GASTROESOPHAGEAL REFLUX DISEASE IN INFANTS AND CHILDREN

Seema Khan and S. R. Orenstein

Division of Pediatric Gastroenterology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Introduction

Gastroesophageal reflux (GER), represents the retrograde movement of gastric contents into the esophagus, and is a frequently experienced benign but symptomatic condition. At the one end of the spectrum are infants with physiologic reflux, also referred to in the United States as "happy spitters", and at the other end are children with objective pathologic sequelae comprising gastroesophageal reflux disease (GERD). GERD also has come to denote symptoms affecting quality of life even in the absence of objective damage. GERD is the most common pediatric esophageal disorder; although precise data are not available in children, GERD accounts for substantial health care costs in children, as it does in adults [1].

Epidemiology

The epidemiology of GERD in children has been studied to a limited extent due to the challenges posed by the evolving disease spