheometer both at basal conditions (25°C, pH 7) and at simulated gastric conditions (37°C, pH 4 and 10 g/100 mL of pepsin), formula containing bean gum (carob seed flour) with 2.9 g/100 g and a protein ratio similar to cow's milk (80% casein/20% whey) showed the highest and consistent viscosity, with significant differences compared to the standard formula and to formula with starch thickeners (rice, potato, and corn). When this thickener was in formulas with a protein ratio similar to breast milk (40% casein/60% whey), the viscosity was lower and the thickener needed to be added at a much higher concentration (4.7 g/100 g) to reach the previous viscosity [24]. Another in vitro model that simulates the GI of young (less than 6 months) infants showed that locust bean gum added to a standard formula at a concentration of 15% up to 50% and 100% of their respective maximum legal limit [21, 22] resulted in a significantly higher viscosity value than corn or rice [25].

Digestibility of Anti-regurgitation Formula

Some concerns regarding the digestibility of a high percentage of carbohydrates in infant formula have been reported [26, 27]. To digest starch to glucose, six enzymes, including two (salivary and pancreatic) alpha-amylases, two sucrase-isomaltases, and two mucosal maltase-glucoamylases, are involved. Sucrase-isomaltase and maltase-glucoamylase are the key enzymes that digest starch in the young infant before pancreatic alpha-amylase secretion matures. The starch digestion rate is correlated to its chemical structures which are determined by the different botanical sources and food processing techniques. Starch granules differ for shapes, sizes, surface pores, and internal channel distributions and are classified into rapidly digestible, slowly digestible, and resistant starch based on the reaction of combined pancreatic alpha-amylase and alpha-glucosidases. The crystalline structures observed in X-ray diffraction classify starch granules into A (such as wheat, normal maize, and rice, which have a high susceptibility to α-amylase hydrolysis), B (such as potato and green banana, with low hydrolysis), and C (such as most of those in beans and seeds, which have an intermediate hydrolysis) types. Cooking and other food processing technologies change the native starch molecule into a relatively more digestible form [27, 28]. Gelatinization greatly lowers the resistance of starch to enzymatic attack [29]. Reaction rates toward alpha-amylase of raw or granular forms of starches are much slower and vary according to the source of starch with increasing resistance from waxy maize to tapioca, sorghum, ordinary corn, wheat, rice, sago, potato, and high-amylose corn [29].

Wheat, tapioca, corn, rice, and potato starch cooked for 10 min in water are digested and efficiently (>98%) absorbed in infants if their concentration is in the range of 45 g/m^2/day equivalent to 1.6–1.9 g/100 mL in 1-month-old or 85 g/m^2/day equivalent to 3.1–3.5 g/100 mL in 3-month-old infants. A larger amount of 5 g/100 mL rice starch was well tolerated, but a slight increase to 6 g/100 mL caused fermentative diarrhea [3].

Locust bean gum is a different thickening agent obtained from the endosperm seed of the locust/carob tree (*Ceratonia siliqua* (L.) Taub) of the plant family of Leguminosae. The substance consists of high molecular weight polysaccharides (50,000–3,000,000 daltons) of which at least 75% are galactomannans. Locust bean gum is coded as INS/E 410 according to food additive numbering and is commonly used in various foodstuffs as a food additive with thickening, stabilizing, emulsifying, or gelling properties. Locust bean gum is resistant to human digestive enzymes, being excreted unchanged in the feces or fermented by the microbiota in the colon [30].

Anti-regurgitation Formula and Gastric Emptying

The role of gastric emptying in patients with symptomatic reflux is controversial. One practical concern of AR formula is that the thickening agent may delay gastric emptying, thus possibly increasing postprandial GER and related symptoms. The negative effect on gastric motility would be theoretically more pronounced for a fiber [31], but it seems also dependent on its viscosity and concentration.

Locust Bean Gum

In 39 regurgitating infants, antral cross-sectional areas measured by ultrasound at various time points after feeding were greater with formula thickened with locust bean gum at concentration of 0.45 g/100 mL (HL-450) compared to a regular formula (ref). The median gastric emptying rate at 120 min was also significantly slower with HL-450 (52.8% vs. 97.9%; $p = 0.0019$) compared to regular formula [32]. Compared to standard formula, no significant difference was shown with a formula thickened with a lower concentration of locust bean gum (0.35 g/100 mL, HL-350) [32, 33]. However, no significant effect on gastric emptying half time occurred in 20 infants fed with another formula with locust bean gum at a concentration up to 0.6 g/100 mL [34].

Cornstarch

A randomized prospective comparative study evaluating the effect of cornstarch-thickened formula or postprandial postural therapy in 63 regurgitating infants reported a similar gastric emptying measured by a 90-min technetium 99m milk scintigraphy [35].

A prospective randomized trial comparing two different formulas (cornstarch-thickened formula versus a 25% strengthened formula) found an accelerated gastric emptying of AR formula in comparison to a 25% strengthened regular formula in 81 regurgitating/vomiting infants [36].

Protein Content and Hydrolysis

The protein content and whey/casein ratio in the formula should also be considered when comparing different (AR) formulas because these components may also influence gastric emptying and thus regurgitation frequency and associated symptoms. In 90 healthy infants, the gastric residual content, 2 h after feeding, was smallest with whey-hydrolyzed formula and breast milk (16% and 18%, respectively) and progressively higher with acidified, whey-predominant, casein, and follow-up formula and whole cow's milk (25%, 26%, 39%, 47%, and 55%, respectively) [37]. Twenty-eight infants diagnosed to have GER by pH monitoring underwent scintigraphy on 3 consecutive days using the same volume (and calories) per single feeding of a casein-predominant, a soy, or a whey pHF in a randomized order. Mean values of gastric emptying, 60 min after feeding, were 39.7%, 44.6%, and 48.5% on casein, soy, and whey formula, respectively. A significant difference was observed ($p < 0.05$) on gastric emptying between casein-predominant and whey-hydrolysate feedings [38].

According to data obtained with a 13C-octanoic acid breath test in a randomized controlled crossover study in 20 healthy newborns, extensive hydrolysates have a significant enhanced gastric emptying (median time 46 min, interquartile range [IQR] 30–58 min) compared to formulas with partial hydrolyzed (median 53 min, IQR 43–75 min) and intact (median time 55 min, IQR 52–83 min) proteins [39].

The above studies show that hydrolyzed protein (extensive hydrolysate more than partial hydrolysate) accelerates gastric emptying compared to intact protein. However, the benefit of whey protein (compared to casein) should also be considered in interpreting these results. And last but not least, other differences in infant formula composition such as supplementation with pre- or probiotics, lipid composition, and amount may as well play a role in gastric emptying.

Clinical Efficacy of Anti-regurgitation Formula

AR formulas differ in composition, such as thickening agent, concentration of the thickener, protein composition, and hydrolysis. The first clinical studies with a formula containing thickening agent in regurgitating infants date back to 1987. Orenstein et al. reported that a formula with 4% rice starch decreased regurgitation and crying and increased sleeping time in 20 infants, even though the number of reflux episodes documented by scintigraphy did not decrease [40]. In the same year, Vandenplas et al. reported a significant decrease in episodes of regurgitation and reflux, clinical and docmumented by pHmetry, (1 g to 115 mL) [41].

Table 19.1 Mean number of episodes of regurgitation in trials with thickened feeds

	At inclusion	With AR formula (after 1–4 weeks)
Chao [35]	3.71 ± 0.69	2.39 ± 0.86
Chao [36]	4.19 ± 1.71	0.93 ± 0.42
Hegar [13]	5.9 ± 1.7	3.3 ± 2.3
Khoshoo [42]	4.33 ± 0.51	2.83 ± 0.40
Miyazawa 2006 (7 days) [32]	22.6 ± 3.9	12.9 ± 3.5
	29.8 ± 3.6	12.8 ± 3.0
Recalculated/day	3.74	1.84
Miyazawa 2007 [33]	5.2	3.2
Vandenplas [11]	8.25	2.32 or 1.89
Vivatkavin [34]	5.7 ± 2.13	2.25 ± 1.45
Wenzl (nO. episodes over 342 h) [43]	68	15
Recalculated per day	4.77	1.05
Xinias [44]	5.60 ± 4.15	2.57 ± 2.71
Mean number of regurgitations/day (all studies)	5.14	2.20

Since then, several randomized trials have confirmed the reduction of the daily number of episodes of regurgitation with about 50%, from a mean of 5.14 episodes/day to 2.20 episodes/day over a period of 1–4 weeks (Table 19.1) [11, 13, 32–36, 42–44]. However, the design of each study differs, with differences in inclusion, method, formula and/or thickener tested, and duration of intervention. Therefore, the figure of a 50% of reduction is indicative.

Additional effects of AR formula have been reported, such as improved sleeping [45], decreased percent feeding with choke-gag-cough [45], or a combination of non-regurgitation symptoms (irritability, cough, choking, night waking) [36].

A soy-fiber-thickened infant formula, in comparison to standard infant formula, showed only a small reduction (−0.40) of episodes of regurgitation and vomiting [46].

A meta-analysis including 14 studies with different thickening agents or commercial AR formulas concluded that the formulas decrease the number of episodes of regurgitation and vomiting and significantly increase the percentage of infants with no regurgitation and increase weight gain per day [20]. In details, a decrease of 0.6 episodes of regurgitation per day [95% CI, −0.7 to −0.5], in fixed-effects model, or 1.8 episodes [95% CI, −2.7 to −0.8], in random-effects model, resulted in the pooled analysis of six studies [20]. All studied thickeners (i.e., corn, carob, and soy fiber) were effective in reducing the number of episodes of regurgitation. Three RCTs, two with carob [43, 47] and one with soy fiber [46], resulted in a significant increase in the number of infants without regurgitation (*RR*, 2.9 [95% CI, 1.7–4.9]; with a number needed to treat of 6 [95% CI, 4–10]). Thickening of infant formula was associated with a statistically significant increase in weight gain (3.55 g/day [95% CI, 2.6–4.5] compared to standard infant formula, in fixed-effects model, and 3.7 g/day [95% CI, 1.55–5.80], in random-effects model) in four RCTs recruiting 265 infants [35, 36, 44, 48].

Comparing different anti-regurgitation formulas, there was no clear benefit from one thickening agent above another. Thus, an AR formula "does what it has to do" as it decreases visual regurgitation and reinforces the effect of parental reassurance. Any additional effect on GER may be considered as an additional benefit but is, in fact, not relevant [49].

Extensive hydrolysates may also resolve regurgitation and distress related to cow's milk protein allergy which may manifest similarly to primary GER or GER disease [4, 5]. Moreover, preliminary results have suggested that both thickened (with a specific starch complex at 1 g/100 mL and 3.6 g/100 g of fibers, mainly originating from pectin with a pH-dependent viscosity of approximately 500 centipoises at pH 4.0–4.5 and 150 centipoises at pH 6.0) and non-thickened extensive casein hydrolysate may reduce equally well regurgitation and reflux symptoms in infants with a positive cow's milk challenge. A trend for a better efficacy of the thickened hydrolysate was reported particularly in those with a negative cow's milk challenge [50].

Comparison of Anti-regurgitation Formulas

Few studies compared the efficacy of different AR formulas in infants. In one crossover trial, 24 infants were randomized to receive a commercial formula thickened with carob bean gum or a traditional formula thickened with rice flour at a concentration of 5%. Parental diaries showed reduction over time in the symptomatic scores for both formulas but significantly greater with the carob bean gum-thickened formula [51].

In another trial, 52 infants were fed either whey-based infant formula thickened with 5% rice cereal or a casein-predominant infant formula pre-thickened with pregelatinized cornstarch. There was a significant decrease in regurgitation with both AR formulas and of vomiting episodes only in the cornstarch group [52].

A prospective, blinded, randomized trial performed in 60 regurgitating infants evaluated the efficacy of parental reassurance in combination with three formula interventions: standard infant formula, standard formula with rice cereal added (5 g/100 mL), or formula manufactured with bean gum as a thickening agent. After the 1-month intervention, regurgitation and vomiting decreased significantly in all three groups with a three times larger effect, but not statistically different, in the group fed with bean gum that showed a significant better weight gain. There was no difference in volume of formula intake, infant comfort, stool composition, or frequency [13].

A recent prospective double-blind, randomized crossover trial, performed for a 1-month period in 115 regurgitating infants, showed a significant decrease in the mean number and volume of regurgitation with two AR formulas (both with locust bean gum), with statistically better results for the pHF with added treated starch [11]. No difference was reported in stool frequency and consistency between the two groups [11].

The effect of AR formula on regurgitation is formula specific because it is determined by different interplaying variables (source and concentration of thickener, osmolarity, kind of protein, degree of hydrolysis) and individual interfering factors (due to frequency and volume of the meal, gastric accommodation, gastric emptying, position of the infant, etc.).

Anti-regurgitation Formula and Reflux Parameters

Only few studies analyzed the effect of thickening on reflux parameters.

Carob Bean Gum

In 1987, Vandenplas reported a normalization of all pH-monitoring parameters in 6 out of 30 infants with carob bean added to infant formula (1 g to 115 mL) and in the remaining 24 infants, a significant decrease of the total number of reflux episodes but a comparable acid (pH < 4.0) exposure (reflux index) and number of long-lasting (longer than 5 min) (acid) reflux episodes. The duration of the longest reflux episode, however, increased significantly suggesting a slower clearance of the thickened acid reflux from the esophagus [41]. In another group of 20 infants fed with a pre-thickened AR formula containing a bean gum preparation, a significant decrease in the reflux index was noted [7]. In an Italian study, the reflux index was also significantly lower in the periods following a feeding with a carob-thickened formula compared to standard formula [51].

A crossover study using intraluminal impedance pH analysis showed a slight but not statistically significant decrease in proximal reflux and in the total number of reflux episodes but a similar number of acid reflux events in 14 infants fed with a formula thickened (0.4 g/100 mL) with a carob bean gum compared to standard formula [43].

Cornstarch

A multicenter trial found a casein-dominant formula pre-thickened with a specifically treated cornstarch to reduce all pH-metric parameters (reflux index, number of reflux episodes longer than 5 min, duration of the longest reflux episode) in 51 infants [44]. In another randomized study with a formula with pre-gelatinized cornstarch [53], reflux index improved in 87% of infants with an AR formula and was significantly lower in the group fed with AR formula than in infants fed with a non-thickened formula [53].

In a comparative trial performed in 52 infants, there was a significant improvement in all pH-monitoring parameters (longest reflux episode, reflux index, reflux episodes per hour) with a casein-predominant AR formula pre-thickened with pre-gelatinized cornstarch [52].

Rice

In a small sample size (six infants) trial, there was a significant reduction in the total number of (acid) reflux episodes but not in the reflux index with an infant formula thickened with rice cereal [42].

No improvement of reflux parameters was reported in the comparative study enrolling 52 infants when fed with a whey-based infant formula thickened with 5% rice cereal [52].

Amylopectin

A preterm formula thickened with amylopectin reduced the number of acid reflux episodes detected by pH monitoring, while it had no influence on reflux index, nor on acid and nonacid reflux detected by esophageal impedance, and height of refluxate in 28 symptomatic preterm newborns [54]. No differences in impedance bolus exposure indexes nor in GER height were detected [55].

In Summary

In the meta-analysis on AR formula (Horvath 2008), only four studies (with a total number of 107 infants and 3 different thickening agents: bean gum, rice, and corn) were analyzed [7, 43, 53, 56]. The pooled results showed that thickened feeding had no effect on pH-metric reflux parameters, although some data suggest a beneficial effect of both cornstarch and bean gum on regurgitation. The degree of the protein hydrolysis should also be considered because hydrolysis may influence reflux parameters as it enhances gastric emptying.

(Home) Thickening Compared to Thickened Commercial AR Formula

In many, but not all, countries, some infant formulas are commercialized under the name of anti-regurgitation (AR) formula. However, parents often add thickening agents to standard infant formula to reduce regurgitation in infants. The main reasons of using a "home brew"-thickened formula are availability and cost. Commercial AR formula is 1.5–2.0 times more expensive than standard formulas.

However, effects of home-thickened feeding on viscosity, calories, digestibility, esophageal reflux parameters, and symptomatic improvement may differ from commercialized AR formula. Homemade thickened formula may lead to inconsistencies in composition with nutrient ratio, calories, osmolarity, and viscosity. It is noteworthy that if parents prepare a thickened formula at home, adding just one tea or coffee spoon of starch (i.e., 3–5 g) [42] largely exceeds the upper limit of thickening content (2 g/100 mL) recommended by an ESPGHAN expert group [57] and present in the AR formulas. This amount of starch changes the carbohydrate/fat ratio of formula and increases the average caloric intake with 20 calories/100 mL. Moreover, parents often over-thicken the formula resulting in a high viscosity that needs an increased sucking effort and/or a cross-cut nipple to flow through [7, 24, 55, 58]. An increased osmolarity of the feeding, as well as gastric

distention and accommodation, may induce inappropriate relaxation of lower esophageal sphincter worsening reflux. Hence, clear advice about thickening modalities should be given, and care should be taken to avoid excessive caloric intake with home-thickened formula. The type and concentration of the thickening agent could cause fermentation causing a decrease in stool consistency and increase in bowel movements.

In contrast, commercialized AR formula has a homogeneous and controlled composition, with thickening components below 2 g/100 mL for starch and below 1 g/100 mL for carob bean gum, and with a caloric content similar to standard formula. Pretreated starch maintains a low initial viscosity which allows it to flow easily through a standard nipple and thicken only when in contact with the acid pH in the stomach [45]. This observation may have consequences in infants on anti-acid medications such as ranitidine and proton pump inhibitors. Carob bean gum, which is not split by salivary amylase, maintains the viscosity of the feed into the stomach.

One prospective case-control study carried out in 100 infants (0–12 months) with regurgitation compared a home-prepared modified infant formula with added cornstarch with a pre-thickened anti-regurgitation infant formula. After 3 months, the group fed with the AR formula showed a higher (although not significant) rate of cure compared to the home-thickened formula (52.1% vs. 40.5%) [59].

Adverse Effect of Anti-regurgitation Formula

Metabolic, intestinal, and systemic effects of thickened or AR formulas have been considered. Already 60 years ago, locust bean-derived indigestible polysaccharides were given to infants with diarrhea and vomiting without adverse effects [60, 61].

Caloric Intake

The increased caloric density of (home) thickened formula may be an appropriate strategy for infants who fail to thrive because of inadequate intake or failure to thrive because of regurgitation or vomiting. However, the vast majority of regurgitating infants do not need an additional caloric intake. As locust bean gum is not absorbed, it does not increase the caloric intake [30].

Malabsorption

An in vitro study reported that the intestinal absorption of dietary nutrients and the bioavailability of calcium, iron, and zinc in infant formula could be decreased by nondigestible carbohydrates [62]. The in vitro effect of adding different concentrations of locust bean gum and modified (pre-gelatinized) corn and rice starch to standard infant formula on mineral (calcium, iron, and zinc) availability (solubility and dialyzability percentages measured by atomic absorption spectrophotometry) has been recently investigated. Regarding mineral solubility, calcium was the only

mineral negatively affected by the three thickening agents and when they were added in high concentrations (>50% of the maximum legal limit). The effect was largest for bean gum. Locust bean gum also affects in vitro the availability of iron and zinc. This effect can be explained by the higher amount of myoinositol hexaphosphoric acid in locust bean gum (47.3 mg/100 g) compared with the amount in modified starch (19.2 mg/100 g in modified cornstarch and 17.5 mg/100 g in modified rice starch). The in vivo nutritional trial testing a 0.4 g/100 mL locust bean gum-thickened (casein/whey ratio 80/20) formula in 20 healthy infants, from birth to 13 weeks of age, reported normal growth and nutritional blood parameters and values of iron, calcium, phosphorus, and zinc similar to the ones found in infants fed with a regular adapted (casein/whey ratio 40/60) formula [63]. In all clinical studies using locust bean gum-thickened formulas in regurgitating infants, neither specific adverse effects nor negative effect on growth occurred [7, 11, 13, 33, 41, 43, 51]. Up to a concentration of 1 g/100 mL as thickener of infant formula or 1 g/100 g in weaning foods is considered acceptable in foods for special medical purposes when prescribed under medical supervision to treat GER [23]. Nowadays, locust-thickened formulas in general contain an average level of 0.5 g/100 mL of bean gum (¼ of the recommended level of thickened starches) that is shown to maintain its high viscosity property and confer a sufficiently protective margin of safety and not being associated with any adverse toxic or nutritional effects in healthy term infants, according to a recent review [30].

An adequate combination of these thickening agents may minimize the negative effect on mineral availability while maximizing the effect on formula viscosity [25]. Therefore, the mineral content in AR formula is often higher than in the standard infant formula. The phytate content in the thickening ingredients has also been analyzed. Despite finding a considerable amount of phytic acid in the raw ingredients, its concentration in the infant formula was insufficient to decrease in vitro mineral availability [25].

An in vivo study showed that adding rice cereal to formula at a concentration of 6.5 g/100 mL results in a normal bioavailability of calcium or iron in 1–3-month-old infants [64]. A risk assessment was conducted based on literature reviews of the reported arsenicum in rice cereal from the US Food and Drug Administration's (FDA) survey and the recommended daily intake of rice cereal by body weight, for infants and toddlers between 4 and 24 months old [65]. While hazard quotients for acute intake were consistently below 1.0, these chronic intake exceeded 1.0 for both rice cereal and total sources [65]. Incremental lifetime cancer risk ranged from 10(−6) (50th) to 10(−5) (75th percentile). Maximum contaminant level for arsenicum in rice cereal reached up to 0.4 mg/kg [65].

Lipid Metabolism

The possible interference of locust bean gum (as a fiber) with lipid metabolism has also been considered [66]. In 25 infants with a mean age 6 weeks, fed for 6 weeks with milk formula containing bean gum, blood cholesterol and triglycerides were similar to the ones in infants fed with standard formula [66].

Cough

Increased cough has been reported in infants fed with thickened formulas with rice [58] but not in formula pre-thickened with rice [45].

Bowel Movements

Rice-thickened formula has been associated with difficulty in defecation in infants with regurgitation treated with smaller volume (one heaping tablespoonful of dry rice cereal added to every 30 mL of formula and feeds given every 4 h to achieve a final intake of about 100–110 kcal/kg/24 h) [42]. In another study, 15% developed mild difficulty, and 21% reported severe difficulty in defecation during rice-based feedings. After rice was substituted by oatmeal cereal, half of them reported no symptoms and a third just mild symptoms, whereas three infants continued to have severe symptoms [67]. Conversely, bean gum may act as vegetable fiber with a prebiotic effect in the colon possibly modifying bowel frequency. In only one study using a formula thickened with locust bean gum, diarrhea occurred in 14 out of 84 infants [47]. No difference in stool consistency or frequency were reported in studies with pre-thickened rice [45] or other AR formulas [11, 20, 34].

Allergy

The risk of allergy to the thickening agents is currently unknown. An isolated case of allergy to carob gum in infants has been published [68].

Preterm Infants

A possible association between thickened feedings and necrotizing enterocolitis in preterm infants has been pointed out [69]. In 2011 the Food and Drug Administration issued a warning regarding the use of a common commercially available thickening agent containing xanthan gum in infants born before 37 weeks gestation currently receiving hospital care or discharged from the hospital in the past 30 days [5].

Moreover, as 0.2–0.5 g/100 mL locust bean gum formula has been correlated to an increased frequency of defecation, metabolic acidosis, and hypokalemia in six premature vomiting infants [70], the use of locust bean gum-thickened formulas should be excluded in premature or low birth weight infants [4].

Positional Treatment

Sleeping positions that have been suggested to reduce GER include prone, immediate right side with later left side after feeding, and supine 40° anti-Trendelenburg [9, 71]. Prone position is considered obsolete in infants because of the increased risk

for sudden infant death (SIDS). Van Wijk et al. concluded that the biggest benefit was achieved with a strategy of right lateral positioning for the first postprandial hour with a position change to the left side thereafter to promote gastric emptying and reduce liquid GER in the late postprandial period [71]. However, later the same group described that small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral position in infants [72]. In GERD patients, TLESRs, GER, distension of proximal stomach, and gastric emptying are increased in right lateral compared to left lateral position [73]. This effect is not seen in healthy controls [73]. However, at least two independent studies reported a significantly increased risk of SID in the side compared to the supine sleeping position [73, 74]. The results of an uncontrolled pilot study with the "Multicare AR-Bed®" suggest that a specially made bed that nurses the infant in a 40° supine body position reduces regurgitation (from a median of six episodes of regurgitation to two in 1-week time), acid reflux (measured with pH monitoring), and reflux-associated symptoms (the mean I-GERQ decreased from 21.64 ± 4.27 to 15.55 ± 5.00 over 1 week) [75]. "Symptomatic gastroesophageal reflux disease" implies disease causation for distressing infant symptoms. In infants with symptoms attributed to GER, left lateral position produced a significant reduction in total GER, but did not result in a significant improvement in symptoms other than vomiting; however, automated analysis appeared to identify infants with GER-associated crying symptoms who responded to positioning therapy [76].

As a consequence, the pros and cons of positional treatment should be considered for each infant. Positional treatment (side sleeping or elevated supine position) cannot be recommended in sleeping infants as there are insufficient data regarding both efficacy and safety. Many parents do put the infant asleep in a slightly head-elevated position. Whether this is helpful has not been validated. Many unapproved infant sleep positioners have been marketed to the general public with claims of preventing sudden infant death syndrome (SIDS), improving health, and enhancing sleep comfort [77]. According to the Center for Disease Control, the American Academy of Pediatrics should not stop recommending against side sleep position, ISPs and pillows, comforters, and other soft bedding [77].

Conclusions

The appropriate first approach in an uncomplicated regurgitating infant is based on parental reassurance and education about position and feeding.

Because thickened formulas reduce regurgitation and improve growth, they should be reserved for infants with frequent persistent regurgitation as a cause of parental anxiousness and/or failure to thrive. Locust bean gum is the most effective agent to increase formula thickness, but there is no clear evidence that one thickener is clinically better than another. Many commercialized AR formulas are available in the market with differences in composition, price, and brands among countries. Commercial thickened formulas present the advantage of homogeneous and balanced composition, better digestibility, reduced viscosity, and controlled calories compared to adding thickening agents to a standard formula. No substantial effects on esophageal acid exposure or gastric emptying occur. The ideal composition of an AR formula is still undefined. The effect of

the thickened infant formula may depend on the agent used, concentration, protein ratio, and grade of hydrolysis. Thickened hydrolyzed formula may have an additional benefit. The cost of anti-regurgitation formulas should limit their possible overuse in healthy well-thriving infants with mild and transient regurgitations. AR formula does not treat GERD, but by decreasing reflux-related symptoms and parental anxiety, they may reduce unnecessary use of medication and medical referring.

References

1. Martin AJ, Pratt N, Kennedy JD, Ryan P, Ruffin RE, Miles H, Marley J. Natural history and familial relationships of infant spilling to 9 years of age. Pediatrics. 2002;109:1061–7.
2. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med. 1997;151:569–72.
3. Hegar B, Dewanti NR, Kadim M, Alatas S, Firmansyah A, Vandenplas Y. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009;98:1189–93.
4. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2009;49:498–547.
5. Lightdale JR, Gremse DA, Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013; 131:e1684–95.
6. Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, Orenstein S, Rudolph C, Vakil N, Vandenplas Y. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104:1278–95.
7. Vandenplas Y, Hachimi IS, Casteels A, Mahler T, Loeb H. A clinical trial with an "antiregurgitation" formula. Eur J Pediatr. 1994;153:419–23.
8. Nelson SP, Chen EH, Syniar GM, Christoffel KK. One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group. Pediatrics. 1998;102:E67.
9. Orenstein SR, Shalaby TM, Kelsey SF, Frankel E. Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy. Am J Gastroenterol. 2006;101:628–40.
10. Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Guarino A, Lifschitz C, Lionetti P, Orel R, Papadopoulou A, Ribes-Koninckx C, Ruemmele FM, Salvatore S, Shamir R, Schäppi M, Staiano A, Szajewska H, Thapar N, Wilschanski M. Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. Acta Paediatr. 2016;105:244–52.
11. Vandenplas Y, Leluyer B, Cazaubiel M, Housez B, Bocquet A. Double-blind comparative trial with two anti-regurgitation formulae. J Pediatr Gastroenterol Nutr. 2013;57:389–93.
12. Nevo N, Rubin L, Tamir A, Levine A, Shaoul R. Infant feeding patterns in the first 6 months: an assessment in full-term infants. J Pediatr Gastroenterol Nutr. 2007;45:234–9.
13. Hegar B, Rantos R, Firmansyah A, De Schepper J, Vandenplas Y. Natural evolution of infantile regurgitation versus the efficacy of thickened formula. J Pediatr Gastroenterol Nutr. 2008;47:26–30.
14. Hegar B, Boediarso A, Firmansyah A, Vandenplas Y. Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. World J Gastroenterol. 2004;10:1795–7.

15. Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, Di Prima L, Scalici C, Indinnimeo L, Averna MR, Carroccio A, Paediatric Study Group on Gastrointestinal Symptoms in Infancy. Gastrointestinal symptoms in infancy: a population-based prospective study. Dig Liver Dis. 2005;37:432–8.
16. Aggett PJ, Agostoni C, Goulet O, Hernell O, Koletzko B, Lafeber HL, Michaelsen KF, Milla P, Rigo J, Weaver LT. Antireflux or antiregurgitation milk products for infants and young children: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2002;34:496–8.
17. Gieruszczak-Białek D, Konarska Z, Skórka A, Vandenplas Y, Szajewska H. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. J Pediatr. 2015;166:767–70.e3.
18. Khoshoo V, Edell D, Thompson A, Rubin M. Are we overprescribing antireflux medications for infants with regurgitation? Pediatrics. 2007;120:946–9.
19. Quitadamo P, Papadopoulou A, Wenzl T, Urbonas V, Kneepkens CM, Roman E, Orel R, Pavkov DJ, Dias JA, Vandenplas Y, Kostovski A, Miele E, Villani A, Staiano A. European pediatricians' approach to children with GER symptoms: survey of the implementation of 2009 NASPGHAN-ESPGHAN guidelines. J Pediatr Gastroenterol Nutr. 2014;58(4):505–9.
20. Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. Pediatrics. 2008;122:e1268–77.
21. European Parliament and Council Directive 2006/141/EC on infant formulae and follow-on formulae. http://ec.europa.eu/food.
22. European Parliament and Council Directive 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners. http://ec.europa.eu/food.
23. SCF. Report of the Scientific Committee on Food on the revision of essential requirements of infant formulae and follow-on formulae. 2003. Accessed 6 Dec 2013 at: http://ec.europa.eu/food/fs/sc/scf/out199_en.pdf.
24. Infante Pina D, Lara-Villoslada F, López Ginés G, Morales Hernández ME. Thickened infant formula, rheological study of the "in vitro" properties. An Pediatr. 2010;72:302–8.
25. González-Bermúdez CA, Frontela-Saseta C, López-Nicolás R, Ros-Berruezo C, Martínez-Graciá C. Effect of adding different thickening agents on the viscosity properties and in vitro mineral availability of infant formula. Food Chem. 2014;159:5–11.
26. Aggett PJ, Agostoni C, Axelsson I, Edwards CA, Goulet O, Hernell O, Koletzko B, Lafeber HN, Micheli J-L, Michaelsen KF, Rigo J, Szajewska H, Weaver LT. Nondigestible carbohydrates in the diets of infants and young children: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2003;36:329–37.
27. Menoyo D, Serrano MP, Barrios V, Valencia DG, Lázaro R, Argente J, Mateos GG. Cereal type and heat processing of the cereal affect nutrient digestibility and dynamics of serum insulin and ghrelin in weanling pigs. J Anim Sci. 2011;89:2793–800.
28. Lin AH-M, Hamaker BR, Nichols BL. Direct starch digestion by sucrase-isomaltase and maltase-glucoamylase. J Pediatr Gastroenterol Nutr. 2012;55:S43–4.
29. Rendleman JA. Hydrolytic action of α-amylase on high amylase starch of low molecular mass. Biotechnol Appl Biochem. 2000;31:171–8.
30. Meunier L, Garthoff JA, Schaafsma A, et al. Locust bean gum safety in neonates and young infants: an integrated review of the toxicological database and clinical evidence. Regul Toxicol Pharmacol. 2014;70:155–69.
31. Benini L, Castellani G, Brighenti F, Heaton KW, Brentegani MT, Casiraghi MC, et al. Gastric emptying of a solid meal is accelerated by the removal of dietary fiber naturally present in food. Gut. 1995;36:825–30.
32. Miyazawa R, Tomomasa T, Kaneko H, Morikawa A. Effect of formula thickened with locust bean gum on gastric emptying in infants. J Paediatr Child Health. 2006;42:808–12.
33. Miyazawa R, Tomomasa T, Kaneko H, Arakawa H, Morikawa A. Effect of formula thickened with reduced concentration of locust bean gum on gastroesophageal reflux. Acta Paediatr. 2007;96:910–4.

34. Vivatvakin B, Buachum V. Effect of carob bean on gastric emptying time in Thai infants. Asia Pac J Clin Nutr. 2003;12:193–7.
35. Chao HC, Vandenplas Y. Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation. Nutrition. 2007;23:23–8.
36. Chao HC, Vandenplas Y. Comparison of the effect of a cornstarch thickened formula and strengthened regular formula on regurgitation, gastric emptying and weight gain in infantile regurgitation. Dis Esophagus. 2007;20:155–60.
37. Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastroesophageal reflux according to the type of milk. Eur J Clin Nutr. 1990;44:577–83.
38. Tolia V, Lin CH, Kuhns LR. Gastric emptying using three different formulas in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1992;15:297–301.
39. Staelens S, Van den Driessche M, Barclay D, Carrié-Faessler AL, Haschke F, Verbeke K, Vandebroek H, Allegaert K, Van Overmeire B, Van Damme M, Veereman-Wauters G. Gastric emptying in healthy newborns fed an intact protein formula (IPF), a partially (PHF) and an extensively hydrolysed (EHF) formula. Clin Nutr. 2008;27:264–8.
40. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. J Pediatr. 1987;110:181–6.
41. Vandenplas Y, Sacre L. Milk-thickening agents as a treatment for gastroesophageal reflux. Clin Pediatr. 1987;26:66–8.
42. Khoshoo V, Ross G, Brown S, Edell D. Smaller volume, thickened formulas in the management of gastroesophageal reflux in thriving infants. J Pediatr Gastroenterol Nutr. 2000;31:554–6.
43. Wenzl TG, Schneider S, Scheele F, Silny J, Heimann G, Skopnik H. Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance. Pediatrics. 2003;111:e355–9.
44. Xinias I, Mouane N, Le Luyer B, Spiroglou K, Demertzidou V, Hauser B, Vandenplas Y. Cornstarch thickened formula reduces oesophageal acid exposure time in infants. Dig Liver Dis. 2005;37:23–7.
45. Vanderhoof JA, Moran JR, Harris CL, Merkel KL, Orenstein SR. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. Clin Pediatr. 2003;42:483–95.
46. Ostrom KM, Jacobs JR, Merritt RJ, Murray RD. Decreased regurgitation with a soy formula containing added soy fiber. Clin Pediatr (Phila). 2006;45:29–36.
47. Iacono G, Vetrano S, Cataldo F, Ziino O, Russo A, Lorello D, D'amico D, Di Rosa C, Le Moli C, Di Prima L, Giannitrapani L, Cavataio F. Clinical trial with thickened feeding for treatment of regurgitation in infants. Dig Liver Dis. 2002;34:532–3.
48. Moya M, Juste M, Cortes E, Auxina A, Ortiz I. Clinical evaluation of the different therapeutic possibilities in the treatment of infant regurgitation. Rev Esp Pediatr. 1999;55:219–23.
49. Vandenplas Y. Thickened infant formula does what it has to do: decrease regurgitation. Pediatrics. 2009;123:e549–50.
50. Vandenplas Y, De Greef E, ALLAR-study group. A randomized double-blind trial comparing a thickened and non-thickened extensively hydrolyzed casein formula: results after one month. Acta Paediatr. 2014;103(6):e243–50.
51. Borrelli O, Salvia G, Campanozzi A, Franco MT, Moreira FL, Emiliano M, Campanozzi F, Cucchiara S. Use of a new thickened formula for treatment of symptomatic gastrooesophageal reflux in infants. Ital J Gastroenterol Hepatol. 1997;29:237–42.
52. Ramirez-Mayans J, Palacio-del Carmen L, Cervantes-Bustamente R. Nutritional management of children with GER: a comparison of formulas. Int Pediatr. 2003;18:78–82.
53. Moukarzel AA, Abdelnour H, Akatcherian C. Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER. J Clin Gastroenterol. 2007;41:823–9.
54. Corvaglia L, Aceti A, Mariani E, Legnani E, Ferlini M, Raffaeli G, Faldella G. Lack of efficacy of a starch-thickened preterm formula on gastro-oesophageal reflux in preterm infants: a pilot study. J Matern Fetal Neonatal Med. 2012;25:2735–8.

55. Corvaglia L, Mariani E, Aceti A, Galletti S, Faldella G. Extensively hydrolyzed protein formula reduces acid gastro-esophageal reflux in symptomatic preterm infants. Early Hum Dev. 2013;89:453–5.
56. Tolia V, Wuerth A, Shashidhar H, Peters J, Lin C. A prospectivestudy with an antiregurgitation (AR) formula in infants with gastroesophageal reflux (GER) symptoms. Gastrointest Endosc. 1999;49:AB186.
57. Koletzko B, Baker S, Cleghorn G, Neto UF, Gopalan S, Hernell O, Hock QS, Jirapinyo P, Lonnerdal B, Pencharz P, Pzyrembel H, Ramirez-Mayans J, Shamir R, Turck D, Yamashiro Y, Zong-Yi D. Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. J Pediatr Gastroenterol Nutr. 2005;41:584–99.
58. Orenstein SR, Shalaby TM, Putnam PE. Thickened feedings as cause of increased coughing when used as therapy for gastroesophageal reflux in infants. J Pediatr. 1992;121:913–5.
59. Penna FJ, Norton RC, Carvalho AS, Pompeu BC, Penna GC, Ferreira MF, Duque CG, Couto J, Maia JX, Flores P, Soares JF. Comparison between pre-thickened and home-thickened formulas in gastroesophageal reflux treatment. J Pediatr. 2003;79:49–54.
60. Beynon D. Arobon in the treatment of infantile gastro-enteritis; a clinical trial. Arch Dis Child. 1949;24:41–4.
61. Rivier C. The effectiveness of nestargel. Schweiz Med Wochenschr. 1952;82:256–8.
62. Bosscher D, Van Caillie-Bertrand M, Van Dyck K, Robberecht H, Van Cauwenbergh R, Deelstra H. Thickening of infant formula with digestible and indigestible carbohydrate: availability of calcium, iron and zinc in vitro. J Pediatr Gastroenterol Nutr. 2000;30:373–8.
63. Levtchenko E, Hauser B, Vandenplas Y. Nutritional value of an “antiregurgitation” formula. Acta Gastroenterol Belg. 1998;61:285–7.
64. Lifschitz CH, Abrams SA. Addition of rice cereal to formula does not impair mineral bioavailability. J Pediatr Gastroenterol Nutr. 1998;26:175–8.
65. Shibata T, Meng C, Umoren J, West H. Risk assessment of arsenic in rice cereal and other dietary sources for infants and toddlers in the U.S. Int J Environ Res Public Health. 2016;13:361.
66. Savino F, Cresi F, Peltran A, Oggero MM. Serurm cholesterol in infants fed with an antiregurgitation milk formula containing bean gum. Acta Paediatr. 1999;88:102–3.
67. Mascarenhas R, Landry L, Khoshoo V. Difficulty in defecation in infants with gastroesophageal reflux treated with smaller volume feeds thickened with rice cereal. Clin Pediatr. 2005;44:671–3.
68. Savino F. Allergy to carob gum in an infant. J Pediatr Gastroenterol Nutr. 1999;29:475–6.
69. Clarke P, Robinson MJ. Thickening milk feeds may cause necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2004;89:F280.
70. Sievers E, Schaub J. Antireflux or antiregurgitation milk products. J Pediatr Gastroenterol Nutr. 2003;36:418.
71. van Wijk MP, Benninga MA, Dent J, Lontis R, Goodchild L, McCall LM, Haslam R, Davidson GP, Omari T. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr. 2007;151:585–90.
72. van Wijk MP, Benninga MA, Davidson GP, Haslam R, Omari TI. Small volumes of feed can trigger transient lower esophageal sphincter relaxation and gastroesophageal reflux in the right lateral position in infants. J Pediatr. 2010;156(5):744–8.
73. Loots C, Smits M, Omari T, Bennink R, Benninga M, van Wijk M. Effect of lateral positioning on gastroesophageal reflux (GER) and underlying mechanisms in GER disease (GERD) patients and healthy controls. Neurogastroenterol Motil. 2013;25:222–9, e161-2
74. Scragg RK, Mitchell EA. Side sleeping position and bed sharing in the sudden infant death syndrome. Ann Med. 1998;30:345–9.
75. Vandenplas Y, De Schepper J, Verheyden S, Devreker T, Franckx J, Peelman M, Denayer E, Hauser B. A preliminary report on the efficacy of the Multicare AR-Bed in 3-week-3-month-old infants on regurgitation, associated symptoms and acid reflux. Arch Dis Child. 2010;95:26–30.

76. Loots C, Kritas S, van Wijk M, McCall L, Peeters L, Lewindon P, Bijlmer R, Haslam R, Tobin J, Benninga M, Davidson G, Omari T. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. J Pediatr Gastroenterol Nutr. 2014;59:237–43.
77. Centers for Disease Control and Prevention (CDC). Suffocation deaths associated with use of infant sleep positioners--United States, 1997-2011. MMWR Morb Mortal Wkly Rep. 2012;61(46):933–7.
78. De Vizia B, Ciccimarra F, De Cicco N, Auricchio S. Digestibility of starches in infants and children. J Pediatr. 1975;86:50–5.

GER and Hypnotherapy

20

A.M. Vlieger

Abstract

During hypnosis, gastric functions, like motility and acid secretion, can be modulated. To date, however, no randomized controlled studies have assessed the efficacy of hypnotherapy in paediatric patients with gastro-oesophageal 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-oesophageal reflux

Introduction

Hypnotherapy (HT) has been investigated for more than 40 years as a treatment for gastrointestinal disorders, and in the last two decades, the popularity of hypnotherapy has increased significantly among (paediatric) gastroenterologists. This has been caused by the numerous positive hypnotherapy trials in both adult and paediatric 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]. Therefore,

A.M. Vlieger
Department of Paediatrics, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands
e-mail: a.vlieger@antoniusziekenhuis.nl

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_20

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-oesophageal reflux (GER), let alone in paediatric patients with GER. A few preclinical studies have investigated whether hypnosis can influence gastric functions, and several clinical trials have showed 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, an absorbed attention, an absence of judging and disorientation towards time and location.

Children are, in general, more hypnotizable than adults, especially before puberty, suggesting that hypnosis is more effective with them [6]. Hypnotherapy is usually applied to children of 7 years and older, although simple hypnotic exercises, like story telling with imbedded hypnotic suggestions, can be done with children from the age of three onwards. Children are often enthusiastic about hypnotic exercises, and side effects are extremely rare, making it a valuable therapeutic tool.

Hypnosis and Gastric Functioning

There is overwhelming experimental and clinical evidence that stress influences gastric functioning (summarized in [7]). Acute stress, stressful life events and chronic psychological stress can affect different functions of the stomach 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-oesophageal reflux disease.

Hypnosis is a well-known relaxation technique, and it is therefore 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 [8]. In another study, stomach-oriented hypnosis appeared to be highly effective in shortening gastric emptying in 15 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 [9]. 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 [10].

Hypnotherapy and Gastric Symptoms

Despite the demonstrated positive effects of hypnosis on gastric functioning, thereby showing its therapeutic potential, to date no RCT's have been conducted on the effect of hypnotherapy in patients with GER. However, several hypnotherapy studies have been performed in other upper GI diseases. First, 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 hypnotherapy 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 [11]. 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 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 oesophageal-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 and a trend for improvement in catastrophizing [12].

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 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.

References

1. Palsson OS. Hypnosis treatment of gastrointestinal disorders: a comprehensive review of the empirical evidence. Am J Clin Hypn. 2015;58(2):134–58.
2. Calvert EL, Houghton LA, Cooper P, Morris J, Whorwell PJ. Long-term improvement in functional dyspepsia using hypnotherapy. Gastroenterology. 2002;123:1778–85.
3. Jones H, Cooper P, Miller V, Brooks N, Whorwell PJ. Treatment of non-cardiac chest pain: a controlled trial of hypnotherapy. Gut. 2006;55:1403–8.
4. Upshaw WN. Hypnosis: medicine's dirty word. Am J Clin Hypn. 2006;49(2):113–22.
5. Elkings GR, Barabasz AF, Council JR, Spiegel D. Advancing research and practice: the revised APA division 30 definition of hypnosis. Int J Clin Exp Hypn. 2015;63:1–9.
6. London P. Hypnosis in children: an experimental approach. Int J Clin Exp Hypn. 1962;10:79–91.
7. Nardone G, Compare D. The psyche and gastric functions. Dig Dis. 2014;32:206–12.
8. Klein K, Spiegel D. Modulation of gastric acid secretion by hypnosis. Gastroenterology. 1989;96:1383–7.
9. Chiarioni G, Vantini I, De Iorio F, Benini L. Prokinetic effect of gut-oriented hypnosis on gastric emptying. Aliment Pharmacol Ther. 2006;23:1241–9.
10. Enck P, Hefner J, Herbert BM, et al. Sensitivity and specificity of hypnosis effects on gastric myoelectrical activity. PloS One. 2013;16:e83486.
11. Colgan SM, Faragher EB, Whorwell PJ. Controlled trial of hypnotherapy in prevention of duodenal ulceration. Lancet. 1988;8598:1299–300.
12. Riehl ME, Pandolfino JE, Palsson OS, Keefer L. Feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn. Dis Esophagus. 2016;29:490–6.

GER and Complementary Medicine

21

H.S. van der Heijden and M.M. Tabbers

Abstract

Complementary and alternative medicine includes practices that are not an integral part of the conventional healthcare system but are used by therapists and patients to supplement their patient's care. The use of complementary and alternative medicine is increasing worldwide for treatment of different acute and chronic diseases including gastroesophageal reflux disease. Even 40% of parents of pediatric gastroenterology patients are using some form of complementary and alternative therapy for their child. Complementary and alternative medicine is especially used in children in whom conventional treatment has failed. In addition, school absenteeism and the occurrence of adverse effects of medication are also important predictors of using these therapies. In this chapter, we will discuss traditional Chinese medicine (acupuncture), herbals and botanicals, and mind-body therapy including breathing exercises and massage therapy. Although interest in using complementary and alternative medicine use is increasing, there is a lack of randomized controlled trials investigating its efficacy and safety in children with gastroesophageal reflux disease. Therefore, well-designed studies in this vulnerable group of children are necessary in order to determine efficacy and safety of these different treatment modalities.

Keywords

GER(D) • Complementary and alternative medicine • Traditional Chinese medicine • Acupuncture • Herbals • Botanicals • Mind-body medicine • Breathing exercises • Massage therapy

H.S.van der Heijden • M.M. Tabbers (✉)
Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, The Netherlands
e-mail: m.m.tabbers@amc.nl

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_21

Introduction

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation and/or vomiting. GER is considered to be pathologic and referred to as *gastroesophageal reflux disease* (GERD) when the reflux leads to troublesome symptoms and/or complications [1]. *Complementary medicine* is alternative medicine used together with conventional medical treatment, in a belief, not based on scientific evidence, that it complements (i.e., improves the efficacy of) treatment [2]. *Alternative medicine* is any practice assumed to have the healing effects of medicine but does not originate from evidence gathered using the scientific method and is not part of biomedicine or is contradicted by scientific evidence or established science [3]. *Complementary and alternative medicine (CAM)* includes practices that are not an integral part of the conventional healthcare system but are used by therapists and patients to supplement their patient's care [4]. CAM is used in conjunction with conventional therapies and cannot replace medical regimens.

In Western countries, there is an increased use of CAM for treating diverse acute and chronic diseases in adults and children [5]. A Dutch survey among parents of pediatric gastroenterology patients showed that even 40% of them were using complementary and alternative medicine for their child [6]. CAM is especially used in children who have low perceived effect of conventional treatment. Pharmacologic therapies with acid suppression do not always effectively treat symptoms related to nonerosive reflux disease and reflux symptoms from non-acidic reflux. For this reason, parents are searching for alternative options for the treatment of their child. In addition, school absenteeism and adverse effects of medication are also important predictors of complementary and alternative medicine use [6]. Interestingly, even 93% of the parents considered it to be important that pediatricians initiate complementary and alternative medicine research, and 51% of parents were willing to participate in future CAM trials [6].

Although many pediatric GER(D) patients use CAM, well-designed studies demonstrating the efficacy of CAM are very scarce. Reasons for this lack of evidence could be that the preferred method, the double-blind, randomized, placebo-controlled trial seems not to be optimal for investigating the efficacy of CAM. Many of the alternative therapies are rooted in the concept of individualized care rather than disease-based care. Secondly, blinding parents and/or children to their treatment arm may be difficult or even often impossible, for example, in massage-based therapies or hypnotherapy. In addition, the lack of funding could be another important reason [6].

Complementary and alternative medicine treatments can be offered to support the patient and represent a broad range of different therapies. In this chapter, we will discuss these therapies in the following groups:

1. Traditional Chinese medicine (acupuncture)
2. Botanicals such as iberogast, licorice, and ginger
3. Mind-body medicine such as breathing exercises, massage, biofeedback, and psychotherapy (for hypnosis: *see chapter GER and Hypnotherapy*)

Traditional Chinese Medicine

In 2006, the TCM sector in China provided health care for over 200 million outpatients and 7 million inpatients, accounting for 10–20% of the health care in China [7]. The main principles of TCM are based on philosophical ideas developed from Taoism and Confucianism [8]. Ancient beliefs on which TCM is based include the human body is a miniature version of a larger, surrounding universe; harmony between two opposing forces, called yin and yang, supports health, and disease results from an imbalance between these forces; five elements—fire, earth, wood, metal, and water—symbolically represent all phenomena, including the stages of human life, and explain the functioning of the body and how it changes during disease; and Qi, a vital energy that flows through the body and performs multiple functions in maintaining health [8].

Acupuncture

Acupuncture is described as a healing modality, which origins are in traditional Chinese medicine. About 1600 A.D., acupuncture was introduced in Western countries [7]. Within acupuncture, fine needles are inserted at certain acupuncture points to balance the body's energy flows.

However, the exact working mechanisms in GERD patients remain unknown; we will discuss some of the postulated explanations [9–11]:

(1) PC6 ("neiguan")
PC6, on the pericardium meridian, is one of the most used and investigated acupuncture for reflux. After acupuncture on point PCS6, MRI studies have shown increased attenuation of the cerebrocerebellum, while compared with control points. This suggests modulation of cerebellar activities, which may play a role in the autonomic regulation of vestibular functions.
(2) ST36 ("zusanli")
ST36, on the stomach meridian, can increase the pressure of the lower esophageal sphincter if stimulated by electric acupuncture.

In children, both auricular acupuncture and body acupuncture have shown to improve postoperative care (e.g., following pediatric tonsillectomy) and also after chemotherapy in reducing induced nausea and vomiting [12–15]. While there are some data published regarding the use of CAM in adults with GERD, well-designed controlled trials whether acupuncture has an additional role in treating GERD in children are lacking [16, 17]. Among adults, certain acupuncture points (e.g., PC6 and ST36) have been found to be effective in improving reflux symptoms, nausea, and vomiting. In a small randomized trial, 30 adults were included with a 3 month history of GERD-related symptoms at least 2 days per week while taking standard-dose PPI (omeprazole 20 mg once daily). Dickman et al. found in this trial that acupuncture therapy during 4 weeks reduced symptoms such as mean daytime and

nighttime heartburn and acid regurgitation scores at the end of treatment when compared with baseline more effectively than doubling the PPI dose [17]. However, mean differences between both groups at week 4 compared to baseline were not calculated.

Although there are currently no published clinical trials on acupuncture in children with GER(D), acupuncture in children seems to be safe. A literature review shows a 1.55 risk of any adverse events occurring in 100 treatments of acupuncture in children [18]. Puncture redness is the most commonly reported side effect, followed by needle pain, and headedness. Studies have reported this risk of a serious adverse event, defined as an event that is life threatening or requires hospitalization, to be as low as 0.05/10,000 treatments in the general population [18].

In conclusion, before firm conclusions can be made about efficacy and safety for acupuncture treatment in children with GERD, well-designed randomized controlled trials are necessary.

Herbals and Botanicals

Herbs are considered to be an essential part of the TCM philosophy. China is rich in plants which encouraged the development of different herbs. Indeed, about 13,000 herbal preparations are currently used and listed in the *Chinese Materia Medica* (CMM). CMM is a reference book that also describes details of all plant preparations, including some nonbotanical elements (animal parts and minerals) which are incorrectly classified as herbal medicines [19]. Outside of China, only around 500 Chinese herbs are commonly used.

According to its philosophy, in herbal TCM therapy, herbs are prescribed tailored to the patient's symptoms, signs, and constitution. These individualized approaches create problems in performing clinical trials of herbal TCM preparations since evidence-based medicine criteria are hardly applicable, if treatment modalities differ from patient to patient [20].

Herbal traditional Chinese medicine is also used to treat GERD. Botanicals such as iberogast, deglycyrrhizinated licorice (DGL), and ginger are often used as adjunct, symptomatic relief therapy [11]. Nevertheless, a recently published review concluded that there is a lack of evidence-based efficacy as shown by high-quality trials for gastrointestinal disorders including GERD [8]. Similar results were obtained by Zhao et al. who also concluded that currently no scientifically proven benefit can be derived from published studies [21]. We will discuss briefly the most frequently used herbs, namely, iberogast, deglycyrrhizinated licorice (DGL), and ginger.

Iberogast

Iberogast (STW-5—Medical Futures Inc., Richmond Hill, Ontario, Canada) is a commercial preparation of nine herbal extracts including bitter candy tuft, lemon balm leaf, chamomile flower, caraway fruit, licorice root, angelica root, milk thistle

fruit, peppermint leaf, and greater celandine herb. In vitro, it has been shown to protect against the development of ulcers by decreasing acid production and leukotrienes but by increasing mucin production and prostaglandin E2 release [22]. Evidence is conflicting, but it seems to be effective by increasing gastric motility in healthy subjects by increasing the motility index of antral pressure waves [23]. The incidence of adverse reactions is reported to be 0.04% in adults and consisted mainly of hypersensitivity reactions such as skin irritation, dyspnea, and pruritus [24]. This reported low incidence of adverse events is confirmed by the spontaneous reporting system in Germany and also worldwide since the product was introduced approximately 50 years ago. However, no randomized trials have been published yet in children with GERD.

Deglycyrrhizinated Licorice (DGL) and Licorice

Licorice root, dried rhizome, or extracts of *Glycyrrhiza glabra* have been used for treatment of gastric inflammation. The mechanism of action is thought to be due to inhibition of prostaglandin synthesis and lipoxygenase. Because glycyrrhizin has mineralocorticoid properties, the deglycyrrhizinated form of licorice is recommended for long-term or higher doses [11]. No randomized trials have been published yet in children with GERD. In a randomized, double-blind, placebo-controlled study of 50 adults with functional dyspepsia according to Rome III criteria, subjects were randomized to placebo or a 75 mg extract of *Glycyrrhiza glabra* (GutGard®, Karnataka, India) for 30 days. Symptoms were assessed with a seven-point Likert scale of dyspepsia symptom severity. Compared to placebo, the licorice extract showed a significant decrease in total symptom scores and improvement in quality of life [25]. Currently, integrative medicine practitioners frequently use deglycyrrhizinated licorice by weaning off from acid suppression.

Ginger

Ginger root, the rhizome of *Zingiber officinale*, has been used traditionally as a kitchen spice but also for treating reflux symptoms and dyspepsia. The mechanism of action is thought to be due to the prokinetic effect that may be mediated by cholinergic action and spasmogenic properties that have been demonstrated in animal models [26]. In healthy adult volunteers, ginger root improved gastric emptying and gastroduodenal motility in both the fasting and fed state [27]. It is important to realize that the ginger rhizome extract is much more concentrated than the dried ginger root powder. Side effects are reported in adults when doses exceed 5 g/day and include heartburn, abdominal discomfort, and diarrhea. In addition, ginger root has an antiplatelet effect due to its ability to inhibit platelet thromboxane [28]. To date, no randomized controlled trials have investigated efficacy and safety of ginger in children.

In conclusion, no evidence is currently available in GERD trials in both adults as in children to support the equivalency of herbal TCM preparations to conventional treatments like proton pump inhibitors (PPI). Future studies should focus on placebo-controlled, randomized, double-blind clinical trials with uniform criteria for diagnosis, treatment, outcome, and assessment of adverse herb reactions.

Mind-Body Medicine

The pathophysiology of GERD in children is complex, and multifactorial and psychosocial stress can exacerbate symptoms. A study in adults showed that patients with dyspepsia also have a higher reported incidence of childhood emotional abuse [29]. Therefore, influencing the mind-body-gut connection could be important in the treatment of GERD patients especially in these patients with increased psychosocial stressors and mild anxiety. Types of mind-body therapy include mindfulness meditation, guided imagery, biofeedback, and yoga [11]. Treatment can be tailored to the interest and motivation of the individual patient. However, there is only one randomized controlled trial conducted to evaluate the efficacy of massage therapy (MT) for relief of symptoms in children with GERD. For all other treatment modalities of mind-body medicine, well-designed studies are lacking. Hypnosis will be discussed in Chapter 20.

We will discuss breathing exercises briefly, and finally we will discuss the study concerning massage therapy.

Breathing Exercises

It is assumed that synergy of the function of the lower esophageal sphincter (LES) and its surrounding crura of the diaphragm are of great importance for closure [30, 31]. For the majority of patients, the pathogenesis of GERD is considered to be an impairment of this closing mechanism of the LES. The LES tone in infants with GER is not different from normal infants, but they do have more spontaneous openings of the esophagogastric junction [32]. This is referred to as a transient relaxation of the lower esophageal sphincter (TLESR). Well-designed controlled trials investigating the efficacy of breathing exercises in children with GERD are lacking. Also in adults, the TLESRs are seen as the main underlying mechanism for GERD. A randomized controlled trial investigated the effect of breathing exercises including 19 adults with nonerosive GERD or healed esophagitis without large hernia and/or previous surgery. Authors hypothesized training of the diaphragm (as partly responsible for TLESR's) with a breathing exercise could decrease reflux and improve symptoms of GERD, since the crura of the diaphragm could be trained by physical exercise leading to improved performance. Authors demonstrated a positive effect of breathing exercise on GERD, measured by pH-metry, quality of life scores, and use of proton pump inhibitors [33]. At long-term follow-up at 9 months, patients who continued breathing exercise (11/19) showed a significant decrease in QoL

scores and PPI usage compared to the control group. However, this study has many limitations such as the small number and the fact that between-group comparisons did not show the significant results as compared with in-group analysis.

Massage Therapy (MT)

There is one single randomized controlled trial by Neu et al. investigating the efficacy of massage during 6 weeks in infants with a diagnosis of "GERD made by the pediatrician" [34]. Control group received sham therapy (non-massage treatment), similar to rocking and touching and holding mothers typically perform. Hypothesis was that, when compared to infants receiving non-massage therapy, infants who received MT would show less GERD symptoms and have greater weight gain, lower cortisol levels before and after treatment, greater amount of sleep, and lower daily cortisol secretion. The lack of an objective diagnostic criterion for GERD is the major weakness of this trial. The I-GERQ-R score was measured at baseline (mean 23, range 0–42) and after 6 weeks, with a statistical significant decrease of the score to 14 in both groups, but without difference between the groups. The primary endpoint being put at 6 weeks intervention is another major weakness of this design, as irritability and crying decreases spontaneously from the age of 3 months onward by natural course. This study seems more to be a study on the effect of massage therapy on infant irritability than on GERD. The number of infants is small, and this pilot trial is still waiting to be reproduced. The conclusion of this trial is that there were no statistical significant differences between both groups, except for the decrease in cortisol after 6 weeks, but without any difference after four weeks [34].

References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
2. Joyce CR. Placebo and complementary medicine. Lancet. 1994;344(8932):1279–81.
3. Beyerstein BL. Alternative medicine and common errors of reasoning. Acad Med. 2001;76(3):230–7.
4. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998;280(18):1569–75.
5. Zuzak TJ, Boňková J, Careddu D, Garami M, Hadjipanayis A, Jazbec J, Merrick J, Miller J, Ozturk C, Persson IA, Petrova G, Saz Peiró P, Schraub S, Simões-Wüst AP, Steinsbekk A, Stockert K, Stoimenova A, Styczynski J, Tzenova-Savova A, Ventegodt S, Vlieger AM, Längler A. Use of complementary and alternative medicine by children in Europe: published data and expert perspectives. Complement Ther Med. 2013;21(Suppl 1):S34–47.
6. Vlieger AM, Blink M, Tromp E, Benninga MA. Use of complementary and alternative medicine by pediatric patients with functional and organic gastrointestinal diseases: results from a multicenter survey. Pediatrics. 2008;122(2):e446–51.
7. Tang JL, Liu BY, Ma KW. Traditional Chinese medicine. Lancet. 2008;372:1938–40.

8. Teschke R, Wolff A, Frenzel C, Eickhoff A, Schulze J. Herbal traditional Chinese medicine and its evidence base in gastrointestinal disorders. World J Gastroenterol. 2015;21(15):4466–90.
9. Bai L, Yan H, Li L, et al. Neural specificity of acupuncture stimulation at pericardium 6: evidence from an FMRI study. J Magn Reson Imaging. 2010;31(1):71–7.
10. Chang FY, Chey WY, Ouyang A. Effect of transcutaneous nerve stimulation on esophageal function in normal subjects – evidence for a somatovisceral reflex. Am J Chin Med. 1996;24(2):185–92.
11. Yeh AM, Golianu B. Integrative treatment of reflux and functional dyspepsia in children. Children (Basel, Switz). 2014;1(2):119–33.
12. Rusy LM, Hoffman GM, Weisman SJ. Electroacupuncture prophylaxis of postoperative nausea and vomiting following pediatric tonsillectomy with or without adenoidectomy. Anesthesiology. 2002;96(2):300–5.
13. Reindl TK, Geilen W, Hartmann R, et al. Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology. Interim results of a multicenter crossover study. Support Care Cancer. 2006;14(2):172–6.
14. Gottschling S, Reindl TK, Meyer S, et al. Acupuncture to alleviate chemotherapy-induced nausea and vomiting in pediatric oncology – a randomized multicenter crossover pilot trial. Klin Padiatr. 2008;220(6):365–70.
15. Yeh CH, Chien LC, Chiang YC, Lin SW, Huang CK, Ren D. Reduction in nausea and vomiting in children undergoing cancer chemotherapy by either appropriate or sham auricular acupuncture points with standard care. J Altern Complement Med (New York, NY). 2012;18(4):334–40.
16. Zhang CX, Qin YM, Guo BR. Clinical study on the treatment of gastroesophageal reflux by acupuncture. Chin J Integr Med. 2010;16(4):298–303.
17. Dickman R, Schiff E, Holland A, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. Aliment Pharmacol Ther. 2007;26(10):1333–44.
18. Jindal V, Ge A, Mansky PJ. Safety and efficacy of acupuncture in children. J Pediatr Hematol Oncol. 2008;30:431–42.
19. Shaw D. Toxicological risks of Chinese herbs. Planta Med. 2010;76:2012–8.
20. Lai JN, Tang JL, Wang JD. Observational studies on evaluating the safety and adverse effects of traditional chinese medicine. Evid Based Complement Alternat Med. 2013;2013:697893.
21. Zhao YH, Liu ZI, Li LH, Jiang SH, Shi CH. Systematic review of randomized controlled trials of traditional Chinese medicine treatment of non-acute bronchial asthma complicated by gastroesophageal reflux. J Tradit Chin Med. 2012;32(1):12–8.
22. Khayyal MT, Seif-El-Nasr M, El-Ghazaly MA, Okpanyi SN, Kelber O, Weiser D. Mechanisms involved in the gastro-protective effect of STW 5 (Iberogast) and its components against ulcers and rebound acidity. Phytomed Int J Phytother Phytopharm. 2006;13:S56–66.
23. Pilichiewicz AN, Horowitz M, Russo A, Maddox AF, Jones KL, Schemann M, Holtmann G, Feinle-Bisset C. Effects of Iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men. Am J Gastroenterol. 2007;102:1276–83.
24. Ottillinger B, Storr M, Malfertheiner P, Allescher HD. STW 5 (Iberogast®) – a safe and effective standard in the treatment of functional gastrointestinal disorders. Wien Med Wochenschr. 2013;163(3–4):65–72.
25. Raveendra KR, Jayachandra SV, Sushma KR, Allan JJ, Goudar KS, Shivaprasad HN, Venkateshwarlu K, Geetharani P, Sushma G, et al. An extract of Glycyrrhiza glabra (gutgard) alleviates symptoms of functional dyspepsia: a randomized, double-blind, placebo-controlled study. Evid Based Complement Alternat Med. 2012;2012:1–9.
26. Ghayur MN, Gilani AH. Species differences in the prokinetic effects of ginger. Int J Food Sci Nutr. 2006;57:65–73.
27. Wu K-L, Rayner CK, Chuah S-K, Changchien CS, Lu SN, Chiu YC, Chiu KW, Lee CM. Effects of ginger on gastric emptying and motility in healthy humans. Eur J Gastroenterol Hepatol. 2008;20:436–40.
28. Thomson M, Al-Qattan KK, Al-Sawan SM, Alnaqeeb MA, Khan I, Ali M. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins Leukot Essent Fatty Acids. 2002;67:475–8.

29. Talley NJ, Boyce P, Jones M. Dyspepsia and health care seeking in a community: how important are psychological factors? Dig Dis Sci. 1998;43:1016–22.
30. Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;336(13):924–32.
31. Loots CM, Benninga MA, Omari TI. Gastroesophageal reflux in pediatrics; (patho)physiology and new insights in diagnostics and treatment. Minerva Pediatr. 2012;64(1):101–19.
32. Barnhart DC. Gastroesophageal reflux disease in children. Semin Pediatr Surg. 2016;25(4):212–8.
33. Eherer AJ, Netolitzky F, Hogenauer C, et al. Positive effect of abdominal breathing exercise on gastroesophageal reflux disease: a randomized, controlled study. Am J Gastroenterol. 2012;107(3):372–8.
34. Neu M, Pan Z, Workman R, Marcheggiani-Howard C, Furuta G, Laudenslager ML. Benefits of massage therapy for infants with symptoms of gastroesophageal reflux disease. Biol Res Nurs. 2014;16(4):387–97.

Gastro-oesophageal Reflux and Probiotic

22

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 whilst 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

Gastro-oesophageal 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.

F. Indrio (✉) • F. Cristofori
Department of Paediatrics, University of Bari Aldo Moro, Bari, Italy
e-mail: f.indrio@alice.it

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_22

Reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response causing forceful expulsion of gastric contents. GER is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals, which last less than 3 min, occur in the postprandial period and cause few or no symptoms. When GER causes or contributes to tissue damage or inflammation (oesophagitis, obstructive apnoea, reactive airway disease, pulmonary aspiration, feeding and swallowing difficulties, failure to thrive), it is called gastro-oesophageal reflux disease (GERD).

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 gastro-oesophageal reflux disease (GERD).

Recently, 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, haematemesis, aspiration, apnoea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing [1].

The practitioner's challenge is to distinguish regurgitation and vomiting caused by GER from vomiting caused by numerous other disorders. This can be confusing since reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response causing forceful expulsion of gastric contents. Vomiting associated with GER is probably a result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents. Laboratory and radiographic investigation may be necessary to exclude other causes of vomiting.

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 22.1) are generally sufficient to establish a clinical diagnosis of

Table 22.1 Warning signals requiring investigation in infants with regurgitation or vomiting

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

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. Intermittently, in an episode of vomiting, even forceful vomiting may occur. 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 3. If "warning signs" for GERD or other diagnoses are present or if regurgitation is not resolving by 18 months of age, consultation with a paediatric gastroenterologist is recommended.

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 that anti-secretory or pro-motility agents improve 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 breast-feeding mother is 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. 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 behaviour. Parents should be advised not to reduce intake to the point of calorie restriction in the attempt to prevent regurgitation. 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 aetiologies 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

hydrolysed or amino acid-based formula is appropriate. Depending on the results of investigations and response to dietary management, the infant should be referred to a paediatric 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 barium upper GI series, upper intestinal endoscopy, and oesophageal pH/MII both to diagnose GERD and 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 oesophagitis. 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 oesophageal, 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 oesophagus. In fact, transient lower oesophageal 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 the 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 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 micro-organism 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; 10 were exclusively breast-fed, 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 those 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 [2].

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 [3].

Finally, in 2014, a prospective, multicentre, 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 [4].

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. As a major consequence of this, many 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 [5].

Moreover, a recent 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 [6].

Del Piano et al. recently 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 [7].

This results has been recently 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 [8].

Finally, a double-blinded, placebo-controlled trial was performed in 70 children treated with 20 mg omeprazole per day for 4 weeks. *Lactobacillus rhamnosus* and *Lactobacillus 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 [9].

While there are no studies demonstrating the efficacy in GERD, 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 [10]. 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 centres 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 behaviour [11, 12].

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 behaviour [13]. Microbiota plays an important role in the modulation of hypothalamic-pituitary-adrenal axis, activated in response to a variety of physical and psychological stressors [14]. One of the important coordinators of the endocrine, behavioural, 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 [15]. 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 [16].

Other authors report in GF mice a reduction in anxiety behaviour and an upregulation in the expression of brain-derived neurotrophic factor (BDNF), a protein involved in multiple aspects of cognitive and emotional behaviours 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 behaviour and altered protein levels of BDNF. The discontinuation of the antibiotic cocktail restored the normal behavioural profile of the animals [17].

Similar perturbation of the microbiota by administration of pathogen bacteria has been shown to increase anxiety-like behaviour 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 [18]. 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 [19]. 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 [20].

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 [21], and in pathogenesis of other gastrointestinal diseases, such as inflammatory bowel disease, food antigen-related adverse responses, peptic ulcer, and gastro-oesophageal reflux disease [22].

Conclusion

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, 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.

References

1. Benninga MA, Nurko S, Faure C, Hyman PE, St. James Roberts I, Schechter NL. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016;150:1443–55.
2. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. J Pediatr. 2008;152(6):801–6.

3. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Filannino A, Cavallo L, Francavilla R. Lactobacillus reuteri accelerates gastric emptying and improves regurgitation in infants. Eur J Clin Investig. 2011 Apr;41(4):417–22.
4. Indrio F, Di Mauro A, Riezzo G, Civardi E, Intini C, Corvaglia L, Ballardini E, Bisceglia M, Cinquetti M, Brazzoduro E, Del Vecchio A, Tafuri S, Francavilla R. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. JAMA Pediatr. 2014;168(3):228–33.
5. Lombardo L, Foti M, Ruggia O, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatology. 2010;8:504–8.
6. Lo WK, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11:483–90.
7. Del Piano M, Anderloni A, Balzarini M, Ballarè M, Carmagnola S, Montino F, Orsello M, Pagliarulo M, Tari R, Soattini L, Sforza F, Mogna L, Mogna G. The innovative potential of Lactobacillus rhamnosus LR06, Lactobacillus pentosus LPS01, Lactobacillus plantarum LP01, and Lactobacillus delbrueckii Subsp. delbrueckii LDD01 to restore the "gastric barrier effect" in patients chronically treated with PPI: a pilot study. J Clin Gastroenterol. 2012;46(Suppl):S18–26.
8. Compare D, Rocco A, Sgamato C, Coccoli P, Campo SM, Nazionale I, Larussa T, Luzza F, Chiodini P, Nardone G. Lactobacillus paracasei F19 versus placebo for the prevention of proton pump inhibitor-induced bowel symptoms: a randomized clinical trial. Dig Liver Dis. 2015;47(4):273–9.
9. Hegar B, Hutapea EI, Advani N, Vandenplas Y. A double-blind placebo-controlled randomized trial on probiotics in small bowel bacterial overgrowth in children treated with omeprazole. J Pediatr. 2013;89(4):381–7.
10. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol. 2009;6:306–14.
11. Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology. 2009;136:2003–14.
12. Romijn JA, Corssmit EP, Havekes LM, et al. Gut-brain axis. Curr Opin Clin Nutr Metab Care. 2008;11:518–21.
13. McLean PG, Bergonzelli GE, Collins SM, et al. Targeting the microbiota-gut-brain axis to modulate behavior: which bacterial strain will translate best to humans? Proc Natl Acad Sci U S A. 2012;109:E174.
14. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. J Physiol Pharmacol. 2011;62:591–9.
15. Larauche M. Novel insights in the role of peripheral corticotropin-releasing factor and mast cells in stress-induced visceral hypersensitivity. Neurogastroenterol Motil. 2012;24:201–5.
16. Bale TL, Lee KF, Vale WW. The role of corticotropin-releasing factor receptors in stress and anxiety. Integr Comp Biol. 2002;42:552–5.
17. Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology. 2011;141:599–609.
18. Diamond B, Huerta PT, Tracey K, et al. It takes guts to grow a brain: Increasing evidence of the important role of the intestinal microflora in neuro- and immune-modulatory functions during development and adulthood. Bioessays. 2011;33:588–91.
19. Heijtz RD, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A. 2011;108:3047–52.
20. Diamond B, Huerta PT, Tracey K, et al. It takes guts to grow a brain: increasing evidence of the important role of the intestinal microflora in neuro- and immune-modulatory functions during development and adulthood. Bioessays. 2011;33:588–91.2.
21. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. JAMA. 2004;292:852–8.
22. Cobrin GM, Abreu MT. Defects in mucosal immunity leading to Crohn's disease. Immunol Rev. 2005;206:277–95.

Gastroesophageal Reflux and Prokinetics

23

Mário C. Vieira

Abstract

Prokinetic agents have been widely employed in pediatric patients in order to reduce the symptoms of GERD. These drugs seem to enhance lower esophageal sphincter (LES) tone, to improve esophageal clearance, and to increase gastric motility thus increasing emptying of gastric contents.

Cisapride was probably the best studied prokinetic agent in children; however, it was taken off the market in the 2000s by the European and American authorities owing to its cardiac side effects. Other agents such as metoclopramide and domperidone have been evaluated, but a high incidence of adverse 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 justify its widespread use. Other agents acting on TLSERs such as arbaclofen and lesogaberan have been evaluated in adult patients, but studies in children are lacking.

M.C. Vieira
Centro de Gastroenterologia Pediátrica, Hospital Pequeno Príncipe, Curitiba, Brazil

Escola de Medicina, Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil
e-mail: gastroped@hpp.org.br

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_23

Overall, although the prokinetic concept is attractive, no effective and safe drug is currently available. Furthermore, all agents have a high incidence of adverse effects that outweigh the benefits achieved with their use.

Keywords
Gastroesophageal reflux disease • Children • Pediatrics • Drug therapy • Prokinetic • Cisapride • Domperidone • Metoclopramide • Bethanechol • Baclofen

Pharmacological treatment of GERD has primarily focused on suppression of acid. However, it has been shown also that nonacid 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 benefit for improving symptoms of GERD by enhancing lower esophageal sphincter (LES) tone and increasing esophageal motility and gastric emptying. From the pathophysiological point of view, the use of prokinetics is the most rational therapeutic approach to treat 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 drug acts by enhancing LES tone and improving gastric emptying [4, 5]. Due to its prokinetic properties, metoclopramide has been widely used in the past as treatment of GERD in infants and children, despite the lack of rigorous evidences approving its prescription [6].

A systematic review and meta-analysis of metoclopramide use in infants concluded that there may be some benefit 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 more

recent 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 compound 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 indicated 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 third class antiarrhythmic agent [18, 19]. The clinical efficacy of cisapride in reducing GER in preterm infants has been demonstrated to decrease the reflux indexes and the number of GER episodes lasting more than 5 minutes, 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 has been widely investigated. A prolongation of QTc interval in infants and children receiving cisapride has also been 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 has been gradually withdrawn, 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 towards studies showing 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 few convincing evidences for its effectiveness [26–30]. The pediatric population is particularly susceptible to side effects, due to an immaturity of the nervous system and blood-brain barrier. Domperidone might occasionally provoke neurologic adverse effects, such as extrapyramidal symptoms, oculogyric crises, and hyperprolactinemia [31, 32]. One of the major 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 which 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]. It is therefore not possible to recommend the use of domperidone in the treatment of GER 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 which 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 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 4 out of 8

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 posttreatment. More recently, a retrospective study of medical charts including 53 children with a mean age of 6.1 years with persistent GER symptoms 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 does not justify its widespread use. More prospective studies are needed to validate these preliminary results and assess safety.

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 [49]. A randomized, placebo-controlled study evaluated the effectiveness of lesogaberan for GERD in 25 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. All lesogaberan doses were well tolerated and were not associated with clinically relevant adverse events [50].

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 cannot be the only solution for all patients. Prokinetic drugs have a potential role for the treatment of GERD in infants and children and may provide additional benefit in special groups. However, as adverse effects of currently available prokinetic drugs exceed the potential therapeutic benefits for treatment of GERD, these compounds are not recommended by pediatric practice guidelines [51, 52].

There is a need for continued research into the therapeutic role of these drugs and further pharmacologic development to provide viable options with therapeutic effectiveness and an acceptable safety profile.

References

1. Bredenoord AJ, Weusten BLAM, Curvers WL, et al. Determinants of perception of heartburn and regurgitation. Gut. 2006;55:313–8.
2. Mittal RK, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. Gastroenterology. 1995;109(2):601–10.

3. Armstrong D. The clinical usefulness of prokinetic agents in gastrooesophageal reflux disease. In: Lundell L, editor. Guidelines for the management of symptomatic gastro-oesophageal reflux disease. London: Science Press; 1998. p. 45–54.
4. Chicella MF, Batres LA, Heesters MS, Dice JE. Prokinetic drug therapy in children: a review of current options. Ann Pharmacother. 2005;39(4):706–11.
5. McCallum RW, Kline MM, Curry N, Sturdevant RA. Comparative effects of metoclopramide and bethanechol on lower esophageal sphincter pressure in reflux patients. Gastroenterology. 1975;68(5 Pt 1):1114–8.
6. Hibbs AM, Lorch SA. Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. Pediatrics. 2006;118:746–52.
7. Craig WR, Hanlon-Dearman A, Sinclair C, Taback S, Moffatt M. Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years. Cochrane Database Syst Rev. 2004;4:CD003502.
8. Hyams JS, Leichtner AM, Zamett LO, Walters JK. Effect of metoclopramide on prolonged intraesophageal pH testing in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1986;5:716–20.
9. Machida HM, Forbes DA, Gall DG, Scott RB. Metoclopramide in gastroesophageal reflux of infancy. J Pediatr. 1988;112(3):483–7.
10. Madani S, Tolia V. Gynecomastia with metoclopramide use in pediatric patients. J Clin Gastroenterol. 1997;24(2):79–81.
11. Putnam PE, Orenstein SR, Wessel HB, Stowe RM. Tardive dyskinesia associated with use of metoclopramide in a child. J Pediatr. 1992;121:983–5.
12. Paturi B, Ryan RM, Michienzi KA, Lakshminrusimha S. Galactorrhea with metoclopramide use in the neonatal unit. J Perinatol. 2009;29:391–2.
13. Mejia NI, Jankovic J. Metoclopramide induced tardive dyskinesia in an infant. Mov Disord. 2005;20:86–9.
14. Dunne CE, Bushee JL, Argikar UA. Metabolism of bromopride in mouse, rat, rabbit, dog, monkey, and human hepatocytes. Drug Metab Pharmacokinet. 2013;28(6):453–61.
15. Shafrir Y, Levy Y, Beharab A, Nitzam M, Steinherz R. Acute dystonic reaction to bethanechol – a direct acetylcholine receptor agonist. Dev Med Child Neurol. 1986;28:646–8.
16. Euler AR. Use of bethanechol for the treatment of gastroesophageal reflux. J Pediatr. 1980;96:321–4.
17. Levi P, Marmo F, Saluzzo C, Dell'Olio D, Ansaldi N, Giuliani L, Guardamagna O, Mostert M, Ponzone A. Bethanechol versus antiacids in the treatment of gastroesophageal reflux. Helv Paediatr Acta. 1985;40:349–59.
18. Dubin A, Kikkert M, Mirmiran M, Ariagno R. Cisapride associated with QTc prolongation in very low birth weight preterm infants. Pediatrics. 2001;107(6):1313–6.
19. Drolet B, Rousseau G, Daleau P, Cardinal R, Turgeon J. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. Circulation. 2000;102:1883–5.
20. Ariagno RL, Kikkert MA, Mirmiran M, Conrad C, Baldwin RB. Cisapride decreases gastroesophageal reflux in preterm infants. Pediatrics. 2001 Apr;107(4):E58.
21. Bernardini S, Semama DS, Huet F, Sgro C, Gouyon JB. Effects of cisapride on QTc interval in neonates. Arch Dis Child Fetal Neonatal Ed. 1997;77(3):F241–3.
22. Corvaglia L, Faldella G, Rotatori R, Lanari M, Capretti MG, Salvioli GP. Intrauterine growth retardation is a risk factor for cisapride-induced QT prolongation in preterm infants. Cardiovasc Drugs Ther. 2004;18(5):371–5.
23. Maclennan S, Augood C, Cash-Gibson L, Logan S, Gilbert RE. Cisapride treatment for gastro-oesophageal reflux in children. Cochrane Database Syst Rev. 2010;4:CD002300.
24. Augood C, MacLennan S, Gilbert R, et al. Cisapride treatment for gastro-oesophageal reflux in children. Cochrane Database Syst Rev. 2003;4:CD002300.
25. Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. Br J Clin Pharmacol. 2005;59(6):725–9.

26. Carroccio A, Iacono G, Montalto G, Cavataio F, Soresi M, Notarbartolo A. Domperidone plus magnesium hydroxide and aluminum hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus placebo. Scand J Gastroenterol. 1994;29(4):300–4.
27. Scott B. Question 2. How effective is domperidone at reducing symptoms of gastro-oesophageal reflux in infants? Arch Dis Child. 2012;97(8):752–5.
28. Clara R. Chronic regurgitation and vomiting treated with domperidone. A multicenter evaluation. Acta Paediatr Belg. 1979;32:203–7.
29. Bines JE, Quinlan J, Treves S, et al. Efficacy of domperidone in infants and children with gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1992;14:400–5.
30. De Loore L, Van Ravenstayn H. Domperidone drops in the symptomatic treatment of chronic paediatric vomiting and regurgitation. A comparison with metoclopramide. Postgrad Med J. 1979;55(Suppl 1):40–2.
31. Sol P, Pelet B. Extrapyramidal reaction due to domperidone. Lancet. 1980;1:802.
32. Shafrir Y, Levy Y. Oculogyric crises due to domperidone therapy. Helv Paediatr Acta. 1985;40:95.
33. Rocha CM, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in an infant. Pediatr Cardiol. 2005;26:720–3.
34. Hondeghem LM. Low safety index of domperidone: mechanism for increased odds ratio for sudden cardiac death. Acta Cardiol. 2011;66:421–5.
35. Rossi M, Giorgi G. Domperidone and long QT syndrome. Curr Drug Saf. 2010;5:257–62.
36. Djeddi D, Kongolo G, Lefaix C, Mounard J, Léké A. Effect of domperidone on QT interval in neonates. J Pediatr. 2008;153:663–6.
37. Günlemez A, Babaoglu A, Artsoy AE, Tûrker G, Gökalp AS. Effect of domperidone on the QTc interval in premature infants. J Perinatol. 2010;30:50–3.
38. Vieira MC, Miyague NI, Van Steen K, Salvatore S, Vandenplas Y. Effects of domperidone on QTc interval in infants. Acta Paediatr. 2012;101:494–6.
39. van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf. 2010;33:1003–14.
40. Cucchiara S, Bortolotti M, Minella R, et al. Fasting and postprandial mechanisms of gastroesophageal reflux in children with gastroesophageal reflux disease. Dig Dis Sci. 1993;38:86–92.
41. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastro gastroesophageal reflux in children. Gastroenterology. 1997;113:399–408.
42. Werlin SL, Dodds WJ, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in children. J Pediatr. 1980;97:244–9.
43. Omari T. Gastro-oesophageal reflux disease in infants and children: new insights, developments and old chestnuts. J Pediatr Gastroenterol Nutr. 2005;41(suppl 1):S21–3.
44. Vandenplas Y, Hassall E. Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2002;35:119–36.
45. Zhang Q, Lehmann A, Rigda R, Dent J, Holloway RH. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. Gut. 2002;50(1):19–24.
46. Kawai M, Kawahara H, Hirayama S, et al. Effect of baclofen on emesis and 24-hour esophageal pH in neurologically impaired children with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2004;38:317–23.
47. Omari TI, Benninga MA, Sansom L, et al. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. J Pediatr. 2006;149:468–74.
48. Vadlamudi NB, Hitch MC, Dimmitt RA, Thame KA. Baclofen for the treatment of pediatric GERD. J Pediatr Gastroenterol Nutr. 2013;57(6):808–12.
49. Vakil NB, Huff FJ, Cundy KC. Randomised clinical trial: arbaclofen placarbil in gastro-oesophageal reflux disease – insights into study design for transient lower sphincter relaxation inhibitors. Aliment Pharmacol Ther. 2013;38(2):107–17.

50. Miner PB Jr, Silberg DG, Ruth M, Miller F, Pandolfino J. Dose-dependent effects of lesogaberan on reflux measures in patients with refractory gastroesophageal reflux disease: a randomized, placebo-controlled study. BMC Gastroenterol. 2014;14:188.
51. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
52. Lightdale JR, Gremse DA, Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013; 131(5):e1684–95.

GER and Antacid Medications

24

Jose M. Garza and Carlo Di Lorenzo

Abstract

Gastric acid secretion is a physiological process essential for food digestion. It is regulated by paracrine, hormonal, and neural pathways. Antacids, surface-protective agents, and antisecretory agents are used for treating gastroesophageal reflux disease (GER). Antacids are helpful for immediate symptomatic relief but are not recommended for chronic use. Histamine-2 receptor antagonists have a role in the management of episodic and mild symptoms, particularly for infrequent GER or reflux-related symptoms. Proton pump inhibitors (PPIs) have become some of the most frequently prescribed medications in both children and adults, and their effectiveness for treatment of peptic conditions in the pediatric population has been established. They are well tolerated in both infants and children, but as with any other pharmacologic therapy, PPIs are not exempt of side effects, and risk-benefit should be assessed in individual cases, especially when a chronic use is necessary.

Keywords

Acid • Parietal cell • Gastrin • Antacid • Surface-protecting agents • Sucralfate • Alginates • Parietal cell • Proton pump inhibitors • H2 receptor antagonists • H2 blockers

J.M. Garza
Children's Center for Digestive Healthcare, Atlanta, GA, USA

Neurogastroenterology and Motility, Children's Healthcare of Atlanta, Atlanta, GA, USA

C. Di Lorenzo (✉)
Pediatrics, The Ohio State University, Columbus, OH, USA

Division of Pediatric Gastroenterology, Nationwide Children's Hospital, Columbus, OH, USA
e-mail: carlo.dilorenzo@nationwidechildrens.org

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_24

Introduction

In virtually all vertebrates, gastric acid secretion is a physiological process that is essential for food digestion. In adult humans the stomach secretes 1–2 L of gastric juice per day [1]. Gastric acid facilitates breakdown of proteins and the absorption of calcium, iron, and vitamin B12 as well as prevents enteric infections and small bowel bacterial overgrowth [2].

Acid is secreted by parietal cells, and this process is regulated by three distinct physiologic pathways (Fig. 24.1): *(a) paracrine*—histamine is released from enterochromaffin-like (ECL) cells and stimulates the parietal cell directly by binding to H_2 receptors coupled to adenylate cyclase. *(b) Hormonal*—gastrin is released from G cells in the antrum through gastric distention [3] and by the presence of amino acids [4]. Gastrin is the major endocrine regulator of secretory

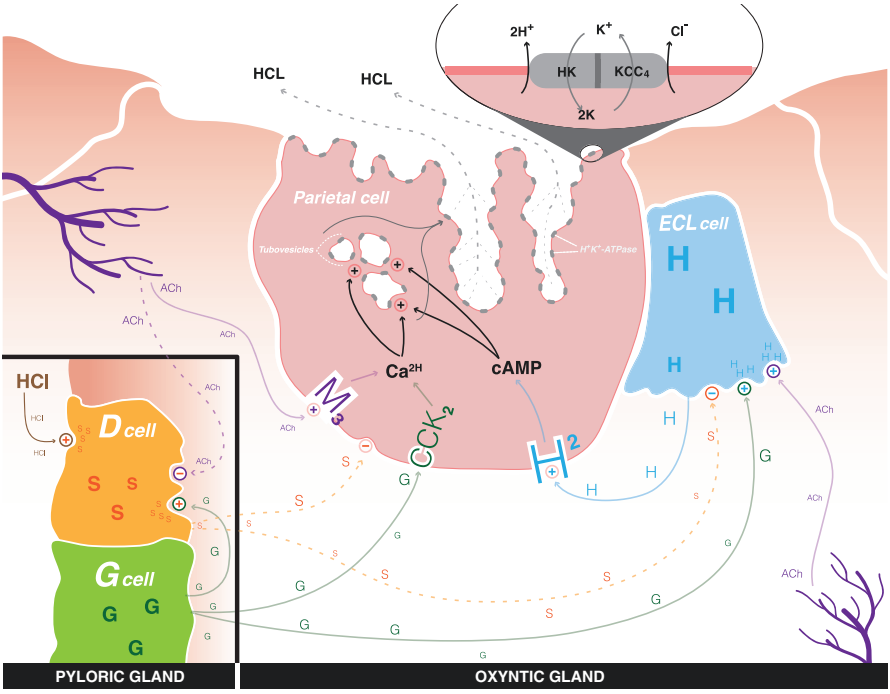


Fig. 24.1 Regulation of acid secretion. Histamine is released from enterochromaffin-like (ECL) cells (*blue*) stimulating parietal cells through H2 receptors. Gastrin is released from G cells (*green*) and enhances acid secretion by stimulating histamine release from ECL cells and directly activating the parietal cells through CCK-2 receptor. Acetylcholine is released from enteric nerves (*purple*) and activates parietal cells through muscarinic receptors, stimulates histamine release from ECLs, and inhibits secretion of somatostatin from D cells (*orange*). Activation of parietal cell causes increase in intracellular calcium and cAMP which leads to fusion of the tubulovesicles with the apical plasma membrane and activates the H^+K^+-ATPase (*grey*) exchanging luminal K^+ for cytoplasmic H^+ (magnified). Somatostatin is a potent inhibitor of acid secretion (*orange dotted line*).

response to a protein meal. Gastrin enhances gastric acid secretion from parietal cells by stimulating synthesis and release of histamine from ECL cells and also through direct action on parietal cells. Additionally, gastrin acts via activation of cholecystokinin (CCK)-2 receptors coupled to phospholipase C and causing the release of intracellular calcium. *(c) Neurocrine*—acetylcholine (ACh) is released from postganglionic enteric neurons. It mediates the gastric response to the cephalic phase, to gastric distention, and to intragastric amino acids. Acetylcholine acts by activation of the muscarinic receptor (M_3) to trigger the release of intracellular calcium leading to the secretion of gastric acid. Acetylcholine also stimulates histamine release from ECL cells and inhibits somatostatin release from D cells [4] (Fig. 24.1).

The main inhibitor of acid secretion is somatostatin which is released from oxyntic and pyloric D cells [2]. In this negative biofeedback loop, somatostatin secretion is increased by gastric acid and by gastrin itself. When intragastric pH rises, such as in response to treatment with proton pump inhibitors (PPIs), somatostatin secretion is inhibited and hypergastrinemia develops [2].

Parietal cell secretion of acid is also increased by cAMP and calcium-dependent pathways that activate H^+K^+-ATPase, an enzyme which then exchanges luminal K^+ for cytoplasmic H^+. In the resting state, H^+K^+-ATPase activity is contained within cytoplasmic tubulovesicles; once stimulated these vesicles fuse with the apical plasma membrane to increase the secretion of gastric acid [2] (Fig. 24.1).

Anticipation of a meal activates central neurons whose input is relayed via the vagus nerve, which then release ACh that stimulates parietal cells. The increase in histamine stimulates acid secretion via H_2 receptors on parietal cells and indirectly via H_3 receptors that mediate suppression of somatostatin secretion. In the antrum, cholinergic neurons stimulate gastrin secretion directly and inhibit somatostatin secretion [2] (Fig. 24.1).

Antacids

Mechanism of Action

Antacids act by directly buffering gastric acid and neutralizing the gastric pH. Most available preparations contain a combination of magnesium or aluminum hydroxide or calcium carbonate. They begin to provide relief within 5 min and duration of effect is 30–60 min. Thus, they are appropriate for short-term relief of heartburn for older children and adolescents. Antacids should be used with caution in infants and young children and are not recommended for chronic antacid therapy [5].

Adverse Events

Treatment with aluminum-containing antacids in infants can increase plasma concentrations of aluminum and can cause osteopenia, microcytic anemia, and neurotoxicity [6]. Other complications of long-term use include hypophosphatemic rickets [7]. Long-term use of calcium carbonate is associated with the milk-alkali syndrome (hypercalcemia, alkalosis, and renal failure) [8].

Surface-Protective Agents

Mechanism of Action

Surface-protective agents act by creating a barrier that impedes acid peptic injury to mucosal surfaces, and within this category two substances have been evaluated in children: alginates and sucralfate.

Alginates

Alginates are insoluble salts of alginic acid, a polysaccharide found in cell walls of seaweed, and typically form a gel that creates a physical barrier. The alginates are usually combined with either sodium or potassium bicarbonate which when in contact with gastric acid is converted to carbon dioxide and gets trapped in the gel forming a "foam raft" that floats on top of gastric contents [8]. Compound alginate preparations for infants contain sodium and magnesium alginate and mannitol. These preparations prevent GER by increasing the viscosity of gastric contents. The infant formulation does not contain sodium or potassium bicarbonate; therefore it does not form a "floating raft," and it also has a high-sodium content that can result in hypernatremia [9]. Multiple studies with alginates have been done in infants, but they have produced conflicting results: decreased number of reflux events and acid exposure [10, 11], decrease in average reflux height [12], and a decrease in symptom scores [13]. These studies not only have used different alginate formulations but for the most part have included small number of infants with a short duration of intervention making it difficult to evaluate drug safety and efficacy. Evidence appears insufficient for a meta-analysis [9].

In adults, adding treatment with alginate to once per day PPI significantly reduced frequency and severity of heartburn, regurgitation, and nighttime symptoms [14]. There seems to benefit also in controlling postprandial esophageal acid exposure due to displacement and neutralization of the postprandial acid pocket [15–17]. No similar studies have been done in children or adolescents.

Adverse Events

Care should be used when alginates that contain aluminum are used in children with vomiting, diarrhea, or at risk for intestinal obstruction. In children whose feeds are already thickened, alginates can cause intestinal obstruction [9]. Precipitation of alginate in the stomach can form a bezoar [13].

Sucralfate

Sucralfate is a compound of sucrose, sulfate, and aluminum, which in an acidic environment forms a gel that binds to the exposed mucosa. There is only one study in pediatrics that showed that sucralfate was as effective as cimetidine [18].

Adverse Events

There are no safety data, and in pediatrics there is risk of aluminum toxicity with long-term use, particularly in those patients with chronic renal failure [5, 8]. Sucralfate can also bind to other drugs if taken simultaneously.

Antisecretory Agents

Histamine-2 receptor antagonists (H2RAs): ranitidine, famotidine, nizatidine, roxatidine, and cimetidine hydrochloride.

Mechanism of Action

The H2 receptor antagonists (H2RAs), or "H2 blockers" as they are often called, inhibit acid secretion by selectively blocking histamine-2 receptors on the parietal cell. They are well absorbed after oral intake, achieve peak serum concentration within 1–3 h, and have a duration of action of 4–10 h. H2 blocker absorption is reduced by 10–20% by concomitant antacid administration, but not by food. H2RAs are eliminated by hepatic and renal metabolism, and their bioavailability is reduced by first-pass metabolism [19].

When compared with proton pump inhibitors (PPIs), H2RAs are slightly less potent in increasing gastric pH, healing reflux esophagitis, and preventing ulcers from bleeding [20]. A Cochrane review concluded that "some" evidence indicates that H2RAs are effective in treating children with GERD, but methodological differences precluded a thorough performance assessment by a meta-analysis of individual agents or of these agents as a class [9]. In children, when H2RAs are compared to placebo, they are more effective in reducing signs and symptoms of GERD as well as healing reflux esophagitis [20]. The evidence is poor when H2RAs are compared to antacids and PPIs. Additionally, there are no randomized controlled trials in children, and at present it is very unlikely for one of such studies to be performed since the patents of all existing H2RAs have expired, and there would be no interest by pharmaceutical companies to support more research on these compounds.

Ranitidine is generally well tolerated in children, used at dose of 4–10 mg/kg/day in 2–3 divided doses. Some authors have advocated increase to 20 mg/kg/day if standard dosing does not control the symptoms, although change to a PPI is arguably safer and more efficacious in those circumstances [8]. There is concern for tachyphylaxis (tolerance to the H2RAs) as it has been demonstrated in children to occur with intravenous ranitidine [21] and in adults taking it orally [22]. Tachyphylaxis develops days to a few weeks after beginning treatment, limiting the efficacy of this class of drugs for long-term management.

H2RAs are now available without need for prescription ("over the counter") in most countries. H2RAs still have a role in the management of episodic and mild symptoms because they can provide rapid symptom relief, particularly for infrequent GER or reflux-related symptoms [23].

Adverse Events

Cimetidine was the first H2RA to be used, and it revolutionized the treatment of peptic ulcer as well as reflux disease. Within a few years, ranitidine, famotidine, and nizatidine were marketed demonstrating a higher affinity for H2 receptors and decreased drug interactions [24]. Cimetidine is now infrequently used due to its drug interactions, risk of acute liver injury, gynecomastia, and interaction with

vitamin D metabolism [20]. With the newer H2RAs, most of the side effects reported are milder and include abdominal pain, diarrhea, headache, somnolence, and pneumonia [25]. The use of H2RA has been associated with an increased risk of enteric infection and community-acquired pneumonia [26]. In some infants, H2RA therapy causes irritability, head banging, headache, somnolence, and other side effects that, if interpreted as persistent symptoms of GERD, could result in an inappropriate increase in dosage [5]. In addition, in a small case series retrospective study, very low birth weight infants that received ranitidine developed a 6.6-fold higher rate of necrotizing enterocolitis [27].

Proton Pump Inhibitors (PPIs)

Mechanism of Action

Proton pump inhibitors are considered "prodrugs" in that they are non-protonated at neutral pH and then become increasingly protonated upon entering an acidic compartment with a pH lower than their pKa. After oral administration, they are absorbed from the small intestine into the systemic circulation and enter the parietal cell, diffuse into the external canaliculus, and, under acidic conditions, are transformed into the pharmacologically active entity that opens and then binds covalently to the surface of the H^+K^+-ATPase (the proton pump), which then leads to irreversible inhibition of this enzyme. Because the proton pump represents the final step of gastric acid production, inhibition of this enzyme suppresses gastric acid secretion regardless of the primary stimulus. The requirement for an acidic environment for PPI accumulation and activation provides the basis for selective action against the *gastric* H^+K^+-ATPase. This molecule is also present in the kidney, colon, heart, pancreas, lung, and cochlea [1, 28]. Restoration of acid production occurs mostly through the novo synthesis of the H^+K^+-ATPase (estimated half-life of 50 h, but it is not known whether infants and children have a turnover similar to that seen in adults). This accounts for the long duration of their antisecretory effect despite the short plasma elimination half-life of about 1 h [29]. Although all PPIs share the same basic mechanism of action, they differ with distinct patterns of binding to the proton pump and variations in pKa.

H^+K^+-ATPase

This acid pump creates a one million-fold gradient in H^+ concentration from inside the parietal cell to the gastric lumen in return for inward transport of K^+ [30]. This molecule is present from week 25 of gestation, and its expression increases with gestational age through the first 82 days after birth [28]. By 6 months of age, maximal acid output is about the same level as in older children and adults [28]. Without stimulation, the H^+K^+-ATPase resides inactive in a tubulovesicle form (Fig. 24.1). Upon stimulation, the H^+K^+-ATPase is translocated to the canalicular membrane where it becomes active. Only actively secreting pumps are inhibited when effective plasma concentrations of PPIs are reached, sparing the inactive pumps. A meal is considered to be the strongest physiological event inducing the translocation of the

H^+K^+-ATPase [28]. Since more than 1 h is needed for an administered PPI to reach gastric parietal cells, the best timing for oral intake is considered to be 30 min before breakfast [31]. Not all the proton pumps are active and inhibited after the first dose, so for most PPIs steady state requires around 3 days to develop [32].

PPI Metabolism

The mean time for most PPIs to reach maximum plasma concentration is between 1 and 3 h, and food intake delays absorption. Since they are acid labile, oral formulations are enteric coated so that they dissolve at pH higher than 6, in order to avoid inactivation in the presence of acid in the stomach. PPIs are highly bound to plasma proteins (>95%). Children rapidly metabolize them with a short half-life of around 1 h. All PPIs are extensively metabolized in the liver by CYP isoforms (CYP2C19 and CYP3A4) into inactive metabolites that are excreted in feces and in urine in different proportions [28].

CYP2C19 is low in the first weeks of life, reaching adult activity by 6–12 months and exceeding adult levels between 1 and 4 years of age, returning then to adult levels by end of puberty. Therefore, there is reduced metabolism of PPIs in newborns [33]. In children, a faster clearance of PPI, faster metabolic capacity, and differences in bioavailability may be responsible for the need for higher doses than required by adults on a per kg basis [34]. Genetic variation in the CYP2C19 gene gives rise to poor and extensive metabolizer phenotypes which influence PPI clearance, efficacy, and exposure [35]. Individuals homozygous for the wild-type CYP2C19 allele demonstrate the greatest degree of activity and are termed extensive metabolizers (EMs). Individuals homozygous to the mutant allele demonstrate the lowest level of activity and are termed poor metabolizers (PMs). Individuals heterozygous for wild-type and mutant allele are termed intermediate metabolizers (IMs). It has been hypothesized that CYP2C19 phenotype may contribute to PPI-associated infections. A study found that risks of upper respiratory infection and sore throat were higher in PMs than EMs taking 30 mg of lansoprazole daily [36]. These authors concluded that conventional PPI dosing regimens may in fact overdose PMs, which comprise a third of the US population and that dosing should be based on CYP2C19 genotype.

Treatment with PPI in Newborns and Infants

At 24-week gestation, the neonate stomach can secrete enough acid to maintain a basal gastric pH of <4. However, gastric acid volume does not reach adult levels until 6 months after birth. The dose-related duration of the effect of PPI in newborns has not been well described, but there may be some evidence to support lower and less frequent dosing than is currently practiced [30]. When irritable infants underwent a randomized, double-blind, placebo-controlled, crossover trial with omeprazole, there was no effect on crying or fussing despite a reduction in the reflux index with the PPI [37]. Similar findings were reported in another study using omeprazole in preterm infants which led to an improvement in reflux index with no changes in symptoms [38]. A multicenter,

double-blind, placebo-controlled trial with lansoprazole in infants who experienced crying, fussing, or irritability within 1 h after feeding found no difference in efficacy between lansoprazole and placebo as measured by symptom quantity and duration [39]. Esomeprazole in a more recent study successfully reduced esophageal acid exposure and the number of acid reflux events in neonates but, much like all the previous PPI studies done in infants, failed to show any difference in symptoms attributed to acid reflux [40]. Furthermore, a more recent study with esomeprazole failed to show a benefit in infants and neonates with reflux-related symptoms when compared with placebo [41]. Another PPI, rabeprazole when evaluated in infants, also failed to show any symptom difference between the treatment arms [42].

In the USA, esomeprazole is the only Food and Drug Administration (FDA)-approved PPI for use in infants. Esomeprazole was approved for healing of erosive esophagitis in patients younger than 1 year of age and as early as 1 month. Even though PPIs have demonstrated effective inhibition of gastric acid secretion and reduction of acid reflux in the infant population, the available evidence does not support their use in infants with symptoms attributed to GERD (unexplained crying, irritability, sleep disturbance, or apneas) due to lack of efficacy [43]. It has been hypothesized that this may in part be due to reflux-related symptoms in neonates being caused by volume-related effects of the refluxate leading to esophageal distention rather than acid-mediated injury in the esophagus. Thus, in infants PPIs are likely only beneficial for those who have true acid-related problems (esophagitis), and the difficulty for the medical provider lies in accurately identifying and diagnosing such infants.

Treatment with PPI in Children and Adolescents

PPIs are so effective at treating acid-related disorders that with the advent of PPIs in the late 1980s, the treatment challenge changed from healing of upper gastrointestinal mucosal lesions to the treatment of persistent or refractory symptoms [44]. The indications for use of PPIs in adolescents are more established than in infants. Healing of erosive esophagitis with PPIs is well documented in both children and adults. A recent Cochrane review [9] concluded that there is moderate-quality evidence from individual studies to suggest that PPI can reduce GERD symptoms in children with confirmed erosive esophagitis. This review further stated that it was not possible to demonstrate statistical superiority of one PPI agent over another [9]. Tolerance such as that observed with the H2RAs has not been described in PPI use. However, abrupt discontinuation of treatment may result in acid rebound resulting in onset or worsening of symptoms in some patients, so PPI-based therapy should be discontinued in a stepwise fashion [45–47].

Omeprazole

Omeprazole was the first PPI to be introduced into the market. Omeprazole pharmacokinetics are dose-dependent, with nonlinear increases in plasma concentration, making its bioavailability at its lowest after a single oral administration [28]. In 1993,

Cucchiara et al. [48] studied 32 children (6 months–13.4 years) with GERD symptoms who failed to improve on ranitidine. The study subjects were randomized to 8 weeks of omeprazole (40 mg/kg/day/1.73 m^2 body surface area) or high-dose ranitidine. Symptoms, esophageal pH-metry parameters, and endoscopy findings improved in both cohorts, but no statistically significant superiority was noted for the omeprazole. A prospective, double-blind study of 18 children, 1–13 years of age receiving omeprazole 1.4 mg/kg with max dose of 60 mg, of whom 89% had nocturnal acid breakthrough, evaluated the benefit of additional ranitidine vs. placebo. The study overall showed significant improvement in symptoms after 3 weeks with no benefit observed from additional ranitidine in those with breakthrough symptoms [49]. Hassall et al. [50] performed an open-label multicenter study in children 1–16 years old with erosive reflux esophagitis, many of whom had failed H2RAs. In this long-term study, 54 (97%) out of 57 patients with erosive esophagitis healed, and symptoms improved in all. Doses required for esophageal healing ranged between 0.7 and 3.5 mg/kg/day.

Lansoprazole

This PPI exhibits similar pharmacokinetic parameters in adolescents to those observed in adults [51]. In an open-label multicenter study of lansoprazole in children with symptomatic GERD and erosive esophagitis, lansoprazole was successful in healing erosive esophagitis and improving symptoms. In this multicenter study, lansoprazole was used initially at 15 or 30 mg once per day, and subjects were allowed to increase the dose up to 60 mg if symptoms persisted after 2 weeks [52]. Borrelli et al. [53] performed a randomized controlled trial comparing alginate, lansoprazole 1.5 mg/kg BID, and lansoprazole 1.5 mg/kg + alginate over 8 weeks. All three groups healed and improved symptoms, with superiority observed in the lansoprazole plus alginate group.

Esomeprazole

Esomeprazole is the s-isomer of omeprazole, with less first-pass metabolism, resulting in higher bioavailability [54]. Gold et al. [55] studied 148 adolescents with GERD symptoms and found that esomeprazole at doses of 20 mg and 40 mg once a day for 8 weeks was well tolerated, and symptoms were significantly reduced in both groups. In a randomized, parallel-group, double-blind (for dose) study, esomeprazole was found to be successful in treating esophagitis in children 1–11 years old (5 mg or 10 mg <20 kg weight and 10 mg or 20 mg for those >20 kg) [56].

Pantoprazole

Tolia et al. [57] performed a multicenter double-blind randomized control trial with pantoprazole comparing 10 mg, 20 mg, and 40 mg for 8 weeks in 53 children 5–11 years of age and demonstrating symptomatic improvement in all groups. Tsou

et al. [58] assessed pantoprazole 20 mg and 40 mg in 136 children, 12–16 years of age, and showed an improvement in the number of vomiting episodes, heartburn symptom score, and epigastric pain score.

Rabeprazole

This PPI has greater antisecretory potency relative to equivalent doses of other PPIs [59]. Rabeprazole seems to maintain same efficacy despite postprandial administration [31]. A population pharmacokinetic study of rabeprazole recommends 5 mg once a day for children <15 kg and 10 mg for those >15 kg [60]. Haddad et al. evaluated safety and efficacy of rabeprazole in 1–11-year-old children, with endoscopically proven GERD [61], and in a follow-up study demonstrated that healing was maintained in 90% of children during a 24-week period [62].

Dexlansoprazole

This R-isomer of lansoprazole has improved bioavailability and metabolism. The active ingredient is released in two phases at different pH values (pH 5.5 in the duodenum and pH of 6.75 in the small intestine about 75%). Consequently, the drug achieves two peak concentrations (within 1–2 h and within 4–5 h), and it can be taken without regard to meal times [63]. Thus, this may offer a therapeutic advantage from a practical standpoint. The pharmacokinetic profile of dexlansoprazole MR (modified release) 30 mg and 60 mg was studied in 36 adolescents and found to be similar to those in healthy adults [64]. Another phase I study in 1–11-year-old children using 15, 30, and 60 mg of dexlansoprazole showed that this medication was well tolerated and provided a mean AUC that is predicted to provide response [65]. A phase II study in pediatrics is currently in progress.

Overall PPIs have been proven more effective than H2RAs at inhibiting acid secretion, healing esophagitis, and reducing symptoms of reflux in older children, adolescents, and adults and should be considered the first-line therapy for moderate to severe symptoms of GERD in children and adolescents. Appropriate administration is important for its effectiveness as low gastric pH in the stomach can render non-enteric-coated drug inactive.

Adverse Events

Side effect profiles of all the different PPIs are fairly comparable. Recently, there has been an increase in reports of severe side effects associated to PPI use, including chronic kidney disease and hypomagnesemia [66, 67], cardiovascular events, bone fractures, osteoporosis [66, 68], gastric cancer [69], and even dementia [70]. However, it is important to note that most of these side effects are uncommon, for the most part have not been reported in children, and still have not been confirmed

by carefully designed prospective studies, making these described associations susceptible to many confounding factors.

Idiosyncratic side effects can occur in up to 14% of children taking PPIs. The most common adverse events reported are headache, diarrhea, constipation, and nausea. These may resolve with a decreased dose or by changing to a different PPI [5]. In a pediatric prospective long-term (2-year) maintenance treatment study with omeprazole, 5 out of 46 patients developed ECL hyperplasia. Side effects in this study included respiratory infections, otitis media, pharyngitis, change in bowel habit, fever, and rhinitis. None of the serious adverse events however were considered causally related to the study drug [71]. A high percentage of children (61%) who receive PPI continuously for up to 10.8 years develop minor degrees of ECL hyperplasia. This histologic finding has no known clinical significance, and children do not appear to develop atrophic gastritis or carcinoid tumors [72]. Another study found parietal cell hyperplasia in up to 16% at follow-up, and gastrin levels were elevated in 73% of children but vitamin B12 remained normal [73].

There is increasing evidence that acid suppression may place susceptible infants and children, particularly those with defective immune system or with indwelling catheters, at risk for the development of lower respiratory tract infections, gastroenteritis, *Clostridium difficile* infection, and small bowel bacterial overgrowth. In premature infants, PPIs may increase the risk of necrotizing enterocolitis and nosocomial infections [25, 74, 75]. This association with infectious diseases may be explained by PPI-induced hypochlorhydria (eliminating the gastric acid barrier), changes in the gut microbiota [76], predisposition to bacterial overgrowth, altered barrier function of the aerodigestive mucosa, attenuation of immune response by direct effects on bacteria, and decreased effectiveness of antibiotics [75].

Thus, as with any other pharmacologic therapy, PPIs are not exempt of side effects, and risk-benefit related to their use should be assessed in individual cases. It is important to remember that GERD can be chronic and relapsing and often requires chronic treatment in order to avoid long-term complications. A 2-year follow-up study in children with esophagitis showed that the majority of the patients required a higher than 1/2 of the healing dose to prevent relapse [71]. Overall, reports in children receiving long-term PPIs have shown that they are efficacious, and side effects are very few and seldom result in discontinuation [73, 77].

References

1. Sakai H, Fujii T, Takeguchi N. Proton-potassium (H(+)/K(+)) ATPases: properties and roles in health and diseases. Met Ions Life Sci. 2016;16:459–83.
2. Schubert ML, Peura DA. Control of gastric acid secretion in health and disease. Gastroenterology. 2008;134(7):1842–60.
3. Schubert ML, Makhlouf GM. Gastrin secretion induced by distention is mediated by gastric cholinergic and vasoactive intestinal peptide neurons in rats. Gastroenterology. 1993;104(3):834–9.
4. Schubert ML, Makhlouf GM. Neural, hormonal, and paracrine regulation of gastrin and acid secretion. Yale J Biol Med. 1992;65(6):553–60. discussion 621-3

5. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
6. Tsou VM, Young RM, Hart MH, Vanderhoof JA. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. Pediatrics. 1991;87(2):148–51.
7. Pivnick EK, Kerr NC, Kaufman RA, Jones DP, Chesney RW. Rickets secondary to phosphate depletion. A sequela of antacid use in infancy. Clin Pediatr (Phila). 1995;34(2):73–8.
8. Carroll MW, Jacobson K. Gastroesophageal reflux disease in children and adolescents: when and how to treat. Paediatr Drugs. 2012;14(2):79–89.
9. Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. Cochrane Database Syst Rev. 2014;11:CD008550.
10. Corvaglia L, Aceti A, Mariani E, De Giorgi M, Capretti MG, Faldella G. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. Aliment Pharmacol Ther. 2011;33(4):466–70.
11. Corvaglia L, Spizzichino M, Zama D, Aceti A, Mariani E, Legnani E, et al. Sodium Alginate (Gaviscon(R)) does not reduce apnoeas related to gastro-oesophageal reflux in preterm infants. Early Hum Dev. 2011;87(12):775–8.
12. Del Buono R, Wenzl TG, Ball G, Keady S, Thomson M. Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. Arch Dis Child. 2005;90(5):460–3.
13. Ummarino D, Miele E, Martinelli M, Scarpato E, Crocetto F, Sciorio E, et al. Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. J Pediatr Gastroenterol Nutr. 2015;60(2):230–5.
14. Reimer C, Lodrup AB, Smith G, Wilkinson J, Bytzer P. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. Aliment Pharmacol Ther. 2016;43(8):899–909.
15. Kwiatek MA, Roman S, Fareeduddin A, Pandolfino JE, Kahrilas PJ. An alginate-antacid formulation (Gaviscon Double Action Liquid) can eliminate or displace the postprandial 'acid pocket' in symptomatic GERD patients. Aliment Pharmacol Ther. 2011;34(1):59–66.
16. De Ruigh A, Roman S, Chen J, Pandolfino JE, Kahrilas PJ. Gaviscon double action liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study. Aliment Pharmacol Ther. 2014;40(5):531–7.
17. Rohof WO, Bennink RJ, Smout AJ, Thomas E, Boeckxstaens GE. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2013;11(12):1585–91. quiz e90
18. Arguelles-Martin F, Gonzalez-Fernandez F, Gentles MG. Sucralfate versus cimetidine in the treatment of reflux esophagitis in children. Am J Med. 1989;86(6A):73–6.
19. Feldman M, Burton ME. Histamine2-receptor antagonists. Standard therapy for acid-peptic diseases. N Engl J Med. 1990;323(24):1672–80.
20. van der Pol R, Langendam M, Benninga M, van Wijk M, Tabbers M. Efficacy and safety of histamine-2 receptor antagonists. JAMA Pediatr. 2014;168(10):947–54.
21. Hyman PE, Garvey TQ 3rd, Abrams CE. Tolerance to intravenous ranitidine. J Pediatr. 1987;110(5):794–6.
22. Wilder-Smith CH, Ernst T, Gennoni M, Zeyen B, Halter F, Merki HS. Tolerance to oral H2-receptor antagonists. Dig Dis Sci. 1990;35(8):976–83.
23. Dutta U, Armstrong D. Novel pharmaceutical approaches to reflux disease. Gastroenterol Clin N Am. 2013;42(1):93–117.
24. Jones AW. Perspectives in drug development and clinical pharmacology: the discovery of histamine H1 and H2 antagonists. Clin Pharmacol Drug Dev. 2016;5(1):5–12.
25. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. Br J Clin Pharmacol. 2015;80(2):200–8.

26. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006;117(5):e817–20.
27. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics. 2012;129(1):e40–5.
28. Litalien C, Theoret Y, Faure C. Pharmacokinetics of proton pump inhibitors in children. Clin Pharmacokinet. 2005;44(5):441–66.
29. Sachs G. Proton pump inhibitors and acid-related diseases. Pharmacotherapy. 1997;17(1):22–37.
30. Ward RM, Kearns GL. Proton pump inhibitors in pediatrics: mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. Paediatr Drugs. 2013;15(2):119–31.
31. Furuta K, Adachi K, Aimi M, Shimura S, Mikami H, Nishimura N, et al. Effect of timing of proton pump inhibitor administration on acid suppression. Digestion. 2016;93(2):111–20.
32. Sachs G, Shin JM, Vagin O, Lambrecht N, Yakubov I, Munson K. The gastric H,K ATPase as a drug target: past, present, and future. J Clin Gastroenterol. 2007;41(Suppl 2):S226–42.
33. Tran A, Rey E, Pons G, Pariente-Khayat A, D'Athis P, Sallerin V, et al. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. Clin Pharmacol Ther. 2002;71(5):359–67.
34. Andersson T, Hassall E, Lundborg P, Shepherd R, Radke M, Marcon M, et al. Pharmacokinetics of orally administered omeprazole in children. International Pediatric Omeprazole Pharmacokinetic Group. Am J Gastroenterol. 2000;95(11):3101–6.
35. Lima JJ, Franciosi JP. Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene-drug pairs. Pharmacogenomics. 2014;15(11):1405–16.
36. Lima JJ, Lang JE, Mougey EB, Blake KB, Gong Y, Holbrook JT, et al. Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. J Pediatr. 2013;163(3):686–91.
37. Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr. 2003;143(2):219–23.
38. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44(1):41–4.
39. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154(4):514–20. e4
40. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. J Pediatr. 2013;163(3):692–8. e1-2
41. Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the treatment of GERD in infants ages 1-11 months. J Pediatr Gastroenterol Nutr. 2012;55(1):14–20.
42. Hussain S, Kierkus J, Hu P, Hoffman D, Lekich R, Sloan S, et al. Safety and efficacy of delayed release rabeprazole in 1- to 11-month-old infants with symptomatic GERD. J Pediatr Gastroenterol Nutr. 2014;58(2):226–36.
43. van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. Pediatrics. 2011;127(5):925–35.
44. Boeckxstaens G, El-Serag HB, Smout AJ, Kahrilas PJ. Symptomatic reflux disease: the present, the past and the future. Gut. 2014;63(7):1185–93.
45. Bjornsson E, Abrahamsson H, Simren M, Mattsson N, Jensen C, Agerforz P, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006;24(6):945–54.
46. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. Aliment Pharmacol Ther. 2005;21(2):149–54.

47. Reimer C, Sondergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology. 2009;137(1):80–7. 7 e1
48. Cucchiara S, Minella R, Iervolino C, Franco MT, Campanozzi A, Franceschi M, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child. 1993;69(6):655–9.
49. Pfefferkorn MD, Croffie JM, Gupta SK, Molleston JP, Eckert GJ, Corkins MR, et al. Nocturnal acid breakthrough in children with reflux esophagitis taking proton pump inhibitors. J Pediatr Gastroenterol Nutr. 2006;42(2):160–5.
50. Hassall E, Israel D, Shepherd R, Radke M, Dalvag A, Skold B, et al. Omeprazole for treatment of chronic erosive esophagitis in children: a multicenter study of efficacy, safety, tolerability and dose requirements. International Pediatric Omeprazole Study Group. J Pediatr. 2000;137(6):800–7.
51. Gunasekaran T, Gupta S, Gremse D, Karol M, Pan WJ, Chiu YL, et al. Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability. J Pediatr Gastroenterol Nutr. 2002;35(Suppl 4):S327–35.
52. Tolia V, Ferry G, Gunasekaran T, Huang B, Keith R, Book L. Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children. J Pediatr Gastroenterol Nutr. 2002;35(Suppl 4):S308–18.
53. Borrelli O, Rea P, de Bueno MM, et al. Efficacy of combined administration of an alginate formulation (Gaviscon) and lansoprazole for children with gastroesophageal reflux disease. Ital J Pediatr. 2002;28(4):304–9.
54. Lind T, Rydberg L, Kyleback A, Jonsson A, Andersson T, Hasselgren G, et al. Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000;14(7):861–7.
55. Gold BD, Gunasekaran T, Tolia V, Wetzler G, Conter H, Traxler B, et al. Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2007;45(5):520–9.
56. Tolia V, Youssef NN, Gilger MA, Traxler B, Illueca M. Esomeprazole for the treatment of erosive esophagitis in children: an international, multicenter, randomized, parallel-group, double-blind (for dose) study. J Pediatr Gastroenterol Nutr. 2015;60(Suppl 1):S24–30.
57. Tolia V, Bishop PR, Tsou VM, Gremse D, Soffer EF, Comer GM, et al. Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5-11 years) with symptomatic gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2006;42(4):384–91.
58. Tsou VM, Baker R, Book L, Hammo AH, Soffer EF, Wang W, et al. Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with gastroesophageal reflux disease (GERD). Clin Pediatr (Phila). 2006;45(8):741–9.
59. Tolman KG, Taubel J, Warrington S, Chiu YL, Pilmer BL, Pan WJ. Comparison of the effects of single and repeated oral doses of lansoprazole and rabeprazole on ambulatory 24-hour intragastric pH in healthy volunteers. Clin Drug Investig. 2006;26(1):21–8.
60. McLeay SC, Green B, Treem W, Thyssen A, Mannaert E, Kimko H. Population pharmacokinetics of rabeprazole and dosing recommendations for the treatment of gastroesophageal reflux disease in children aged 1-11 years. Clin Pharmacokinet. 2014;53(10):943–57.
61. Haddad I, Kierkus J, Tron E, Ulmer A, Hu P, Sloan S, et al. Efficacy and safety of rabeprazole in children (1-11 years) with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2013;57(6):798–807.
62. Haddad I, Kierkus J, Tron E, Ulmer A, Hu P, Silber S, et al. Maintenance of efficacy and safety of rabeprazole in children with endoscopically proven GERD. J Pediatr Gastroenterol Nutr. 2014;58(4):510–7.
63. Skrzydlo-Radomanska B, Radwan P. Dexlansoprazole – a new – generation proton pump inhibitor. Prz Gastroenterol. 2015;10(4):191–6.

64. Kukulka M, Wu J, Perez MC. Pharmacokinetics and safety of dexlansoprazole MR in adolescents with symptomatic GERD. J Pediatr Gastroenterol Nutr. 2012;54(1):41–7.
65. Kukulka M, Nudurupati S, Perez MC. Pharmacokinetics and safety of dexlansoprazole MR in pediatric patients with symptomatic gastroesophageal reflux disease. Clin Exp Gastroenterol. 2014;7:461–71.
66. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. JAMA Intern Med. 2016;176(2):172–4.
67. Nand B, Bhagat M. Serious and commonly overlooked side effect of prolonged use of PPI. Am J Med. 2014;127(9):e5.
68. Arj A, Razavi Zade M, Yavari M, Akbari H, Zamani B, Asemi Z. Proton pump inhibitors use and change in bone mineral density. Int J Rheum Dis. 2016;19(9):864–8.
69. Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of proton pump inhibitors and risks of fundic gland polyps and gastric cancer: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14(12):1706–19.
70. Gomm W, von Holt K, Thome F, Broich K, Maier W, Fink A, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol. 2016;73(4):410–6.
71. Hassall E, Shepherd R, Koletzko S, Radke M, Henderson C, Lundborg P. Long-term maintenance treatment with omeprazole in children with healed erosive oesophagitis: a prospective study. Aliment Pharmacol Ther. 2012;35(3):368–79.
72. Hassall E, Owen D, Kerr W, Sturby T, Richardson P, El-Serag H. Gastric histology in children treated with proton pump inhibitors long term, with emphasis on enterochromaffin cell-like hyperplasia. Aliment Pharmacol Ther. 2011;33(7):829–36.
73. Tolia V, Boyer K. Long-term proton pump inhibitor use in children: a retrospective review of safety. Dig Dis Sci. 2008;53(2):385–93.
74. Freedberg DE, Lamouse-Smith ES, Lightdale JR, Jin Z, Yang YX, Abrams JA. Use of acid suppression medication is associated with risk for C. difficile infection in infants and children: a population-based study. Clin Infect Dis. 2015;61(6):912–7.
75. Stark CM, Nylund CM. Side effects and complications of proton pump inhibitors: a pediatric perspective. J Pediatr. 2016;168:16–22.
76. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut. 2016;65(5):749–56.
77. Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. J Pediatr. 2007;150(3):262–7. 7 e1

Gastroesophageal Reflux and Surgery

25

Juan A. Tovar

Abstract

Gastroesophageal reflux (GER) is a complex phenomenon involving always a failure of the anti-reflux barrier and often other components like dysmotility, alkaline refluxate, or delayed gastric emptying. Acid exposure of the esophageal mucosa can be fought with PPI, but no effective medication for alkaline reflux or dysmotility is available. The anti-reflux barrier can be surgically refashioned by elongation of the intra-abdominal esophagus and accentuation of the angle of His (gastropexy) accompanied by creation of a half-valve (Thal and Boix-Ochoa operations) or incomplete (Toupet operation) or complete wraparound using the fundus (Nissen operation). All these operations can be performed laparoscopically. Sometimes, the anti-reflux procedure is accompanied by a gastrostomy for nutritional purposes, and very rarely, a gastric outlet procedure is necessary for facilitating gastric emptying.

All operations may have complications like wrap failure, gas bloat, dumping, and even mortality. In some particular indications in which the various pathogenic factors persist after operation (like in neurologic, respiratory, esophageal atresia, or diaphragmatic hernia patients), the proportion of failures is considerable.

When GER cannot be controlled by anti-reflux surgery, esophagogastric dissociation or feeding jejunostomy with gastrostomy may help.

Surgery is the only effective way of addressing barrier failure, but it would be as naïf to pretend that it is always the solution as to trust solely long-term acid suppression medication. A reasonable combination of both approaches is certainly the most appropriate way of treating GER.

J.A. Tovar
Department of Pediatrics, Universidad Autonoma de Madrid, Madrid, Spain

Department of Pediatric Surgery, Hospital Universitario La Paz, Madrid, Spain
e-mail: juan.tovar@salud.madrid.org

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_25

Keywords
Gastroesophageal reflux • Surgery • Fundoplication • Boerema • Nissen • Thal-Ashcraft • Boix-Ochoa • Toupet • Esophagogastric dissociation • Jejunostomy • Gastrostomy • Gas bloat • Dumping • Dysphagia

Introduction

Gastroesophageal reflux (GER) is a complex phenomenon in which gastric contents ascends into the esophagus with the consequent risks of mucosal damage and/or aspiration into the airway. When this phenomenon happens too often or for too long periods of time, it becomes pathologic and is then designated gastroesophageal reflux disease (GERD).

GER involves always a failure of the anti-reflux barrier, and it is tempting to pretend that reconstructing it should adequately deal with this frequent condition. Unfortunately, this is not always true because others factors, like pressure driving forces, gastric secretion, or esophageal and gastric motility, play a role that cannot be addressed by operations. However, it remains that anti-reflux procedures can create a long-lasting, competent anti-reflux barrier and that, therefore, surgery offers important tools for the treatment of GERD overall.

The purpose of the present chapter is to recall the fundamentals of the surgical anti-reflux techniques, to propose a set of indications, and to point out its complications and limitations.

Components of the Anti-reflux Barrier

In the normal individual, a permanent gastroesophageal pressure gradient favors GER. The esophagus is located in the thorax, where negative pressures predominate during inspiration, whereas the stomach is within the abdomen where positive pressures are permanent. Gastric peristalsis further reinforces this gradient. Since the esophageal mucosa is not prepared for acid exposure, a tight anti-reflux barrier is interposed between the stomach and the esophagus. The components of this barrier are the following: (1) the lower esophageal sphincter (LES) that results from the permanent contraction of the distal smooth circular muscle fibers of the esophagus that extend into the stomach where they are arranged as "sling" and "clasp" fibers that, respectively, straddle the *incisura angularis* and extend from the lesser curvature into both faces of the organ [1]. These fibers act as an "internal sphincter" that maintains a permanent status of contraction and creates a "high-pressure zone" (HPZ) at the gastroesophageal junction while maintaining an acute angle of His. The LES relaxes during deglutition for allowing the passage of the bolus. (2) Superimposed to the LES, the striated muscle fibers of the diaphragmatic hiatus form a crural sling that contracts rhythmically during

each inspiratory movement. These contractions displace the *incisura angularis* downward accentuating its angle and lengthening the intra-abdominal esophagus. The diaphragm acts as an "external sphincter" that complements the participation of the LES in the HPZ. (3) The intra-abdominal esophagus is permanently compressed by pressure that precludes GER. (4) Finally, the gastric fundus also exerts some pressure on the intra-abdominal portion of the esophagus.

These mechanisms fight efficiently the GER driving forces, but even in normal individuals, they often fail, particularly after meals, and for this reason there are additional mechanisms that constitute a "second anti-reflux barrier": (1) the esophageal peristalsis that clears the esophagus after deglutition and reflux, (2) the alkaline secretions of salivary and esophageal glands that buffer the acid refluxed into the esophagus, and (3) the permanent contraction of the upper esophageal striated sphincter that only relaxes during deglutition and therefore protects the airway from aspiration of pharyngeal contents.

Why the Anti-reflux Barrier Fails

The complexity of the abovementioned mechanisms explains the multiple causes of failure that can lead to GER:

Changes in the GER driving forces contribute to this phenomenon: excessive thoracic negative pressures due to airway stenosis or permanent increases of the positive abdominal pressures (in adults, pregnancy is a good example of this) indeed facilitate the overriding of the barrier.

Anatomic changes like displacement of the gastroesophageal junction upward (hiatal hernia) weaken the barrier. Relaxation or distortion of the phreno-esophageal attachments facilitate shortening of the intra-abdominal esophagus and inactivate this component of the barrier. However, only a few refluxers have actually hiatal hernia, and GER can occur even with only minor or no displacements of the junction.

Abolition of the angle of His by shortening of the esophagus and/or reduction of the size of the gastric fundus inactivates the effects of compression of the intra-abdominal esophagus.

Permanent decreases of the tone of the LES may play a role in the phenomenon of GER, but GERD has been demonstrated also in individuals with normal LES pressures. Refined prolonged micro-manometric studies and, more recently, impedance measurements demonstrated that refluxing patients suffer transient relaxations of the LES not related to deglutition and that this is probably the cause of the disease at all ages [2–4]. The mechanisms of these relaxations are not well known, and their control by medication is not possible so far.

Finally, reflux is facilitated by permanently increased intragastric pressure. Delayed gastric emptying, hypertrophic pyloric stenosis, malrotation, or any cause of incomplete obstruction below the duodenum facilitates GER, and these factors must be taken into account whenever anti-reflux surgery is considered.

Aims of Anti-reflux Surgery

Surgery can repair some of the insufficiencies of the barrier, but it cannot act on several other functional components like pressure gradients and dysmotility. The success of operations will therefore require the integrity of the valve but may be limited by the persistence of these other components. Anti-reflux procedures cannot aim at recreating the exquisite barrier mechanisms, but they replace them by relocating the junction below the diaphragm, by tightening the hiatal enlargement when present, by replacing a segment of the distal esophagus into the abdomen, and by accentuating the angle of His. Most techniques add some form of valve using the gastric fundus to create a partial or complete wrap around the esophagus.

Obviously, surgery cannot influence the occurrence of transient relaxations of the LES and modify acid secretion or dysmotility, but if it creates a competent barrier, abnormal esophageal mucosal exposure will be precluded. In selected cases in which delayed gastric emptying plays a demonstrable role in the disease, some form of pyloric weakening can also help fighting GER.

History of Anti-reflux Surgery

Until manometry of the esophagus demonstrated the presence of a high-pressure zone at its lower end, the causes for reflux were sought in the anatomic anomalies of the gastroesophageal junction. Hiatal hernia was relatively frequent in adults with GER, and the operations used at that time were directed to the reconstruction of the anatomic "normality." Allison proposed in 1951 an operation consisting of freeing the terminal esophagus from the thorax, replacing it below the diaphragm and fixing the junction radially to the hiatus [5].

Recognition of the failure of the sphincter itself and of the loss of compression of the intra-abdominal esophagus by ascent of the junction invited to try other procedures aimed at elongating this part of the esophagus while accentuating the gastroesophageal angle of His. These aims were achieved either by fixation of the anterior wall of the stomach to the abdominal wall (gastropexy [6]) or by anchoring the junction posteriorly to the previously sutured diaphragmatic crura [7].

The use of the fundal chamber to add some compression on the previously mobilized lower esophagus relocated below the diaphragm evolved from the Thal hemi-fundoplication [8] to the Belsey Mark IV operation in which the fundus was sutured to the esophagus and the valve was fixed in a proper position [9].

There were other more radical approaches that focused on the completion of an effective valve interposed between the esophagus and the stomach. Rudolph Nissen used fundoplication for covering and protecting the esophagogastric suture after resecting a peptic stenosis in 1937. Esophagitis disappeared in his patient and he decided to try the same procedure for GERD since 1956 [10]. This operation became the more common procedure used to treat GERD.

Toupet in 1963 proposed an incomplete posterior hemi-fundoplication [11] potentially less obstructive and suitable for patients with dysmotility.

In cases with short esophagus (brachyesophagus) and obtuse angle of His with small fundus, Collis proposed to create such angle by incising longitudinally the eso-gastric junction aiming at lengthening the esophagus and at the same time creating a sort of fundus that could eventually be used for a plication [12].

Some other procedures have been tried: Angelchik used a crescent-shaped silicone prosthesis around the lower esophagus [13]. Purely esophagoscopic intraluminal reinforcement of the gastroesophageal barrier by plication of the cardial area has been tried in adults [14]. Another intraluminal technique is the application of radiofrequency to the distal esophagus [15]. This Stretta device releases thermic energy to the mucosa, submucosa, and muscle layers inducing burns and edema that would contribute to create an anti-reflux barrier. Finally, another possible method is the submucosal implantation of collagen [16] or other nondegradable, biocompatible polymers like those currently used for the treatment of vesicoureteral reflux at the lower esophageal or cardial levels.

Laparoscopy became the preferred approach for anti-reflux operations shortly after it was introduced in France in the early 1990s [17–19].

The history of surgical treatment of GERD in children followed approximately the same pattern. However, the limitations of the application of diagnostic tests in children accounted for some delay in its development. Since the 1960s, anti-reflux surgery was relatively common in European children [20–23], whereas it was practically unknown in the American continent. Only after introduction of extended pH monitoring in pediatrics the disease gained acknowledgement in the United States and other countries, and its surgical treatment took progressively more place until becoming a more frequent treatment than it ever was in Europe [24–27].

Complications of anti-reflux surgery, particularly in neurologically impaired children, led to leading pediatric gastroenterologists to be very restrictive in indicating anti-reflux surgery [28, 29], and these restrictions were included in their collegial guidelines [30].

The introduction in the 1990s of laparoscopic anti-reflux operations in children boosted the number of surgical indications because they are more easily acceptable by both patients' families and pediatricians in spite of being identical to open operations [31–35]. Nowadays, the vast majority of anti-reflux operations are performed laparoscopically.

Indications for Anti-reflux Operations

The multiple factors involved in the phenomenon of GER make the indications for the different treatments a matter of debate. It has to be acknowledged that little can be done to enhance the salivary and esophageal gland alkaline secretions, that the efficacy of prokinetic medications was certainly overrated for many years [36], and that the potential harm caused by alkaline reflux cannot be fought. Therefore, the only weapons against GERD are long-term reduction of acid secretion and surgical reconstruction of an anti-reflux barrier.

This chapter is devoted to the latter, but a reflection on the limitations of acid control alone is in order prior to proposing surgical indications. For years, when the

diagnosis of GERD was based on prolonged pH monitoring, the focus was on the harm caused by acid refluxate, ignoring the evidence established in adults of the concurrent participation of alkaline reflux in the disease [37, 38]. Some reports alerted on the possible participation of nonacidic refluxate in pediatric GERD [39, 40], but only after the introduction of extended simultaneous impedance and pH-metric recordings it was shown that children, like adults, undergo many episodes of "nonacidic" or "weakly acidic" (perhaps alkaline) reflux [41]. On the other hand, it should be acknowledged that the refluxate might cause harm by other ways than damaging the mucosa (particularly respiratory pathology). The strong reliance of the pediatric world on chronic administration of PPIs should be somewhat tempered in a number of cases in which the potential harm caused by acid is only a part of the pathogenesis and in which a tendency to spontaneous improvement is not to be expected. The indications for anti-reflux surgery correspond precisely to these patients.

With some limitations, surgery can offer effective treatment in patients with GERD. However, it would be as naïf to pretend that reconstructing a competent barrier is the final solution as to maintain that chronic administration of PPIs can deal with all the problems. Anti-reflux operations can only offer a new barrier (always less perfect than the original), but they cannot influence either dysmotility or alkaline reflux. On top of that, if other factors contribute to the original failure of the barrier, they will remain active after the operation, and this conditions its long-term performance. A reasonable proposal for indications would be the following.

Failure of a Well-Conducted Medical Treatment

GERD in children cannot become a chronic disease limiting forever the physical activity and involving administration of PPIs for life. Whereas many patients are relieved of their symptoms after a reasonable time of well-conducted treatment, others remain symptomatic and deserve a trial of other alternatives. The establishment of time limits for accepting that the medical treatment has failed is a personal, scarcely scientific matter. However, it should be kept in mind that well-treated children or adolescents who have to restrict their physical activity and take medication for long time due to GER symptoms could certainly benefit from an operation. Patients with comorbidities that condition or participate in the pathogenesis of GERD are particular cases that will be discussed in more detail herewith.

Neurologically Impaired (NI) Patients

Children with brain damage due to congenital or acquired conditions (particularly cerebral palsy) have often GERD because the neural control of the esophageal sphincters is deficient in them. There is experimental [42] and clinical [43] evidence of LES pressure weakening after brain injury. The contribution of non-deglutory transient LES relaxations to GER in NI patients is still unclear [44, 45]. In addition, these children are often in recumbent position; they have dysautonomic regulation

of digestive motility, frequent respiratory problems, spasticity, and constipation that increase permanently abdominal pressure; and they often suffer scoliosis that distorts the hiatal area or drooling that reduces the buffering role of saliva. In addition, many have episodes of alkaline reflux that last for long time [46]. For all these reasons, acid-suppressor treatment that indeed helps to alleviate esophagitis, peptic ulcers, and pain is obviously insufficient in many of these patients.

NI patients constitute one of the more frequent indications for anti-reflux operations in many series [27, 47] and are among the indications recommended by both the NASPGHAN and the ESPGHAN [30].

These children are so difficult to feed that a gastrostomy may be necessary for nutritional purposes, and an anti-reflux procedure has been performed simultaneously in many cases. This has generated much debate because probably there is no reason for using fundoplication in a "prophylactic" way. Conversely, it is reasonable to add a gastrostomy to a well-indicated fundoplication when feeding problems interfere with nutrition and/or further burden the task of parents or caretakers. In this group of children, it should be born in mind that all factors facilitating GER in them will remain active for life and that this might limit the success of the treatment.

Reflux with Respiratory Symptoms

GER may cause respiratory symptoms because of direct aspiration of the refluxate into the airway, bronchoconstrictive reflexes consecutive to acidification of the esophagus, inflammation of the larynx, and/or sensitization of the respiratory tract to allergens after aspiration. These circumstances either increase the positive intra-abdominal pressures or reinforce the negative thoracic pressures, thus accentuating the GER driving forces. It is difficult to determine whether respiratory disease causes GER or conversely, if GER accounts for the respiratory disease. This issue generated huge amounts of inconclusive studies.

GER is particularly relevant in prematures and newborns with bronchopulmonary conditions. Delayed maturation, recumbence, upper airway obstruction, respiratory assistance with positive airway pressure [48, 49], xanthine medication [50], nasogastric tubes [51], and probably other reasons account for this as well as micro-aspiration or esophago-bronchial reflexes [52]. Weaning off ventilator may be impossible until GER ceases, and bronchopulmonary dysplasia, that has also other origins, is aggravated by GER [53]. In some of these situations, anti-reflux surgery can be indicated.

Apparent life-threatening events (ALTEs), like pauses of apnea or cardiorespiratory arrests, have been related to GER. Again it is difficult to demonstrate this relationship: pH tracings, polysomnographic recordings [54, 55], and MII coupled with pH recordings [41, 56] clarified only in part this issue. Nonacidic reflux episodes are frequent at this age [57], and ALTE could be related to both acidic and nonacidic reflux [58] although this interpretation is widely contradicted [59–61]. It remains that, since ALTE may be lethal, it is wise to offer anti-reflux operations to a very

limited number of patients in whom temporal coincidence of apnea and GER is evidenced.

Reconstruction of a functional anti-reflux barrier would probably better fight GER in respiratory refluxers than chronic suppression of acid secretion that is obviously a secondary aim. If aspiration is demonstrated or very likely (repeated atelectasis/pneumonia in children with GER, evidence of lipid-laden macrophages, or pepsin in bronchoalveolar lavage), anti-reflux surgery should be offered. This is particularly so in individuals in which extended pH monitoring demonstrated many reflux episodes during the day and long nocturnal periods of esophageal acidification [62]. Good results on the respiratory symptoms have been shown in these cases [63].

It is a more difficult task to propose indications for anti-reflux surgery in patients with bronchoconstrictive, atopic or not, asthmatic disease in which acid secretion suppressants do not suffice [64]. Modest results of surgery in these cases have been reported [65, 66], but on the other hand, persistence of severe crises in spite of all treatments led to accepting surgery as a desperate measure. Interestingly, some reports have shown that although the "asthmatic" episodes do not disappear after fundoplication, their severity declines in terms of number of episodes or medication consumption [67].

Patients Treated for Esophageal Atresia (EA) and Tracheoesophageal Fistula (TEF)

Babies treated successfully for EA-TEF have often GER. This happens for the following reasons: (1) The esophagus is structurally abnormal, and its extrinsic [68] and intrinsic innervations [69, 70] are deficient. (2) The hiatus and the position of the gastroesophageal junction are distorted as a consequence of either the malformation [71] or their repair under tension [72]. Long-gap cases have high incidence of GER [73–75]. (3) Frequent upper airway obstruction due to tracheomalacia or tracheobronchial stenosis. (4) Abnormal innervation and function of the stomach [76]. In this environment, the anti-reflux barrier fails, while the peristaltic pump is scarcely operative. Functional studies repeatedly demonstrated weak propulsive force and decreased lower sphincteric pressure [77–80]. Finally, gastrostomy that facilitates GER [81–83] is occasionally used, particularly in long-gap and in pure EA cases.

EA-TEF patients have often barking cough, repeated atelectasis or pneumonia, and respiratory tract disease that may last for life. High proportions of survivors have restrictive or obstructive respiratory tract diseases (or both) [84]. GER has been demonstrated to account in part for these symptoms.

Recurrent anastomotic stricture refractory to dilatation is probably in part due to a peptic component [85], and it can only be managed after reflux is cured by fundoplication.

In EA-TEF survivors, GER tends to be clinically more expressive in the first months of life [86, 87]. For some authors, it tends to improve over time [88], whereas for others, it aggravates along the years [89]. Esophagitis [79] and Barrett's

esophagus [90, 91] are found in adolescents and adults after repair of EA-TEF, and esophageal cancer has been occasionally reported [92, 93] demonstrating that GER remains a long-standing problem. A recent report shows that EA-TEF survivors have 50-fold higher risk of having esophageal carcinoma than the population at random [94].

Whenever symptomatic GER is shown in EA-TEF patients, active treatment should be undertaken. Prospective assessment of reflux and appropriate postoperative medical treatment have been conducted in EA-TEF survivors with some success [88]. However, surgical correction of reflux is a widely accepted option [95, 96]. It should be recalled that the mechanisms that facilitate GER in EA-TEF patients persist for life and, therefore, that little spontaneous tendency for improvement should be expected.

Patients Treated for Congenital Diaphragmatic Hernia (CDH)

CDH, a posterolateral diaphragmatic defect that permits prenatal herniation of abdominal contents into the thorax, is accompanied by lung hypoplasia with persistent pulmonary hypertension and, often, by other malformations that cause mortality of up to 50% in population-based studies. However, 70–80% of babies survive, and many of them suffer subsequently respiratory tract disease, neurodevelopmental deficiencies, hearing loss, and GERD. The association between CDH and GERD was pointed out years ago [97] after a dysfunctional, dilated esophagus was described in some babies with CDH [98]. GERD was found more frequently in patients requiring ECMO [99, 100] and in those with large hernias [101]. It persists beyond childhood, causes problems in up to 54% of cases [89, 102], and produces esophagitis in more than 50% of patients and Barrett's esophagus in some of them [103].

There are several explanations for this: (1) The hiatus is under tension after closure of the diaphragmatic orifice and/or by its replacement by a prosthetic patch. (2) Esophageal extrinsic and intrinsic innervations are abnormal, as shown in animals [104, 105] and human autopsies [106], and, consequently, the gastroesophageal barrier and the peristaltic pump might fail. (3) The small lung, the flattened diaphragm [107], and the tight abdominal closure exaggerate the GER driving forces [108]. (4) Gastric emptying may be delayed [101] or the small bowel partially obstructed due to non-rotation or malrotation. (5) Gastrostomy is sometimes used for overcoming the nutritional difficulties that these patients experience postoperatively [109].

GER is frequent during the first year after CDH repair [110, 111], but it tends to taper off in the ensuing years [89] unless chronic respiratory disease and/or neurologic impairment maintains it. Recent pH and manometric studies show that only a small proportion of patients maintain sphincteric and peristaltic dysfunctions over the years [112]. However, the severity of the respiratory disease in CDH patients and the difficulties for feeding make simultaneous performance of gastrostomy and fundoplication in early infancy, a fully justified and relatively common indication.

Patients Treated for Anterior Abdominal Wall Defects (AAWDs)

AAWDs are developmental anomalies in which the body wall is incomplete or abnormal. In omphalocele, there is a periumbilical wall defect covered by a gelatinous sac that contains the bowel and sometimes the liver. In gastroschisis or laparoschisis, there is an orifice located on the right side of the umbilical stalk that allows the bowel, and sometimes other organs, to eviscerate into the amniotic fluid. In both cases, the abdominal space is reduced at birth, and surgical reintegration of the viscera is invariably accompanied by increased abdominal pressure [113]. This, together with the difficulties for reestablishing intestinal transit after the operation and with the constant presence of non-rotation or malrotation, creates a pressure environment that facilitates GER and may even produce hiatal hernia [114]. The anterior location of the hiatus itself may also interfere with the anti-reflux mechanisms. Most often GER is a transient situation in this context that tapers off when abdominal content reaccomodates itself into a progressively enlarged abdominal space, but in a number of cases, this does not happen. GER often accompanied by esophagitis has been found in 43% of patients with omphalocele and in 16% of those with gastroschisis [115]. Once again, some patients require gastrostomies for overcoming the first and sometimes long postoperative phase of gastrointestinal dysfunction, and this may either aggravate GER. Anti-reflux surgery may be necessary in such cases.

Anti-reflux Operations Used in Children

Gastropexy

Anchoring the anterior face of the stomach to the abdominal wall is a relatively easy way of lengthening the intra-abdominal esophagus while accentuating the gastroesophageal angle of His. Gastropexy has been performed in children as originally proposed by Boerema. Several nonabsorbable stitches are placed under tension between the lesser curvature of the stomach and the right rim of a midline incision. This operation was recommended for patients without comorbidities [116]. The functional aspects of gastropexies have been less studied than those of other techniques, but it was shown that the manometric effects did not match those of fundoplication [117]. To our knowledge, no posterior, Hill-type gastropexies have been used in children although some of their elements were incorporated in the partial fundoplications.

Nissen Fundoplication

The complete fundoplication involves full mobilization of the distal esophagus including intra-mediastinal dissection, freeing the upper part of the greater curvature of the stomach by dividing the short gastric vessels, tightening the hiatus by

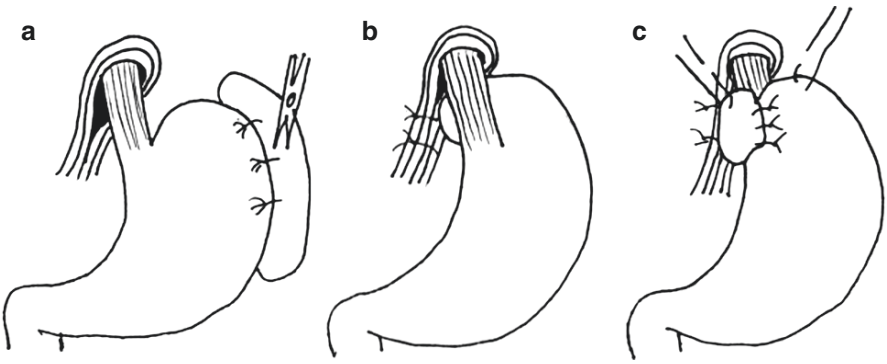


Fig. 25.1 Nissen fundoplication consists of dissection of the lower esophagus and the hiatus with division of the short gastric vessels (**a**), suturing the crura (**b**) and passing the posterior face of the fundus behind the esophagus to suture it to the anterior face confectioning a 360° wrap (**c**)

suturing the diaphragmatic crura, and confectioning a floppy gastric wrap by passing the posterior face of the fundus behind the esophagus and suturing it to the anterior face with nonabsorbable sutures. The wrap is constructed over a large bougie located within the lumen in order to prevent any excessive tightening [118]. At the end of the operation, the wrap is anchored to the diaphragm (Fig. 25.1).

Nissen fundoplication satisfies all aims of anti-reflux operations since it reestablishes a long intra-abdominal esophagus, accentuates the angle of His, and creates a 360° valve particularly effective when the stomach is full and the risks of reflux are greater. Its efficacy was attested by postoperative increase in the LES pressure and reduced acid exposure [26, 117, 119]. However, the full wrap involves some changes that explain why the opponents to this technique found it "excessive" or "non-physiologic." A too tight or too long wrap might compress the lower esophagus, causing partial obstruction and dysphagia. However, unchanged motility has been demonstrated after fundoplication by functional studies [120]. Gastric compliance is temporarily reduced because the fundus is used for confectioning the wrap, and it causes early satiety or accelerates gastric emptying contributing to dumping. Finally, a competent wrap interferes with burping and eventually with vomiting, and this may cause gas bloat and various degrees of discomfort, particularly in patients with retching [121] in which fundoplication could be avoided [122]. These inconveniences are usually transient, and although the inability to vomit can be permanent, most patients do not experience dysphagia, gas bloat, or dumping or get rid of them after some time and are able to take normal meals.

It remains that the anti-reflux effect of Nissen fundoplication is the more effective and stands better the passage of time than other techniques [123], and this explains why it has been the more used one in all groups of children with GER [27, 31, 34, 124–132]. NF has been extensively studied with physiologic techniques of assessment. The LESP is reestablished, reflux is prevented, and, eventually, it has been shown that extemporaneous relaxations of the sphincter became less frequent [133].

Anterior Fundoplications

In these operations the focuses are again replacing the junction below the diaphragm and moving the fundus in front of the esophagus, thus lengthening its intra-abdominal segment while accentuating the angle of His and creating an anterior hemi-valve.

The Thal-Ashcraft procedure involved the suture of the fundus to the hiatal muscular rim to achieve such goals (Fig. 25.2). It has been widely used with good results [25, 134, 135] even in NI, respiratory [67, 136], and EA-TEF patients [32, 137, 138].

The Boix-Ochoa procedure consisted of mobilization of the distal esophagus, closure of the crura with several stitches, anchoring the esophagus to the hiatal rim and, after suturing its left border to the fundus, creation of an anterior hemi-valve in front of the esophagus by suturing it to the right border of the esophagus. The operation is completed after anchoring the hemi-valve to the diaphragm (Fig. 25.3).

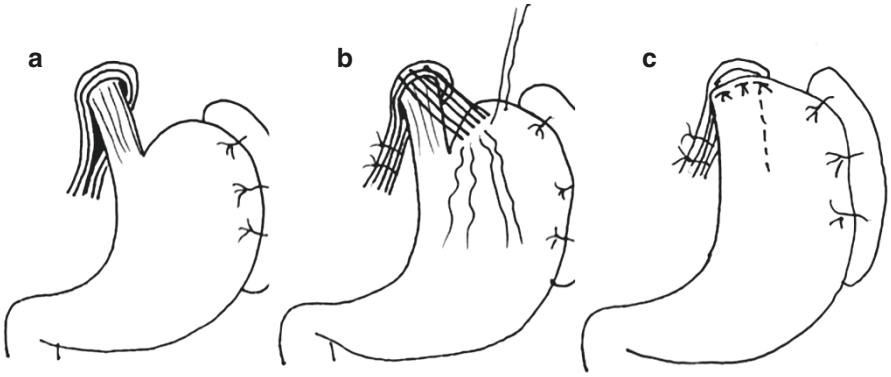


Fig. 25.2 Thal-Ashcraft anterior fundoplication involves dissection of the lower esophagus and hiatus (without division of the short vessels) (**a**), closure of the hiatus and suture of the anterior face of the fundus to the muscular rim of the hiatus to form an anterior hemi-valve (**b** and **c**)

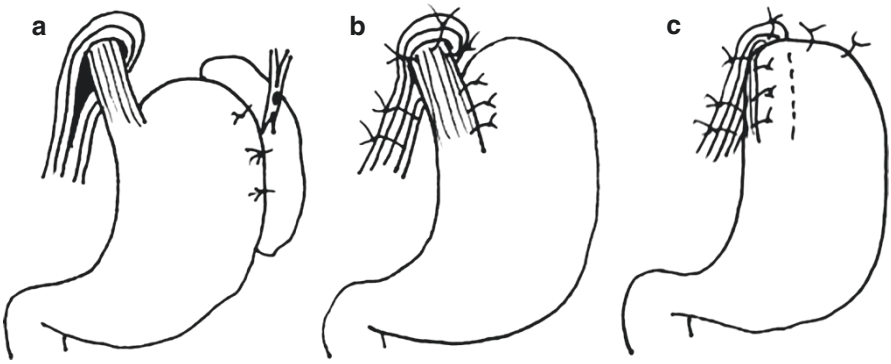


Fig. 25.3 Boix-Ochoa anterior fundoplication involves esophageal and hiatal dissections with division of the short vessels (**a**), closure of the hiatus and anchoring of the esophagus to the hiatal rim while suturing the stomach to the esophagus on the left to accentuate the angle of His (**b**). Finally, the anterior face of the fundus is reclined to the right to suture it to the esophagus achieving an anterior hemi-valve (**c**)

Its supporters pretended that such arrangements were more "physiologic" than a complete fundoplication and that the operation actually reestablished and enhanced mechanisms that are present in normal children [22]. This technique has been applied with good results to regular refluxers, NI, EA-TEF, and CDH patients [139–141]. However, it should be noticed that since de popularization of the laparoscopic Nissen, Thal and Boix-Ochoa procedures lost some of their supporters, probably because this approach is not only more suitable for the classic Nissen but also because after all, a full wrap is not so bad as the proposers of anterior fundoplication pretended.

Posterior Fundoplication (Toupet)

This procedure has been used in all groups of children with GER [142–146]. It is in fact an incomplete 270° Nissen fundoplication in which the fundal wrap is passed behind the esophagus and sutured to its right border, whereas the anterior face of the fundus is sutured to the esophagus in its left border (Fig. 25.4). The wrap again lengthens the intra-abdominal esophagus, closes the angle of His, and further protects the reconstructed hiatal orifice by interposing the plication. Toupet operation is supposed to make burping easier and to have reduced risks of gas-bloat syndrome. This technique is particularly attractive in patients with small fundus like those previously operated for esophageal atresia.

Collis Gastroplasty, "Uncut Collis," and Collis-Nissen

In cases of short esophagus and/or when the angle of His is obtuse or inexistent, Collis proposed to staple and divide the junction along the axis of the esophagus on its left border. This lengthens the esophagus and recreates a sort of angle of His

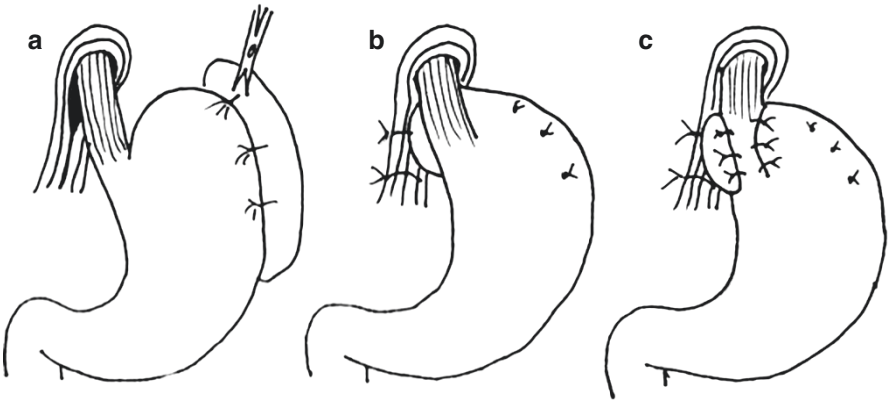


Fig. 25.4 Toupet's operation is identical in its first steps to Nissen operation (**a** and **b**) except for the completion of the wrap that in this case is a posterior 270° one (**c**) instead of a complete 360° one

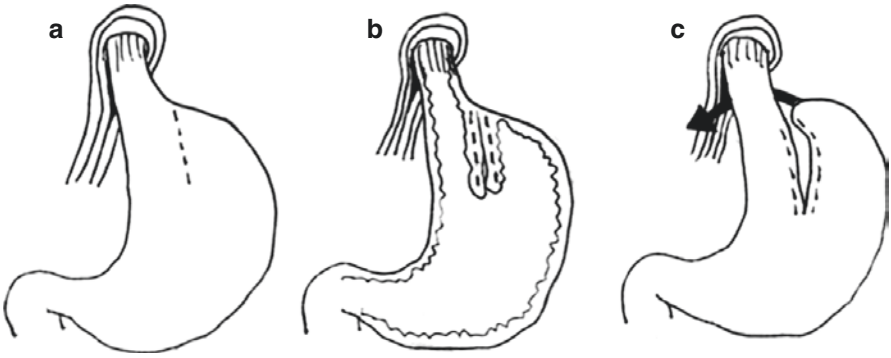


Fig. 25.5 Collis gastroplasty attempts at elongating a short esophagus by stapling only (uncut Collis) or stapling and dividing the gastroesophageal junction in the direction of the esophagus (**a**). The new esophagus is obviously lined by gastric mucosa (**b**) but now a fundus is obtained that allows plication (Collis-Nissen) (**c**)

(Fig. 25.5). In fact, although pictorially convincing, this procedure creates a neo-esophageal tube that is lined by gastric, secreting mucosa. Thus, if the neo-fundus so arranged is used for confectioning a wrap around the "esophagus," secretory mucosa will always be above it.

There are so many pediatric reports on this operation [147], but postoperative functional studies showed that at least in four cases of refluxing EA-TEF patients, the functional results were good [148].

A recent modification of Collis procedure has been used in children. It consists in stapling the junction in the above-described fashion but without cutting it (uncut Collis). In this way, an esophageal tube and an acute angle of His are created (Fig. 25.5). The operation is relatively easy, and the limited results reported so far were satisfactory [149] although breakdown of the staples has been reported [150].

Other Anti-Reflux Procedures

Endoluminal gastroplication was introduced in children after it had been used by some in adults [151]. It requires bulky intraluminal equipment that makes performance difficult in small size esophagus. This explains why there were only a few adolescents treated in this manner [152].

Endoluminal application of radiofrequency to the lower esophagus (Stretta procedure) has been another alternative in adults, but the results have not been demonstrated in well-designed studies [153], and it has been only occasionally used in children [154, 155].

Esophagogastric disconnection or dissociation is a radical procedure that may be indicated when GERD is severe, like in NI children, and when repeated anti-reflux operations fail [156, 157]. It consists of dividing the lower esophagus and anastomosing it to a jejunal loop arranged in a Roux-en-Y manner (the jejunum is sectioned 40 cm below the duodenojejunal angle and mobilized; it is then

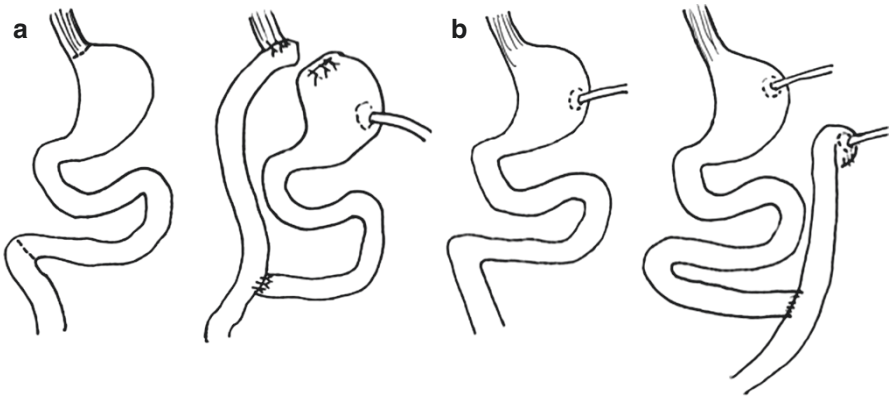


Fig. 25.6 (**a**) Esophagogastric dissociation or disconnection consists of dividing the distal esophagus and anastomosing it to a Roux-en-Y jejunal loop. Gastrostomy allows gastric decompression and supplemental feeding while esophago-jejunal intake is possible without reflux. (**b**) Feeding jejunostomy allows management of severely retarded NI children, while gastrostomy allows gastric venting and reflux control

anastomosed end-to side to the jejunum and end-to-end or end-to-side to the esophagus (Fig. 25.6a)). GER becomes impossible because the gastric acid (and eventually the biliopancreatic juice) is diverted far from the esophago-jejunal junction. A gastrostomy is left permanently in place to complete oral nutrition and to vent the stomach if necessary. This operation is rarely used, but it has been extremely helpful in some difficult cases [158–160]. Interestingly, after some time, a number of these patients are able to take a reasonably normal oral diet.

Another less radical procedure has been used by some authors [161–163] in neurologic patients in which the anti-reflux operation fails: a permanent gastrostomy (often previously established) allows decompression of the stomach and reduction of the persisting GER, while a permanent feeding jejunostomy permits adequate enteral feeding (Fig. 25.6b).

Complementary Procedures

Gastrostomy and pyloroplasty/pyloromyotomy are sometimes associated with anti-reflux techniques.

Gastrostomy is extremely useful in patients that cannot be properly fed per os for various reasons. NI children are particularly benefited by this additional access to the stomach. The improvement of nutrition can even reduce GER [164]. On the other hand, the time and effort spent by parents and caregivers is reduced [165]. Some babies previously operated upon for esophageal atresia or for congenital diaphragmatic hernia also benefit from gastrostomy because they cannot eat properly by mouth due to dysphagia, dyspnea, or other respiratory problems. Experimental and clinical evidence has shown that the operation itself facilitates GER, and this has invited to offer it simultaneously with fundoplication. This is probably wise

when GER is a problem, but it is probably excessive particularly in NI patients except when they have severe GERD [166–169]. On the other hand, gastrostomy acts as a gastropexy and could help to fight GER [170, 171].

The contribution of delayed gastric emptying and surgical procedures on the gastric outlet aimed at treating this are a matter of discussion [172–175]. There is no doubt that antro-pyloric or infra-pyloric obstruction facilitates reflux [121, 176], but in their absence, it is difficult to demonstrate that gastric emptying is delayed in regular GER. Isotope studies tend to show that this happens in some patients, but it should be taken into account that reflux itself delays emptying of the refluxed fluid and that any test should reveal some retention of the isotope in the stomach. The problem is that there are no universally accepted isotope studies for children. Liquid and solid tests have been used [177], but the fact is that there are no reliable normal values for children and that the routine use of these tests is not widespread. Delayed gastric emptying can be suspected in children with GER by some indirect signs: the stomach may be enlarged (a rare event in refluxers) or double gastroesophageal pH monitoring may show prolonged postprandial neutralization of gastric juice after feeds revealing delayed emptying [46]. Recent studies with modern methods failed to show any significant contribution of delayed gastric emptying to GERD in children [178].

The fact is that for years, particularly in Europe, but also in America, extramucosal pyloromyotomy [179], pyloroplasty [180], or antroplasty [181] were used as an addition to anti-reflux operations. There has never been convincing evidence of the pertinence of such addition, and it is not surprising for similar results being reported by groups offering fundoplication with or without gastric outlet procedures [182]. Moreover, since laparoscopic fundoplication became the preferred approach, these procedures have been practically abandoned without impact on the results.

On the other hand, pyloroplasty could facilitate duodeno-gastric alkaline reflux that may be harmful for the stomach in the long term even if the esophagus is protected by a fundoplication. This effect has been shown to be limited [183].

In summary, gastric emptying procedures cannot be recommended except in the rare cases in which this is a demonstrable pathogenic component of the GERD.

Complications of Anti-reflux Procedures

All operations, including anti-reflux procedures, can have complications, and this has to be taken into account before indicating them. Leaving aside the surgical complications, like wound infection, incisional hernia, adhesive obstruction, or pneumothorax, which will not be addressed in this chapter, the main complications can be summarized as follows:

1. *Wrap failure*: The surgically confectioned valve may mechanically fail. This happens mainly by disruption of the sutures that anchor the wrap to the diaphragm most times behind the esophagus. Postoperative cough or retching may facilitate disruption during the healing period. The result is the ascent or herniation into the thorax of the posterior part of the wrap (or all of it) through the

hiatus that is again enlarged. This is the most frequent form of wrap failure, and it can inactivate the anti-reflux valve and cause retching, dysphagia, and pain or simply GER recurrence [184]. Complete disruption of the wrap can also happen, and the failure of the makeshift valve is then complete. In all these cases, technical insufficiencies of the operation can play a role, but as previously mentioned, more often the persistence of GER pathogenic factors (increased pressure gradients, short esophagus, scoliosis, etc.) accounts in part for the failure.

2. *Persistent dysphagia*: Some dysphagia is probably experienced by most patients immediately after the operation, but it is transient and recedes in the first days or weeks. However, when this unpleasant symptom last longer, it is probably due to a too tight, too long, or distorted wrap that either reduce or angulate the intra-abdominal esophagus. A properly fashioned wrap is the best preventive measure against this complication.
3. *Early satiety and Gas bloat*: A competent anti-reflux valve prevents burping and therefore gastric decompression after meals. Accumulation of ingested air or gas into the stomach may cause an unpleasant sensation of fullness that is called in extreme cases "gas-bloat syndrome." This condition is particularly marked in the rare cases in which there is delayed gastric emptying that has not been dealt with during the operation [185]. In such cases, the stomach undergoes a bipolar near closure that may be considerably bothersome. Gas bloat is in fact different from the early sensation of satiety that all patients having a fundoplication experience during meals. This is a constant and transient phenomenon due to the reduction of gastric compliance caused by the confection of the wrap. Patients and families should be informed about this symptom and about its transient nature because, after some weeks, the stomach regains its normal volume and admits normal meals.
4. *Dumping syndrome*: This is a rare [186], but relevant, complication of anti-reflux surgery. It involves a picture of postprandial tachycardia, diaphoresis, lethargy, retching, meteorism or gas bloat, watery diarrhea, and refusal to eat. It has been interpreted as the result of rapid invasion of the small bowel by the gastric contents as a consequence of a faster gastric emptying post-fundoplication. Massive disaccharide absorption in the duodenum would cause hyperglycemia. Reactive hyperinsulinemia would then cause hypoglycemia with all its constellation of symptoms. Glucose tolerance test can help to clarify if this mechanism is involved, but this is not always the case, because not all patients react in this way. Screening of postprandial hypoglycemia after fundoplication may help to detect dumping [187]. A vagal origin has been proposed as a mechanism for children in whom this is not demonstrated [188]. Gastric emptying tests did not confirm that rapid transit played a role in dumping cases [189]. Dumping is usually a transient phenomenon in these patients, and it can be usually treated with dietary changes like lactose-free diets, fat emulsions, addition of pectin [189] or corn starch [190] to the meals, acarbose [191, 192], and, in rare unmanageable cases, continuous intragastric or enteral feeding [193] or total parenteral nutrition for some time.
5. *Mortality*: There is neither operation nor medication without some risk that may involve mortality. Anti-reflux procedures are not minor procedures and can lead

to lethal complications. Fortunately, these are rare in the present settings, but up to 1% of patients can die as a consequence of surgery itself. Most critics of the benefits of anti-reflux surgery include in the mortalities those caused by the comorbidities, particularly by NI. Although NI patients that often require fundoplication have a considerable mortality rate [194], it would be unfair to attribute this solely to the procedure. Most of these children or adolescents die as a consequence of the neurologic disease, severe respiratory complications, or other causes. Only a few patients die due to operation-related causes.

Results of Anti-reflux Surgery

Anti-reflux operations do indeed fight efficiently GER as attested by manometric evidence of reestablishment of the LES pressure and pH-metric and impedance evidence of decreased number and duration of reflux episodes after operation. In addition, the occurrence of non-deglutory transient relaxations of the sphincter is also decreased postoperatively. This anti-reflux effect is durable and stands the test of time in the majority of patients treated. But not all procedures are alike, and the different categories of refluxing children behave differently after the operation. The following issues should be addressed: (1) results of the different techniques, (2) any differences in the results according to the open or laparoscopic approach, and (3) the results in children without and with comorbidities and those in each group of them. It should be pointed out that there are few strong-evidence reports on the results of surgical (or medical, by the way) treatment of GERD. Most studies are retrospective and most randomized ones aimed at comparing two modalities of surgical approach.

Most surgical techniques have been shown to be effective. However, when the objectives of the intervention were less ambitious, the proportion of failures was higher. Operations aimed exclusively at lengthening the intra-abdominal esophagus and at accentuating the angle of His fared indeed well, but did not stand the test of time like those including incomplete or complete wraps. For instance, immediate postoperative pH-monitoring results were worse for gastropexy than for Nissen [195], and a combined Anglo-Belgian report demonstrated that Boerema's operation fared definitely less well than Nissen fundoplication in the long term [196]. However, a more recent report from the Netherlands claimed more than 80% successes of gastropexy in the long run although these results were worst in NI and EA-TEF patients [197].

Anterior fundoplications worked well in children with pure GERD. A Thal fundoplication in 59 refluxing EA-TEF patients had a failure rate of 15% that compares favorably with other techniques [138]. A multicenter study comparing the results of Thal, Nissen, and Toupet laparoscopic operations in 300 consecutive patients did not find any relevant difference in terms of failures, but 66 NI patients were excluded from the study [198]. In fact, anterior fundoplications did not fare as well as a full Nissen in children with comorbidities, particularly in NI individuals. A prospective, long-term assessment of 53 patients, 48% with NI, revealed 43% failure of the Thal-Ashcraft anterior plication prompting careful evaluation after some years [199]. A

report on 45 children operated by the Boix-Ochoa technique showed that after an average follow-up of 8 years, 87% had satisfactory results. However, no comorbidities were mentioned, and the authors advised Nissen fundoplication for NI and EA-TEF patients [139]. Another report on 109 Boix-Ochoa and Nissen fundoplications in a cohort of children that included 60% of NI showed that most of the failed operations were anterior Boix-Ochoa plications, and the authors concluded that Nissen is definitely better in NI patients [140].

The Toupet posterior fundoplication behaved well in the long term [142, 145, 146] and compared well with Nissen fundoplication, a technique based on very similar principles.

Nissen should therefore be considered the gold standard that all other operations should match, and it has been repeatedly shown to be effective many years after its confection [27, 123, 132, 200, 201].

The question of whether laparoscopic approach could match the results of the open operations is now solved. For some years, it was argued that laparoscopic fundoplication was not as durable and efficient as the open one. It is true that for some years the introduction of laparoscopic surgery was more or less overtly opposed by a number of surgeons on the basis of the allegedly less perfect makeshift of the wrap and on the many "learning curves" imposed by the acquisition of the necessary skills. Nowadays, when the laparoscopic approach has been preferred for this operation for a number of years, there is no doubt that the procedure is the same (should be the same) and that similar results should therefore be expected. With some exceptions [202], most retrospective [203] and prospective randomized studies have documented that there are no differences between open and laparoscopic procedures [204, 205] except for wound infection, cost, and OR time [206].

Failures of anti-reflux surgery are definitely more frequent in children with comorbidities. In a series of 360 children treated with Nissen fundoplication, of which 28% were NI, 14 % had been treated at birth for EA-TEF, 6% for CDH, and 2% for AAWD, GER recurred in 12% after an average follow-up of 7 years. The proportions of failure were 13%, 24%, 29%, 5%, and 15% for NI, EA-TEF, CDH, and AAWD patients, respectively. In this series, like in others, failures occurred in the first 18–24 postoperative months [186].

NI patients receiving anti-reflux surgery have more complications than other groups of refluxers and a failure rate ranging from 12% to 20% [27, 140, 186, 201, 207]. Wrap herniation or disruption due to persistent GER-conditioning factors may account for this but also the persistence of excessive number and duration of non-deglutory sphincter relaxations in these children [45].

Close to 50% of children previously treated for EA-TEF had GERD in a combined series and the same proportion of these required an anti-reflux operation. However, for the reasons explained herewith, the proportion of failures was very high, ranging from 9% to 47% in a combined series (mean 18%) [208]. It remains that GER is a more relevant problem in EA-TEF during infancy and that anti-reflux surgery benefits these patients particularly during this period of life. Failures beyond it pose other problems that are also relevant but rarely life-threatening. Recently it was shown that fundoplications failed in patients treated for EA-TEF with duodenal

atresia attesting the relevant role of duodeno-gastric reflux and delayed gastric emptying in GERD in such patients [209].

Up to 50% of children operated upon for CDH have GER and up to 20% require anti-reflux procedures [89, 210]. The respiratory and nutritional consequences of both the malformation and GER require often gastrostomies and sometimes fundoplication that have been performed prophylactically at the time of CDH repair [141, 211, 212]. Fundoplication helps to outgrow the consequences of GER in the first months of life that can be very difficult, but the proportions of failure are close to one third [186].

Patients operated at birth for AAWD like omphalocele and gastroschisis have GER in high proportions, and they may require fundoplication that is particularly difficult in this setting [114, 213]. However, the proportion of failures is limited [186].

References

1. Liebermann-Meffert D, Allgower M, Schmid P, Blum AL. Muscular equivalent of the lower esophageal sphincter. Gastroenterology. 1979;76(1):31–8.
2. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. Gastroenterology. 1997;113(2):399–408.
3. Omari TI, Miki K, Davidson G, Fraser R, Haslam R, Goldsworthy W, et al. Characterisation of relaxation of the lower oesophageal sphincter in healthy premature infants. Gut. 1997;40(3):370–5.
4. Omari T, Barnett C, Snel A, Davidson G, Haslam R, Bakewell M, et al. Mechanism of gastroesophageal reflux in premature infants with chronic lung disease. J Pediatr Surg. 1999;34(12):1795–8.
5. Allison PR. Reflux esophagitis, sliding hiatal hernia, and the anatomy of repair. Surg Gynecol Obstet. 1951;92(4):419–31.
6. Boerema I. Hiatus hernia: repair by right-sided, subhepatic, anterior gastropexy. Surgery. 1969;65(6):884–93.
7. Hill LD. Intraoperative measurement of lower esophageal sphincter pressure. J Thorac Cardiovasc Surg. 1978;75(3):378–82.
8. Thal AP, Kurtzman R. A new method for reconstruction of the esophagogastric junction. Surg Gynecol Obstet. 1965;120:1225–31.
9. Orringer MB, Skinner DB, Belsey RH. Long-term results of the Mark IV operation for hiatal hernia and analyses of recurrences and their treatment. J Thorac Cardiovasc Surg. 1972;63(1):25–33.
10. Nissen R. Eine einfache Operation zur Beeinflussung der Refluxoesophagitis. Schweiz Med Wochenschr. 1956;86(Suppl 20):590–2.
11. Toupet A. Technic of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasms. Mem Acad Chir (Paris). 1963;89:384–9.
12. Collis JL. Gastroplasty. Thorax. 1961;16:197–206.
13. Angelchik JP, Cohen R. A new surgical procedure for the treatment of gastroesophageal reflux and hiatal hernia. Surg Gynecol Obstet. 1979;148(2):246–8.
14. Mellinger JD, MacFadyen BV, Kozarek RA, Soper ND, Birkett DH, Swanstrom LL. Initial experience with a novel endoscopic device allowing intragastric manipulation and plication. Surg Endosc. 2007;21(6):1002–5.
15. Triadafilopoulos G, Utley DS. Temperature-controlled radiofrequency energy delivery for gastroesophageal reflux disease: the Stretta procedure. J Laparoendosc Adv Surg Tech A. 2001;11(6):333–9.

16. O'Connor KW, Lehman GA. Endoscopic placement of collagen at the lower esophageal sphincter to inhibit gastroesophageal reflux: a pilot study of 10 medically intractable patients. Gastrointest Endosc. 1988;34(2):106–12.
17. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc. 1991;1(3):138–43.
18. Champault G. Gastroesophageal reflux. Treatment by laparoscopy. 940 cases – French experience. Ann Chir. 1994;48(2):159–64.
19. Dallemagne B, Weerts JM, Jeahes C, Markiewicz S. Results of laparoscopic Nissen fundoplication. Hepato-Gastroenterology. 1998;45(23):1338–43.
20. Bettex M, Kuffer F. Long-term results of fundoplication in hiatus hernia and cardioesophageal chalasia in infants and children. Report of 112 consecutive cases. J Pediatr Surg. 1969;4(5):526–30.
21. Carcassonne M, Bensoussan A, Aubert J. The management of gastroesophageal reflux in infants. J Pediatr Surg. 1973;8(5):575–86.
22. Boix-Ochoa J. The physiologic approach to the management of gastric esophageal reflux. J Pediatr Surg. 1986;21(12):1032–9.
23. Pellerin D, Nihoul-Fekete C, Revillon Y, Jan D. Esophagoplasty in caustic esophageal stenosis in children. Chirurgie. 1989;115(Suppl 1):86–91.
24. Follette D, Fonkalsrud EW, Euler A, Ament M. Gastroesophageal fundoplication for reflux in infants and children. J Pediatr Surg. 1976;11(5):757–64.
25. Ashcraft KW, Goodwin CD, Amoury RW, McGill CW, Holder TM. Thal fundoplication: a simple and safe operative treatment for gastroesophageal reflux. J Pediatr Surg. 1978;13(6D):643–7.
26. Berquist WE, Fonkalsrud EW, Ament ME. Effectiveness of Nissen fundoplication for gastroesophageal reflux in children as measured by 24-hour intraesophageal pH monitoring. J Pediatr Surg. 1981;16(6):872–5.
27. Fonkalsrud EW, Ashcraft KW, Coran AG, Ellis DG, Grosfeld JL, Tunell WP, et al. Surgical treatment of gastroesophageal reflux in children: a combined hospital study of 7467 patients. Pediatrics. 1998;101(3 Pt 1):419–22.
28. Hassall E. Wrap session: is the Nissen slipping? Can medical treatment replace surgery for severe gastroesophageal reflux disease in children? Am J Gastroenterol. 1995;90(8):1212–20.
29. Hassall E. Antireflux surgery in children: time for a harder look. Pediatrics. 1998;101(3 Pt 1):467–8.
30. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
31. Lobe TE, Schropp KP, Lunsford K. Laparoscopic Nissen fundoplication in childhood. J Pediatr Surg. 1993;28:358–61.
32. van der Zee DC, Bax NM. Laparoscopic Thal fundoplication in mentally retarded children. Surg Endosc. 1996;10(6):659–61.
33. Georgeson KE. Laparoscopic fundoplication and gastrostomy. Semin Laparosc Surg. 1998;5(1):25–30.
34. Rothenberg SS. Experience with 220 consecutive laparoscopic Nissen fundoplications in infants and children. J Pediatr Surg. 1998;33(2):274–8.
35. Esposito C, Montupet P, Amici G, Desruelle P. Complications of laparoscopic antireflux surgery in childhood. Surg Endosc. 2000;14(7):622–4.
36. Maclennan S, Augood C, Cash-Gibson L, Logan S, Gilbert RE. Cisapride treatment for gastro-oesophageal reflux in children. Cochrane Database Syst Rev. 2010;4:CD002300.
37. Attwood SEA, DeMeester TR, Bremner CG, Barlow AP, Hinder RA. Alkaline gastroesophageal reflux: implications in the development of complications in Barrett's columnar-lined lower esophagus. Surgery. 1989;106:764–70.
38. Pellegrini CA, DeMeester TR, Wernly JA, Johnson LF, Skinner DB. Alkaline gastroesophageal reflux. Am J Surg. 1978;135:177–84.

39. Vandenplas Y, Loeb H. Alkaline gastroesophageal reflux in infancy. J Pediatr Gastroenterol Nutr. 1991;12:448–52.
40. Tovar JA, Angulo JA, Gorostiaga L, Arana J. Surgery for gastroesophageal reflux in children with normal pH studies. J Pediatr Surg. 1991;26(5):541–5.
41. Lopez-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macias M, Silny J, et al. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. Pediatrics. 2006;118(2):e299–308.
42. Vane DW, Shiffler M, Grosfeld JL, Hall P, Angelides A, Weber TR, et al. Reduced lower esophageal sphincter (LES) pressure after acute and chronic brain injury. J Pediatr Surg. 1982;17(6):960–4.
43. Shteyer E, Rothman E, Constantini S, Granot E. Gastroesophageal reflux in infants with hydrocephalus before and after ventriculo-peritoneal shunt operation. Pediatr Neurosurg. 1998;29(3):138–41.
44. Pensabene L, Miele E, Del Giudice E, Strisciuglio C, Staiano A. Mechanisms of gastroesophageal reflux in children with sequelae of birth asphyxia. Brain and Development. 2008;30(9):563–71.
45. Kawahara H, Nakajima K, Yagi M, Okuyama H, Kubota A, Okada A. Mechanisms responsible for recurrent gastroesophageal reflux in neurologically impaired children who underwent laparoscopic Nissen fundoplication. Surg Endosc. 2002;16(5):767–71.
46. Tovar JA, Wang W, Eizaguirre I. Simultaneous gastroesophageal pH monitoring and the diagnosis of alkaline reflux. J Pediatr Surg. 1993;28(10):1386–91.
47. Fonkalsrud EW, Ellis DG, Shaw A, Mann CM Jr, Black TL, Miller JP, et al. A combined hospital experience with fundoplication and gastric emptying procedure for gastroesophageal reflux in children. J Am Coll Surg. 1995;180(4):449–55.
48. Wang W, Tovar JA, Eizaguirre I, Aldazabal P. Airway obstruction and gastroesophageal reflux: an experimental study on the pathogenesis of this association. J Pediatr Surg. 1993;28(8):995–8.
49. Wang W, Tovar JA, Eizaguirre I, Aldazabal P. Continuous positive airway pressure and gastroesophageal reflux: an experimental study. J Pediatr Surg. 1994;29(6):730–3.
50. Vandenplas Y, De Wolf D, Sacre L. Influence of xanthines on gastroesophageal reflux in infants at risk for sudden infant death syndrome. Pediatrics. 1986;77(6):807–10.
51. Peter CS, Wiechers C, Bohnhorst B, Silny J, Poets CF. Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: a multiple intraluminal impedance study. J Pediatr. 2002;141(2):277–9.
52. See CC, Newman LJ, Berezin S, Glassman MS, Medow MS, Dozor AJ, et al. Gastroesophageal reflux-induced hypoxemia in infants with apparent life-threatening event(s). Am J Dis Child. 1989;143(8):951–4.
53. Hrabovsky EE, Mullett MD. Gastroesophageal reflux and the premature infant. J Pediatr Surg. 1986;21(7):583–7.
54. Bhat RY, Rafferty GF, Hannam S, Greenough A. Acid gastroesophageal reflux in convalescent preterm infants: effect of posture and relationship to apnea. Pediatr Res. 2007;62(5):620–3.
55. Paul K, Melichar J, Miletin J, Dittrichova J. Differential diagnosis of apneas in preterm infants. Eur J Pediatr. 2009;168(2):195–201.
56. Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. Pediatrics. 2004;113(2):e128–32.
57. Trachterna M, Wenzl TG, Silny J, Rau G, Heimann G. Procedure for the semi-automatic detection of gastro-oesophageal reflux patterns in intraluminal impedance measurements in infants. Med Eng Phys. 1999;21(3):195–201.
58. Corvaglia L, Zama D, Gualdi S, Ferlini M, Aceti A, Faldella G. Gastro-oesophageal reflux increases the number of apnoeas in very preterm infants. Arch Dis Child Fetal Neonatal Ed. 2009;94(3):F188–92.
59. Di Fiore JM, Arko M, Churbock K, Hibbs AM, Martin RJ. Technical limitations in detection of gastroesophageal reflux in neonates. J Pediatr Gastroenterol Nutr. 2009;49(2):177–82.

60. Slocum C, Arko M, Di Fiore J, Martin RJ, Hibbs AM. Apnea, bradycardia and desaturation in preterm infants before and after feeding. J Perinatol. 2009;29(3):209–12.
61. Di Fiore J, Arko M, Herynk B, Martin R, Hibbs AM. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. J Perinatol. 2010;30(10):683–7.
62. Jolley SG, Herbst JJ, Johnson DG, Matlak ME, Book LS. Esophageal pH monitoring during sleep identifies children with respiratory symptoms from gastroesophageal reflux. Gastroenterology. 1981;80(6):1501–6.
63. Eizaguirre I, Tovar JA. Predicting preoperatively the outcome of respiratory symptoms of gastroesophageal reflux. J Pediatr Surg. 1992;27:848–51.
64. Stordal K, Johannesdottir GB, Bentsen BS, Knudsen PK, Carlsen KC, Closs O, et al. Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. Arch Dis Child. 2005;90(9):956–60.
65. Bowrey DJ, Peters JH, DeMeester TR. Gastroesophageal reflux disease in asthma: effects of medical and surgical antireflux therapy on asthma control. Ann Surg. 2000;231(2):161–72.
66. Theodoropoulos DS, Pecoraro DL, Efstratiadis SE. The association of gastroesophageal reflux disease with asthma and chronic cough in the adult. Am J Respir Med. 2002;1(2):133–46.
67. Frongia G, Ahrens P, Capobianco I, Kossler-Ebs J, Stroh T, Fritsche R, et al. Long-term effects of fundoplication in children with chronic airway diseases. J Pediatr Surg. 2015;50(1):206–10.
68. Davies M. Anatomy of the extrinsic nerve supply in oesophageal atresia of the common type. Pediatr Surg Int. 1996;11:230–3.
69. Qi BQ, Uemura S, Farmer P, Myers NA, Hutson JM. Intrinsic innervation of the oesophagus in fetal rats with oesophageal atresia. Pediatr Surg Int. 1999;15(1):2–7.
70. Pederiva F, Burgos E, Francica I, Zuccarello B, Martinez L, Tovar JA. Intrinsic esophageal innervation in esophageal atresia without fistula. Pediatr Surg Int. 2008;24(1):95–100.
71. Zhou B, Hutson JM, Myers NA. Investigation of the intra-abdominal oesophagus and hiatus in fetal rats with oesophageal atresia and tracheo-oesophageal fistula. Pediatr Surg Int. 2001;17(2-3):97–100.
72. Montedonico S, Diez-Pardo JA, Possogel AK, Tovar JA. Effects of esophageal shortening on the gastroesophageal barrier: an experimental study on the causes of reflux in esophageal atresia. J Pediatr Surg. 1999;34(2):300–3.
73. Puri P, Ninan GK, Blake NS, Fitzgerald RJ, Guiney EJ, O'Donnell B. Delayed primary anastomosis for esophageal atresia: 18 months' to 11 years' follow-up. J Pediatr Surg. 1992;27(8):1127–30.
74. Bagolan P, Iacobelli Bd B, De Angelis P, di Abriola GF, Laviani R, Trucchi A, et al. Long gap esophageal atresia and esophageal replacement: moving toward a separation? J Pediatr Surg. 2004;39(7):1084–90.
75. Foker JE, Kendall Krosch TC, Catton K, Munro F, Khan KM. Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results. Semin Pediatr Surg. 2009;18(1):23–9.
76. Cheng W, Spitz L, Milla P. Surface electrogastrography in children with esophageal atresia. Pediatr Surg Int. 1997;12(8):552–5.
77. Tovar JA, Diez Pardo JA, Murcia J, Prieto G, Molina M, Polanco I. Ambulatory 24-hour manometric and pH metric evidence of permanent impairment of clearance capacity in patients with esophageal atresia. J Pediatr Surg. 1995;30(8):1224–31.
78. Dutta HK, Grover VP, Dwivedi SN, Bhatnagar V. Manometric evaluation of postoperative patients of esophageal atresia and tracheo-esophageal fistula. Eur J Pediatr Surg. 2001;11(6):371–6.
79. Tomaselli V, Volpi ML, Dell'Agnola CA, Bini M, Rossi A, Indriolo A. Long-term evaluation of esophageal function in patients treated at birth for esophageal atresia. Pediatr Surg Int. 2003;19(1-2):40–3.
80. Kawahara H, Kubota A, Hasegawa T, Okuyama H, Ueno T, Watanabe T, et al. Lack of distal esophageal contractions is a key determinant of gastroesophageal reflux disease after repair of esophageal atresia. J Pediatr Surg. 2007;42(12):2017–21.

81. Canal DF, Vane DW, Goto S, Gardner GP, Grosfeld JL. Reduction of lower esophageal sphincter pressure with Stamm gastrostomy. J Pediatr Surg. 1987;22(1):54–7.
82. Isch JA, Rescorla FJ, Scherer LR 3rd, West KW, Grosfeld JL. The development of gastroesophageal reflux after percutaneous endoscopic gastrostomy. J Pediatr Surg. 1997;32(2):321–2.
83. Papaila JG, Vane DW, Colville C, Berend M, Mallik G, Canal D, et al. The effect of various types of gastrostomy on the lower esophageal sphincter. J Pediatr Surg. 1987;22(12):1198–202.
84. Sistonen SJ, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, et al. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. Ann Surg. 2010;251(6):1167–73.
85. Pieretti R, Shandling B, Stephens CA. Resistant esophageal stenosis associated with reflux after repair of esophageal atresia: a therapeutic approach. J Pediatr Surg. 1974;9:355–7.
86. Okada A, Usui N, Inoue M, Kawahara H, Kubota A, Imura K, et al. Esophageal atresia in Osaka: a review of 39 years' experience. J Pediatr Surg. 1997;32(11):1570–4.
87. Thomas EJ, Kumar R, Dasan JB, Chandrashekar N, Agarwala S, Tripathi M, et al. Radionuclide scintigraphy in the evaluation of gastro-oesophageal reflux in post-operative oesophageal atresia and tracheo-oesophageal fistula patients. Nucl Med Commun. 2003;24(3):317–20.
88. Bergmeijer JH, Hazebroek FW. Prospective medical and surgical treatment of gastroesophageal reflux in esophageal atresia. J Am Coll Surg. 1998;187(2):153–7.
89. Koivusalo AI, Pakarinen MP, Lindahl HG, Rintala RJ. The cumulative incidence of significant gastroesophageal reflux in patients with congenital diaphragmatic hernia-a systematic clinical, pH-metric, and endoscopic follow-up study. J Pediatr Surg. 2008;43(2):279–82.
90. Somppi E, Tammela O, Ruuska T, Rahnasto J, Laitinen J, Turjanmaa V, et al. Outcome of patients operated on for esophageal atresia: 30 years' experience. J Pediatr Surg. 1998;33(9):1341–6.
91. Deurloo JA, Ekkelkamp S, Taminiau JA, Kneepkens CM, ten Kate FW, Bartelsman JF, et al. Esophagitis and Barrett esophagus after correction of esophageal atresia. J Pediatr Surg. 2005;40(8):1227–31.
92. Deurloo JA, Ekkelkamp S, Bartelsman JF, Ten Kate FJ, Schoorl M, Heij HA, et al. Gastroesophageal reflux: prevalence in adults older than 28 years after correction of esophageal atresia. Ann Surg. 2003;238(5):686–9.
93. Sistonen SJ, Koivusalo A, Lindahl H, Pukkala E, Rintala RJ, Pakarinen MP. Cancer after repair of esophageal atresia: population-based long-term follow-up. J Pediatr Surg. 2008;43(4):602–5.
94. Jayasekera CS, Desmond PV, Holmes JA, Kitson M, Taylor AC. Cluster of 4 cases of esophageal squamous cell cancer developing in adults with surgically corrected esophageal atresia – time for screening to start. J Pediatr Surg. 2012;47(4):646–51.
95. Corbally MT, Muftah M, Guiney EJ. Nissen fundoplication for gastro-esophageal reflux in repaired tracheo-esophageal fistula. Eur J Pediatr Surg. 1992;2(6):332–5.
96. Ogita S, Goto Y, Hashimoto K, Iwai N, Nishioka B, Majima S. Prevention of gastroesophageal reflux using Nissen fundoplication in the staged repair of esophageal atresia with distal tracheoesophageal fistula. Jpn J Surg. 1983;13(6):554–6.
97. Koot VC, Bergmeijer JH, Bos AP, Molenaar JC. Incidence and management of gastroesophageal reflux after repair of congenital diaphragmatic hernia. J Pediatr Surg. 1993;28(1):48–52.
98. Stolar CJ, Levy JP, Dillon PW, Reyes C, Belamarich P, Berdon WE. Anatomic and functional abnormalities of the esophagus in infants surviving congenital diaphragmatic hernia. Am J Surg. 1990;159(2):204–7.
99. Lally KP, Paranka MS, Roden J, Georgeson KE, Wilson JM, Lillehei CW, et al. Congenital diaphragmatic hernia. Stabilization and repair on ECMO. Ann Surg. 1992;216(5):569–73.
100. Van Meurs KP, Robbins ST, Reed VL, Karr SS, Wagner AE, Glass P, et al. Congenital diaphragmatic hernia: long-term outcome in neonates treated with extracorporeal membrane oxygenation. J Pediatr. 1993;122(6):893–9.
101. Sigalet DL, Nguyen LT, Adolph V, Laberge JM, Hong AR, Guttman FM. Gastroesophageal reflux associated with large diaphragmatic hernias. J Pediatr Surg. 1994;29(9):1262–5.

102. Su W, Berry M, Puligandla PS, Aspirot A, Flageole H, Laberge JM. Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. J Pediatr Surg. 2007;42(10):1639–43.
103. Vanamo K, Rintala RJ, Lindahl H, Louhimo I. Long-term gastrointestinal morbidity in patients with congenital diaphragmatic defects. J Pediatr Surg. 1996;31(4):551–4.
104. Martinez L, Gonzalez-Reyes S, Burgos E, Tovar JA. The vagus and recurrent laryngeal nerves in experimental congenital diaphragmatic hernia. Pediatr Surg Int. 2004;20(4):253–7.
105. Martinez L, Pederiva F, Martinez-Calonge W, Aras-Lopez R, Tovar JA. The myenteric plexus of the esophagus is abnormal in an experimental congenital diaphragmatic hernia model. Eur J Pediatr Surg. 2009;19(3):163–7.
106. Pederiva F, Rodriguez JI, Ruiz-Bravo E, Martinez L, Tovar JA. Abnormal intrinsic esophageal innervation in congenital diaphragmatic hernia: a likely cause of motor dysfunction. J Pediatr Surg. 2009;44(3):496–9.
107. Fasching G, Huber A, Uray E, Sorantin E, Lindbichler F, Mayr J. Gastroesophageal reflux and diaphragmatic motility after repair of congenital diaphragmatic hernia. Eur J Pediatr Surg. 2000;10(6):360–4.
108. Qi B, Soto C, Diez-Pardo JA, Tovar JA. An experimental study on the pathogenesis of gastroesophageal reflux after repair of diaphragmatic hernia. J Pediatr Surg. 1997;32(9):1310–3.
109. Muratore CS, Utter S, Jaksic T, Lund DP, Wilson JM. Nutritional morbidity in survivors of congenital diaphragmatic hernia. J Pediatr Surg. 2001;36(8):1171–6.
110. Kamiyama M, Kawahara H, Okuyama H, Oue T, Kuroda S, Kubota A, et al. Gastroesophageal reflux after repair of congenital diaphragmatic hernia. J Pediatr Surg. 2002;37(12):1681–4.
111. Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics. 2008;121(3):627–32.
112. Kawahara H, Okuyama H, Nose K, Nakai H, Yoneda A, Kubota A, et al. Physiological and clinical characteristics of gastroesophageal reflux after congenital diaphragmatic hernia repair. J Pediatr Surg. 2010;45(12):2346–50.
113. Qi B, Diez-Pardo JA, Soto C, Tovar JA. Transdiaphragmatic pressure gradients and the lower esophageal sphincter after tight abdominal wall plication in the rat. J Pediatr Surg. 1996;31(12):1666–9.
114. Wang ZQ, Todani T, Watanabe Y, Toki A, Sato Y, Ogura K, et al. Esophageal hiatal hernia after omphalocele repair. Pediatr Surg Int. 1998;13(5-6):414–5.
115. Koivusalo A, Rintala R, Lindahl H. Gastroesophageal reflux in children with a congenital abdominal wall defect. J Pediatr Surg. 1999;34(7):1127–9.
116. Johnson DG, Herbst JJ, Oliveros MA, Stewart DR. Evaluation of gastroesophageal reflux surgery in children. Pediatrics. 1977;59(1):62–8.
117. Jolley SG, Tunell WP, Hoelzer DJ, Smith EI. Intraoperative esophageal manometry and early postoperative esophageal pH monitoring in children. J Pediatr Surg. 1989;24(4):336–40.
118. Ostlie DJ, Miller KA, Holcomb GW 3rd. Effective Nissen fundoplication length and bougie diameter size in young children undergoing laparoscopic Nissen fundoplication. J Pediatr Surg. 2002;37(12):1664–6.
119. Euler AR, Fonkalsrud EW, Ament ME. Effect of Nissen fundoplication on the lower esophageal sphincter pressure of children with gastroesophageal reflux. Gastroenterology. 1977;72(2):260–2.
120. Kawahara H, Imura K, Nakajima K, Yagi M, Kamata S, Okada A. Motor function of the esophagus and the lower esophageal sphincter in children who undergo laparoscopic nissen fundoplication. J Pediatr Surg. 2000;35(11):1666–71.
121. Jolley SG, Tunell WP, Leonard JC, Hoelzer DJ, Smith EI. Gastric emptying in children with gastroesophageal reflux. II. The relationship to retching symptoms following antireflux surgery. J Pediatr Surg. 1987;22(10):927–30.
122. Richards CA, Milla PJ, Andrews PL, Spitz L. Retching and vomiting in neurologically impaired children after fundoplication: predictive preoperative factors. J Pediatr Surg. 2001;36(9):1401–4.

123. Bergmeijer JH, Harbers JS, Molenaar JC. Function of pediatric Nissen-Rossetti fundoplication followed up into adolescence and adulthood. J Am Coll Surg. 1997;184(3):259–61.
124. Fonkalsrud EW, Ament ME, Byrne WJ, Rachelefsky GS. Gastroesophageal fundoplication for the management of reflux in infants and children. J Thorac Cardiovasc Surg. 1978;76(5):655–64.
125. Nihoul-Fekete C, Lortat-Jacob S, Jehannin B, Pellerin D. Resultats de l'intervention de reposition-Nissen-pyloroplastie et indications chirurgicales dans le traitement du reflux gastrooesophagien et de la hernie hiatale du nourrisson et de l'enfant. A propos de 267 interventions. Chirurgie. 1983;109(10):875–81.
126. St. Cyr JA, Ferrara TB, Thompson TR, Johnson DE, Foker JE. Nissen fundoplication for gastroesophageal reflux in infants. J Thorac Cardiovasc Surg. 1986;92(4):661–6.
127. Kazerooni NL, Vancamp J, Hirschl RB, Drongowski RA, Coran AG. Fundoplication in 160 children under 2 years of age. J Pediatr Surg. 1994;29:677–81.
128. van der Zee DC, Bax NM, Ure BM. Laparoscopic refundoplication in children. Surg Endosc. 2000;14(12):1103–4.
129. Georgeson K. Results of laparoscopic antireflux procedures in neurologically normal infants and children. Semin Laparosc Surg. 2002;9(3):172–6.
130. Lima M, Bertozzi M, Ruggeri G, Domini M, Libri M, Parigi GB, et al. Laparoscopic antireflux surgery in neurologically impaired children. Pediatr Surg Int. 2004;20(2):114–7.
131. Mattioli G, Sacco O, Gentilino V, Martino F, Pini Prato A, Castagnetti M, et al. Outcome of laparoscopic Nissen-Rossetti fundoplication in children with gastroesophageal reflux disease and supraesophageal symptoms. Surg Endosc. 2004;18(3):463–5.
132. Rothenberg SS. Two decades of experience with laparoscopic nissen fundoplication in infants and children: a critical evaluation of indications, technique, and results. J Laparoendosc Adv Surg Tech A. 2013;23(9):791–4.
133. Kawahara H, Imura K, Yagi M, Yoneda A, Soh H, Tazuke Y, et al. Mechanisms underlying the antireflux effect of Nissen fundoplication in children. J Pediatr Surg. 1998;33(11):1618–22.
134. Lelli JL, Ashcraft KW. Gastroesophageal reflux. Semin Thorac Cardiovasc Surg. 1994;6(4):240–6.
135. Roy-Choudhury S, Ashcraft KW. Thal fundoplication for pediatric gastroesophageal reflux disease. Semin Pediatr Surg. 1998;7(2):115–20.
136. Ahrens P, Heller K, Beyer P, Zielen S, Kuhn C, Hofmann D, et al. Antireflux surgery in children suffering from reflux-associated respiratory diseases. Pediatr Pulmonol. 1999;28(2):89–93.
137. Ramachandran V, Ashcraft KW, Sharp RJ, Murphy PJ, Snyder CL, Gittes GK, et al. Thal fundoplication in neurologically impaired children. J Pediatr Surg. 1996;31(6):819–22.
138. Snyder CL, Ramachandran V, Kennedy AP, Gittes GK, Ashcraft KW, Holder TM. Efficacy of partial wrap fundoplication for gastroesophageal reflux after repair of esophageal atresia. J Pediatr Surg. 1997;32(7):1089–91.
139. Cohen Z, Fishman S, Yulevich A, Kurtzbart E, Mares AJ. Nissen fundoplication and Boix-Ochoa antireflux procedure: comparison between two surgical techniques in the treatment of gastroesophageal reflux in children. Eur J Pediatr Surg. 1999;9(5):289–93.
140. Subramaniam R, Dickson AP. Long-term outcome of Boix-Ochoa and Nissen fundoplication in normal and neurologically impaired children. J Pediatr Surg. 2000;35(8):1214–6.
141. Guner YS, Elliott S, Marr CC, Greenholz SK. Anterior fundoplication at the time of congenital diaphragmatic hernia repair. Pediatr Surg Int. 2009;25(8):715–8.
142. Bensoussan AL, Yazbeck S, Carceller-Blanchard A. Results and complications of Toupet partial posterior wrap: 10 years' experience. J Pediatr Surg. 1994;29(9):1215–7.
143. Meehan JJ, Georgeson KE. Laparoscopic fundoplication in infants and children. Surg Endosc. 1996;10(12):1154–7.
144. Weber TR. Toupet fundoplication for pediatric gastroesophageal reflux disease. Semin Pediatr Surg. 1998;7(2):121–4.
145. Montupet P. Laparoscopic Toupet's fundoplication in children. Semin Laparosc Surg. 2002;9(3):163–7.

146. Miyano G, Yamoto M, Morita K, Kaneshiro M, Miyake H, Nouso H, et al. Laparoscopic Toupet fundoplication for gastroesophageal reflux: a series of 131 neurologically impaired pediatric cases at a single children's hospital. Pediatr Surg Int. 2015;31(10):925–9.
147. Richardson JD, Richardson RL. Collis-Nissen gastroplasty for shortened esophagus: long-term evaluation. Ann Surg. 1998;227(5):735–40.
148. Kawahara H, Imura K, Yagi M, Kubota A, Okada A. Collis-Nissen procedure in patients with esophageal atresia: long-term evaluation. World J Surg. 2002;26(10):1222–7.
149. Cameron BH, Cochran WJ, McGill CW. The uncut Collis-Nissen fundoplication: results for 79 consecutively treated high-risk children. J Pediatr Surg. 1997;32(6):887–91.
150. Liacouras CA, Hoffman MA, Maller ES. Breakdown of gastric staple line as a complication of the uncut Collis-Nissen fundoplication in children. J Clin Gastroenterol. 1996;23(3):174–6.
151. Goldsmith H, Herman L. Endoluminal gastroplication. A new therapeutic endoscopic procedure for gastroesophageal reflux disease. Gastroenterol Nurs. 2002;25(1):15–9.
152. Thomson M, Fritscher-Ravens A, Hall S, Afzal N, Ashwood P, Swain CP. Endoluminal gastroplication in children with significant gastro-oesophageal reflux disease. Gut. 2004;53(12):1745–50.
153. Galmiche JP, Bruley d, Varannes S. Endoluminal therapies for gastro-oesophageal reflux disease. Lancet. 2003;361(9363):1119–21.
154. Islam S, Geiger JD, Coran AG, Teitelbaum DH. Use of radiofrequency ablation of the lower esophageal sphincter to treat recurrent gastroesophageal reflux disease. J Pediatr Surg. 2004;39(3):282–6. discussion -6
155. Liu DC, Somme S, Mavrelis PG, Hurwich D, Statter MB, Teitelbaum DH, et al. Stretta as the initial antireflux procedure in children. J Pediatr Surg. 2005;40(1):148–51. discussion 51-2
156. Danielson PD, Emmens RW. Esophagogastric disconnection for gastroesophageal reflux in children with severe neurological impairment. J Pediatr Surg. 1999;34(1):84–6. discussion 7
157. Buratti S, Kamenwa R, Dohil R, Collins D, Lavine JE. Esophagogastric disconnection following failed fundoplication for the treatment of gastroesophageal reflux disease (GERD) in children with severe neurological impairment. Pediatr Surg Int. 2004;20(10):786–90.
158. Bianchi A. Total esophagogastric dissociation: an alternative approach. J Pediatr Surg. 1997;32(9):1291–4.
159. Gatti C, di Abriola GF, Villa M, De Angelis P, Laviani R, La Sala E, et al. Esophagogastric dissociation versus fundoplication: which is best for severely neurologically impaired children? J Pediatr Surg. 2001;36(5):677–80.
160. Lall A, Morabito A, Dall'Oglio L, di Abriola F, De Angelis P, Aloi I, et al. Total oesophagogastric dissociation: experience in 2 centres. J Pediatr Surg. 2006;41(2):342–6.
161. Dalla Vecchia LK, Grosfeld JL, West KW, Rescorla FJ, Scherer LR 3rd, Engum SA. Reoperation after Nissen fundoplication in children with gastroesophageal reflux: experience with 130 patients. Ann Surg. 1997;226(3):315–21.
162. Langer JC. The failed fundoplication. Semin Pediatr Surg. 2003;12(2):110–7.
163. Esposito C, Settimi A, Centonze A, Capano G, Ascione G. Laparoscopic-assisted jejunostomy: an effective procedure for the treatment of neurologically impaired children with feeding problems and gastroesophageal reflux. Surg Endosc. 2005;19(4):501–4.
164. Lewis D, Khoshoo V, Pencharz PB, Golladay ES. Impact of nutritional rehabilitation on gastroesophageal reflux in neurologically impaired children. J Pediatr Surg. 1994;29(2):167–9.
165. Stringel G, Delgado M, Guertin L, Cook JD, Maravilla A, Worthen H. Gastrostomy and Nissen fundoplication in neurologically impaired children. J Pediatr Surg. 1989;24(10):1044–8.
166. Langer JC, Wesson DE, Ein SH, Filler RM, Shandling B, Superina RA, et al. Feeding gastrostomy in neurologically impaired children: is an antireflux procedure necessary? J Pediatr Gastroenterol Nutr. 1988;7(6):837–41.
167. Borowitz SM, Sutphen JL, Hutcheson RL. Percutaneous endoscopic gastrostomy without an antireflux procedure in neurologically disabled children. Clin Pediatr (Phila). 1997;36(1):25–9.
168. Burd RS, Price MR, Whalen TV. The role of protective antireflux procedures in neurologically impaired children: a decision analysis. J Pediatr Surg. 2002;37(3):500–6.

169. Ponsky TA, Gasior AC, Parry J, Sharp SW, Boulanger S, Parry R, et al. Need for subsequent fundoplication after gastrostomy based on patient characteristics. J Surg Res. 2013;179(1):1–4.
170. Heloury Y, Plattner V, Mirallie E, Gerard P, Lejus C. Laparoscopic nissen fundoplication with simultaneous percutaneous endoscopic gastrostomy in children. Surg Endosc. 1996;10(8):837–41.
171. Kawahara H, Tazuke Y, Soh H, Yoneda A, Fukuzawa M. Does laparoscopy-aided gastrostomy placement improve or worsen gastroesophageal reflux in patients with neurological impairment? J Pediatr Surg. 2014;49(12):1742–5.
172. Di Lorenzo C, Piepsz A, Ham H, Cadranel S. Gastric emptying with gastro-oesophageal reflux. Arch Dis Child. 1987;62(5):449–53.
173. Fonkalsrud EW. Surgical treatment of the gastroesophageal reflux syndrome in childhood. Z Kinderchir. 1987;42(1):7–11.
174. Fonkalsrud EW, Berquist W, Vargas J, Ament ME, Foglia RP. Surgical treatment of the gastroesophageal reflux syndrome in infants and children. Am J Surg. 1987;154(1):11–8.
175. Omari TI, Barnett CP, Benninga MA, Lontis R, Goodchild L, Haslam RR, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut. 2002;51(4):475–9.
176. Bustorff-Silva J, Fonkalsrud EW, Perez CA, Quintero R, Martin L, Villasenor E, et al. Gastric emptying procedures decrease the risk of postoperative recurrent reflux in children with delayed gastric emptying. J Pediatr Surg. 1999;34(1):79–83.
177. Knatten CK, Avitsland TL, Medhus AW, Fjeld JG, Pripp AH, Emblem R, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. J Pediatr Surg. 2013;48(9):1856–61.
178. Kawahara H, Tazuke Y, Soh H, Usui N, Fukuzawa M. Causal relationship between delayed gastric emptying and gastroesophageal reflux in patients with neurological impairment. Pediatr Surg Int. 2015;31(10):917–23.
179. Okuyama H, Urao M, Starr GA, Drongowski RA, Coran AG, Hirschl RB. A comparison of the efficacy of pyloromyotomy and pyloroplasty in patients with gastroesophageal reflux and delayed gastric emptying. J Pediatr Surg. 1997;32(2):316–9.
180. Alexander F, Wyllie R, Jirousek K, Secic M, Porvasnik S. Delayed gastric emptying affects outcome of Nissen fundoplication in neurologically impaired children. Surgery. 1997;122(4):690–7.
181. Fonkalsrud EW, Ament ME, Vargas J. Gastric antroplasty for the treatment of delayed gastric emptying and gastroesophageal reflux in children. Am J Surg. 1992;164(4):327–31.
182. Brown RA, Wynchank S, Rode H, Millar AJ, Mann MD. Is a gastric drainage procedure necessary at the time of antireflux surgery? J Pediatr Gastroenterol Nutr. 1997;25(4):377–80.
183. Buchmiller TL, Curr M, Fonkalsrud EW. Assessment of alkaline reflux in children after Nissen fundoplication and pyloroplasty. J Am Coll Surg. 1994;178(1):1–5.
184. Kimber C, Kiely EM, Spitz L. The failure rate of surgery for gastro-oesophageal reflux. J Pediatr Surg. 1998;33(1):64–6.
185. Papaila JG, Wilmot D, Grosfeld JL, Rescorla FJ, West KW, Vane DW. Increased incidence of delayed gastric emptying in children with gastroesophageal reflux. A prospective evaluation. Arch Surg. 1989;124(8):933–6.
186. Lopez-Fernandez S, Hernandez F, Hernandez-Martin S, Dominguez E, Ortiz R, De La Torre C, et al. Failed Nissen fundoplication in children: causes and management. Eur J Pediatr Surg. 2014;24(1):79–82.
187. Calabria AC, Gallagher PR, Simmons R, Blinman T, De Leon DD. Postoperative surveillance and detection of postprandial hypoglycemia after fundoplasty in children. J Pediatr. 2011;159(4):597–601. e1
188. Bufler P, Ehringhaus C, Koletzko S. Dumping syndrome: a common problem following Nissen fundoplication in young children. Pediatr Surg Int. 2001;17(5–6):351–5.
189. Samuk I, Afriat R, Horne T, Bistritzer T, Barr J, Vinograd I. Dumping syndrome following Nissen fundoplication, diagnosis, and treatment. J Pediatr Gastroenterol Nutr. 1996;23(3):235–40.

190. Khoshoo V, Reifen RM, Gold BD, Sherman PM, Pencharz PB. Nutritional manipulation in the management of dumping syndrome. Arch Dis Child. 1991;66(12):1447–8.
191. Ng DD, Ferry RJ Jr, Kelly A, Weinzimer SA, Stanley CA, Katz LE. Acarbose treatment of postprandial hypoglycemia in children after Nissen fundoplication. J Pediatr. 2001;139(6):877–9.
192. De Cunto A, Barbi E, Minen F, Ventura A. Safety and efficacy of high-dose acarbose treatment for dumping syndrome. J Pediatr Gastroenterol Nutr. 2011;53(1):113–4.
193. Veit F, Heine RG, Catto-Smith AG. Dumping syndrome after Nissen fundoplication. J Paediatr Child Health. 1994;30(2):182–5.
194. Smith CD, Othersen HB Jr, Gogan NJ, Walker JD. Nissen fundoplication in children with profound neurologic disability. High risks and unmet goals. Ann Surg. 1992;215(6):654.
195. Strecker-McGraw MK, Lorenz ML, Hendrickson M, Jolley SG, Tunell WP. Persistent gastroesophageal reflux disease after antireflux surgery in children: I. immediate postoperative evaluation using extended esophageal pH monitoring. J Pediatr Surg. 1998;33(11):1623–7.
196. De Laet M, Spitz L. A comparison of Nissen fundoplication and Boerema gastropexy in the surgical treatment of gastro-oesophageal reflux in children. Br J Surg. 1983;70(2):125–7.
197. Kloek JJ, van de Laar GA, Deurloo JA, Aronson DC, Benninga MA, Taminiau JA, et al. Long-term results of boerema anterior gastropexy in children. J Pediatr Gastroenterol Nutr. 2006;43(1):71–6.
198. Esposito C, Montupet P, van Der Zee D, Settimi A, Paye-Jaouen A, Centonze A, et al. Long-term outcome of laparoscopic Nissen, Toupet, and Thal antireflux procedures for neurologically normal children with gastroesophageal reflux disease. Surg Endosc. 2006;20(6):855–8.
199. Mauritz FA, van Herwaarden-Lindeboom MY, Zwaveling S, Houwen RH, Siersema PD, van der Zee DC. Laparoscopic Thal fundoplication in children: a prospective 10- to 15-year follow-up study. Ann Surg. 2014;259(2):388–93.
200. Bourne MC, Wheeldon C, MacKinlay GA, Munro FD. Laparoscopic Nissen fundoplication in children: 2-5-year follow-up. Pediatr Surg Int. 2003;19(7):537–9.
201. Tovar JA, Luis AL, Encinas JL, Burgos L, Pederiva F, Martinez L, et al. Pediatric surgeons and gastroesophageal reflux. J Pediatr Surg. 2007;42(2):277–83.
202. Fyhn TJ, Knatten CK, Edwin B, Schistad O, Aabakken L, Kjosbakken H, et al. Randomized controlled trial of laparoscopic and open Nissen fundoplication in children. Ann Surg. 2015;261(6):1061–7.
203. Siddiqui MR, Abdulaal Y, Nisar A, Ali H, Hasan F. A meta-analysis of outcomes after open and laparoscopic Nissen's fundoplication for gastro-oesophageal reflux disease in children. Pediatr Surg Int. 2011;27(4):359–66.
204. Knatten CK, Fyhn TJ, Edwin B, Schistad O, Emblem R, Bjornland K. Thirty-day outcome in children randomized to open and laparoscopic Nissen fundoplication. J Pediatr Surg. 2012;47(11):1990–6.
205. Pacilli M, Eaton S, McHoney M, Kiely EM, Drake DP, Curry JI, et al. Four year follow-up of a randomised controlled trial comparing open and laparoscopic Nissen fundoplication in children. Arch Dis Child. 2014;99(6):516–21.
206. Papandria D, Goldstein SD, Salazar JH, Cox JT, McIltrot K, Stewart FD, et al. A randomized trial of laparoscopic versus open Nissen fundoplication in children under two years of age. J Pediatr Surg. 2015;50(2):267–71.
207. Pearl RH, Robie DK, Ein SH, Shandling B, Wesson DE, Superina R, et al. Complications of gastroesophageal antireflux surgery in neurologically impaired versus neurologically normal children. J Pediatr Surg. 1990;25(11):1169–73.
208. Tovar JA, Fragoso AC. Gastroesophageal reflux after repair of esophageal atresia. Eur J Pediatr Surg. 2013;23(3):175–81.
209. Fragoso AC, Ortiz R, Hernandez F, Olivares P, Martinez L, Tovar JA. Defective upper gastrointestinal function after repair of combined esophageal and duodenal atresia. J Pediatr Surg. 2015;50(4):531–4.
210. Verbelen T, Lerut T, Coosemans W, De Leyn P, Nafteux P, Van Raemdonck D, et al. Antireflux surgery after congenital diaphragmatic hernia repair: a plea for a tailored approach. Eur J Cardiothorac Surg. 2013;44(2):263–7.

211. Chamond C, Morineau M, Gouizi G, Bargy F, Beaudoin S. Preventive antireflux surgery in patients with congenital diaphragmatic hernia. World J Surg. 2008;32(11):2454–8.
212. Dariel A, Roze JC, Piloquet H, Podevin G. Impact of prophylactic fundoplication on survival without growth disorder in left congenital diaphragmatic hernia requiring a patch repair. J Pediatr. 2010;157(4):688–90, 90 e1.
213. Beaudoin S, Kieffer G, Sapin E, Bargy F, Helardot PG. Gastroesophageal reflux in neonates with congenital abdominal wall defect. Eur J Pediatr Surg. 1995;5(6):323–6.

Endoscopic Approaches to the Treatment of GERD

26

Mike Thomson

Abstract

Gastroesophageal reflux treatment aims to achieve symptom relief while preventing complications. Patients who fail to achieve control with medical therapy, have persistent severe esophagitis or become long-term dependent on anti-reflux treatments may have an anti-reflux procedure indicated [1]. The principle of surgery in gastroesophageal reflux disease 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 this is invasive and associated with a degree of morbidity and mortality. In recent years laparoscopic fundoplication has become popular and, in general, has replaced the open Nissen's procedure—equal, though not superior, efficacy and safety have been demonstrated. However, 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 paediatrics.

Three general endoscopic techniques have been devised and used for the treatment of GERD and have received extensive attention in adult studies and limited scrutiny in paediatric series. These are described below.

Keywords

Children • Endoscopy • Gastro-oesophageal reflux • Fundoplication • Esophyx Stretta

M. Thomson
Sheffield Children's Hospital, Weston Bank, Sheffield S10 2TH, UK
e-mail: mike.thomson@sch.nhs.uk

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
DOI 10.1007/978-3-319-60678-1_26

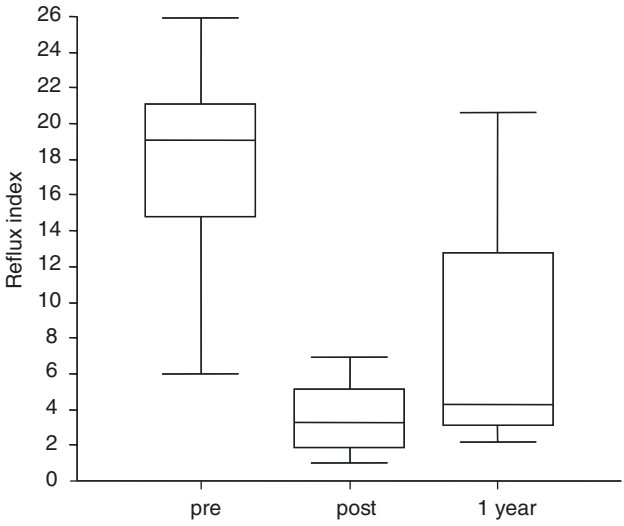


Fig. 26.1 Persisting normality at 12 months of reflux index following Endocinch®

Endoscopic Suturing Devices

The first generation, the endoluminal gastroplication, made use of an EndoCinch® sewing machine attached to the endoscope (gastroscope) placing three pairs of stitches below the gastroesophageal junction to create three internal plications of the stomach. Reasonable results were achieved in one small paediatric series at 12 months as evidenced by pH, cessation of PPI usage and quality of life [2] and 36 months by PPI cessation and quality of life [3]. This study involved 17 children (8 males), median (range) age 12.9 (6.1–17.7) years, median (range) weight 45 (16.5–75) kg with gastroesophageal reflux disease refractory to, or dependent on (>12 months), proton pump inhibitors. At 12 months follow-up, all pH parameters improved and had returned to normal in 8/9 who underwent pH studies (reflux index (RI) decreased from 16.6% (0.9–67%) to 2.5% (0.7–15.7%) ($p < 0.0001$)) (Fig. 26.1). Gastric bleeding was observed in one patient, which resolved spontaneously. All patients showed post-treatment improvement in symptom severity, frequency and validated reflux-related quality of life scores ($p < 0.0001$) at 3 years post-procedure (Fig. 26.2). At 36 months median follow-up, 11/17 patients were asymptomatic and off all anti-reflux medications.

Another technique reliant on suture placement with a full-thickness plication was the Full-Thickness Plicator® (Ndo-surgical). This was 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 allowed observation of firstly 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 (Figs. 26.3 and 26.4). A small multicentre adult study had acceptable efficacy and a reduction of PPI requirement [4]. This is no longer in use.

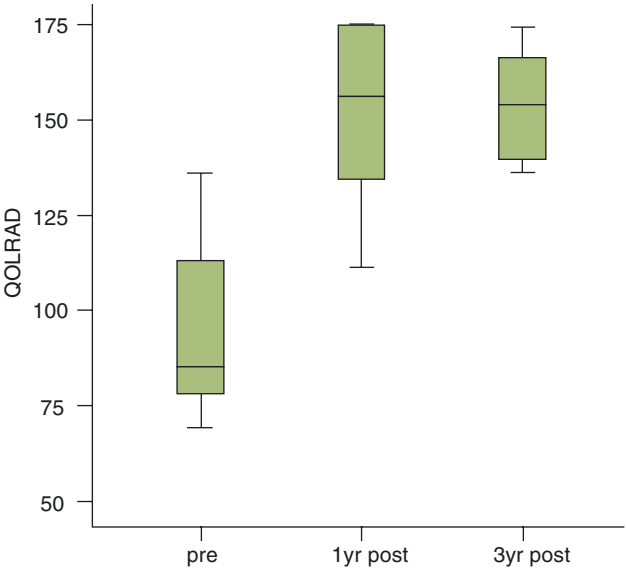


Fig. 26.2 Persistence of normality of quality of life specific to reflux at 3 years following Endocinch®

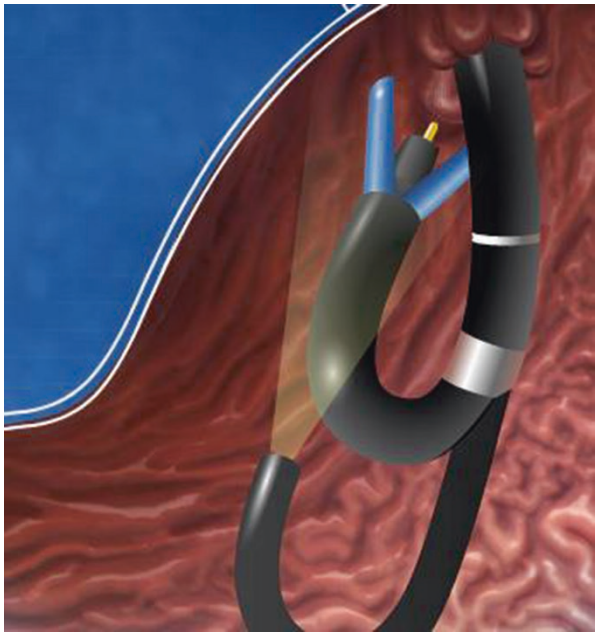


Fig. 26.3 Retroflexion with the small endoscope allowing direct vision of the Full Thickness Plicator®

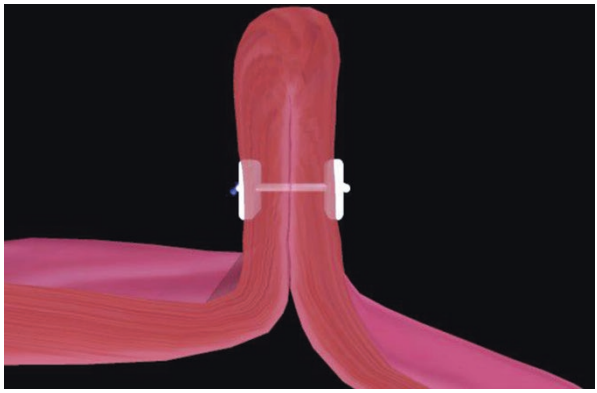


Fig. 26.4 Application of a Full-Thickness Plicator®

Trans-Oral Incisionless Fundoplication (TIF)

These devices are representative of an alternative to the Plicator technology along a similar theme, although not identical.

The novel trans-oral incisionless fundoplication (TIF) procedure using EsophyX mimics anti-reflux surgery in constructing an anterior partial fundoplication with tailored delivery of multiple fasteners during a single-device insertion (Fig. 26.5). The TIF procedure is designed to restore the anti-reflux competency of the gastroesophageal junction through reducing small hiatal hernias, increasing LES resting pressure, narrowing cardia and recreating acute angle of His (Fig. 26.6).

The valve is constructed by drawing tissue into the device with the aid of a helical retractor. The tissue mould is then closed over the retracted tissue, and the fasteners are deployed. The fastener is delivered by a pusher that slides over a stylet [6] (Fig. 26.8). Clinical results with TIF at 1, 2 and 3 years support its efficacy in eliminating heartburn and regurgitation, reducing the daily use of PPIs, normalising oesophageal acid exposure and reducing proximal extent of refluxate [5, 7, 8]. Based on one-year results, FDA cleared EsophyX in September 2007 for the treatment of GERD and small (<2 cm) hiatal hernia.

The TIF procedure has been demonstrated to be safe in adults. Post-TIF adverse events are mild and transient and include musculoskeletal and epigastric pain, nausea and dysphagia up to one week secondary to sore throat [5, 7–9]. Only three oesophageal perforations have been reported to date for 3000 cases performed worldwide. None of the subjects experienced chronic dysphagia, gas bloating and diarrhoea at long-term follow-up.

A feasibility audit has occurred in the use of the EsophyX device and TIF2 procedure in children, but it has not been widely taken up [10].

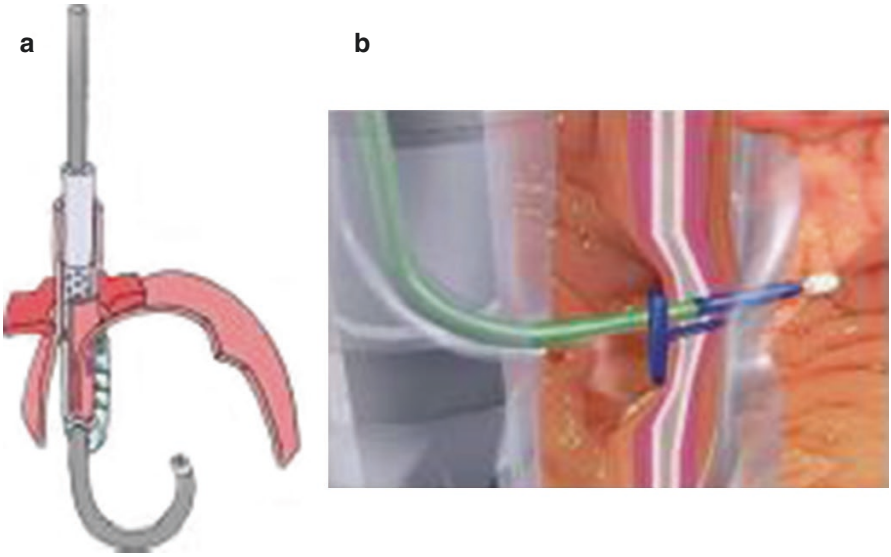


Fig. 26.5 Distal end of the EsophyX device (**a**) and SerosaFuse fastener (**b**)

This feasibility and safety audit was conducted with 12 children (8 male) with a median age of 12.25 years (8–17) and weight of 38.2 kg (26–91). The median duration of GERD symptoms was 45 months (24–70), and all subjects were on GERD medication for more than 6 months. The median (range) pre-TIF reflux index off treatment was 11.4 (6–48)%. Hiatus hernia was present in 17% (2/12). Median (range) operative time was 42 (25–94) min. This is significantly shorter in duration than either laparoscopic or open fundoplication. Adverse events were experienced by three subjects and consisted of mild or moderate pharyngeal irritation and epigastric pain. Two of the three subjects also had retrosternal chest pain and were subsequently found to have pneumomediastinum on 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 mediastinal gas leak. Median stay in hospital was less than 48 h compared to LF and OF of 4 and 9 days, respectively.

At 12-month follow-up, all children had discontinued PPIs, and 80% were asymptomatic. Seventy percent had normalised or clinically significantly reduced reflux index (<4% time pH < 4). The results of this feasibility audit indicated that the TIF procedure was feasible, safe (with CO_2 insufflation), and clinically effective in treating GERD in children in the medium term. A significant issue also is cost saving. Median cost is around half that of open and less than laparoscopic with our nested controlled comparative groups if a child is treated as a day case.

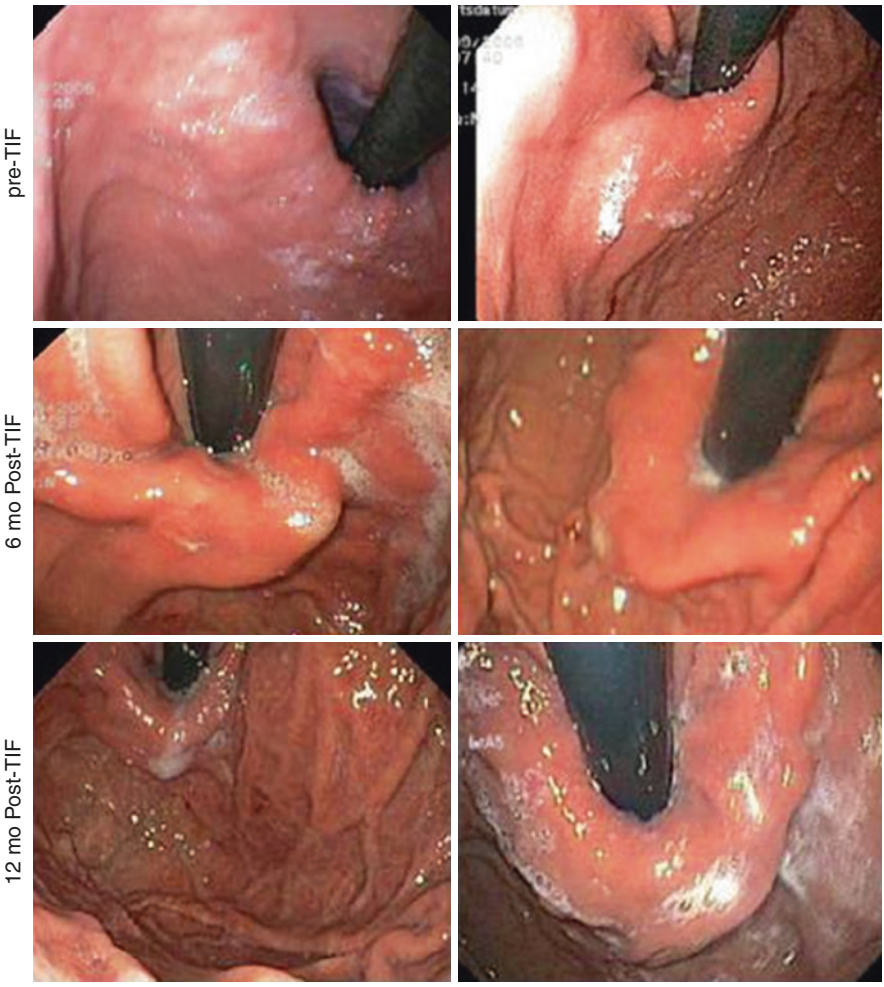


Fig. 26.6 Endoscopic images of gastroesophageal valves from two subjects before and at 6 and 12 months after TIF1 (Illustration from Cadiere et al. 2008 [5])

Delivery of Radiofrequency Energy (The STRETTA® System)

The Stretta System® is a radiofrequency (RF) energy device intended to treat GERD. During the procedure, known as Stretta Therapy®, RF energy is delivered to treatment sites above and below the gastro-oesophageal junction. The manufacturer states that Stretta Therapy® is non-ablative because it does not remove or destroy tissue but regenerates the target tissue by creating hypertrophy that thickens the musculature to improve GERD symptoms.

The Stretta System® consists of a reusable, pole-mounted 4-channel RF generator and a sterile, single-use RF-delivery catheter that houses four needle electrodes.

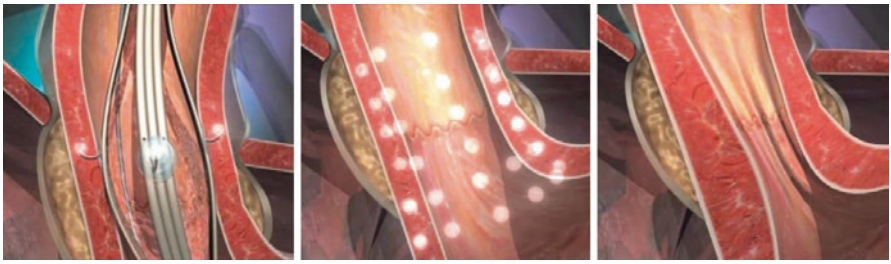


Fig. 26.7 Stretta diagrammatical representation of needle points and energy delivery

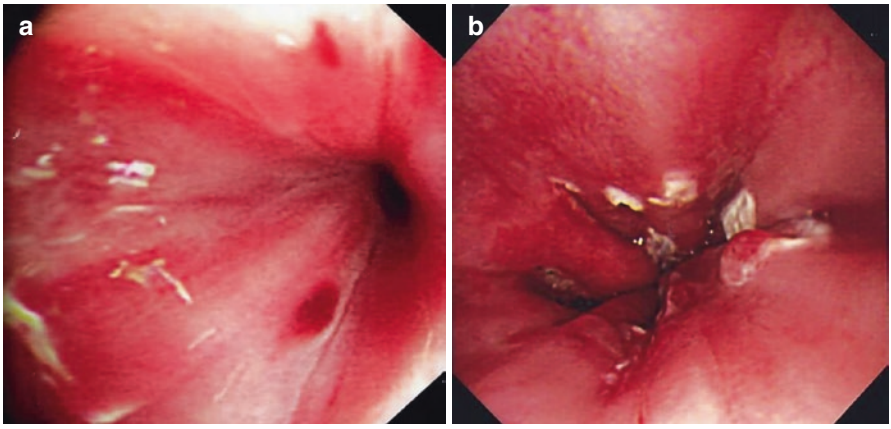


Fig. 26.8 Stretta endoluminal distal oesophageal views

A single-use, gel-type patient return electrode completes the RF circuit. It delivers low power (5 W) thermal energy at 65 °C–85 °C. The generator has an integrated irrigation pump to cool the mucosal tissue during therapy and a colour display to guide the user through equipment setup and the treatment procedure. The catheter consists of a balloon basket with four needle electrodes positioned radially at 90° angle from one another around the balloon. Electrode tip and surface tissue temperatures are measured by thermocouples in the tip and base of the electrode, respectively. The operator controls energy delivery through a footswitch (Figs. 26.7 and 26.8).

To begin treatment, the distance to the gastroesophageal junction is measured using the endoscope and then a guide wire with a flexible tip is passed through the endoscope into the stomach, where it stays during the treatment session. The endoscope is withdrawn, and the RF-delivery catheter is inserted, following the guide wire. The manufacturer recommends that Stretta Therapy® is carried out at six different points in the oesophagus: four across the lower oesophageal sphincter muscle, one at the gastro-oesophageal junction and one in the gastric cardia. Typically, Stretta Therapy® takes less than 1 h, and an adult can return to normal activity the

next day. Many medium-term studies in adults are now reported revealing excellent safety and significant efficacy in all parameters, both subjective and objective, of GERD.

The Stretta System® is the only RF energy device indicated for treating GERD. Stretta Therapy® is a minimally invasive procedure that can be performed as an outpatient or day-case procedure [9–12].

In a meta-analysis by Perry K et al., 1441 patients from 18 studies were included to assess the impact of Stretta in GERD. RF improved heartburn scores ($p = 0.001$) and produced improvements in quality of life as measured by GERD-HRQoL ($p = 0.001$) and quality of life in reflux and dyspepsia scores ($p = 0.001$). Oesophageal acid exposure decreased from a mean pre-procedure DeMeester score of 44.4–28.5 ($p = 0.007$) but was not normalised. [13]. NICE have recently issued guidance on this procedure [14].

This treatment has been reported in an uncontrolled study of a group of eight children with a variable follow-up period of 5–15 months [15]. It was reported that 6/8 children improved and the cohort included three neurologically impaired children who also had concomitant PEG placement. One of 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's fundoplication [16].

Paediatric gastroenterologists may be guarded in using this form of treatment as clearly using thermal energy treatment in a 70-year-old is different to a child who may have unknown consequences in the long term. Nevertheless the safety of the newer iteration of this technology lends itself to further paediatric studies.

Gastroesophageal Biopolymer Injection

In the Enteryx® procedure, a liquid polymer was injected into the lower oesophageal sphincter (LES) with a needle catheter via an endoscope (Fig. 26.9). After the injection, the polymer solidifies into a sponge-like permanent implant. This improves the gastroesophageal junction, by supporting and improving its elasticity and therefore reducing the degree of gastroesophageal reflux.

An open-label clinical trial on 144 patients showed a greater than 50% reduction in PPI in 84% at the end of one year and 72% by two years with elimination in 67% patients [17]. To date there are no published records of its use in paediatrics, and it is unlikely to occur in this age group now due to the FDA & Boston Scientific notifying healthcare professionals and patients about serious adverse events, including death, occurring in patients treated with the Enteryx® device.

In summary these trans-oral techniques are evolving and require further objective comparison with established laparoscopic fundoplication approaches in longitudinal prospective randomised studies stratified for morbidity, in particular neurological compromise. Only then will these minimally invasive procedures be recognised as a viable alternative with its provisional advantages to date being applicable to mainstream paediatric reflux management.

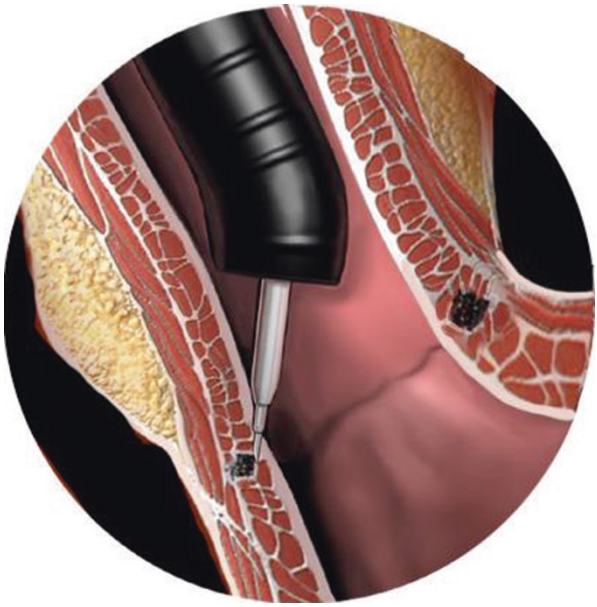


Fig. 26.9 Injection of liquid polymer into the oesophageal mucosa. The Enteryx® procedure

References

1. Vandenplas Y, Rudolph C, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of NASPGHAN and ESPGHAN. J Pediatr Gastroenterol Nutr. 2009;49(4):498–547.
2. Thomson M, et al. Endoluminal gastroplication in children with significant gastro-oesophageal reflux disease. Gut. 2004;53:1745–50.
3. Thomson M, et al. Medium-term outcome of endoluminal gastroplication with the Endocinch device in children. J Pediatr Gastroenterol Nutr. 2008;46:172–7.
4. Pleskow D, et al. Endoscopic full-thickness plication for the treatment of GERD: a multicenter trial. Gastrointest Endosc. 2004;59:163–71.
5. Cadiere G, Buset M, Muls V, Rajan A, Rosch T, Eckardt AJ, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. World J Surg. 2008;32:1676–88.
6. Cadière G-B, van Sante N, Graves J, Gawlicka A, Rajan A. Two year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. Surg Endosc. 2009;23(5):957–64.
7. Repici A, Fumagalli U, Malesci A, Barbera R, Gambaro C, Rosati R. Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-month follow-up in a single-center experience. J Gastrointest Surg. 2010;14(1):1–6.
8. Testoni PA, Vailati C. Transoral incision less fundoplication with EsophyX® for treatment of gastro-oesphageal reflux disease. Dig Liver Dis. 2012;44(8):631–5.
9. Noar M, Squires P, Noar E, Lee M. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. Surg Endosc. 2014;28(8):2323–33.
10. Chen S, Jarboe M, Teitelbaum D. Effectiveness of a transluminal endoscopic fundoplication for the treatment of pediatric gastroesophageal reflux disease. Pediatr Surg Int. 2012;28(3):229–34.
11. Thomson M. Endoscopic approaches to the treatment of GERD. J Pediatr Gastroenterol Nutr. 2011;53(Suppl 2):S11–3.

12. Reymunde S, Santiago N. Long term results of radio-frequency energy delivery for the treatment of GERD: sustained improvements in symptoms, quality of life, and drug use at 4-year follow up. Gastrointest Endosc. 2007;65:361–6.
13. Perry K, Banerjee A, Melvin W. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech. 2012;22:283–8.
14. Endoscopic radiofrequency ablation for gastrooesophageal reflux disease. Interventional procedure guidance. Published: 28 August 2013. nice.org.uk/guidance/ipg46.
15. Islam S, Geiger J, Coran A, Teitelbaum D. Use of radiofrequency ablation of the lower esophageal sphincter to treat recurrent gastroesophageal reflux disease. J Pediatr Surg. 2004;39:282–6.
16. Liu DC, et al. Stretta as the initial antireflux procedure in children. J Pediatr Surg. 2005;40:148–51.
17. Cohen L, et al. Enteryx implantation for GERD: expanded multicenter trial results and interim post-approval follow-up to 24 months. Gastrointest Endosc. 2005;61:650–8.

Correction to: Esophageal Clearance in Gastroesophageal Reflux

Maheen Hassan, Frederick W. Woodley, and Hayat Mousa

Correction to:
Chapter 3 in: Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*, https://doi.org/10.1007/978-3-319-60678-1_3

We received following corrections from author after publication of this book.

The name of an author was spelt incorrectly as Frederick W. Woodey in original version. His name has been corrected to Frederick W. Woodley throughout the book.

The updated original online version for this chapter can be found at https://doi.org/10.1007/978-3-319-60678-1_3

Y. Vandenplas (ed.), *Gastroesophageal Reflux in Children*,
https://doi.org/10.1007/978-3-319-60678-1_27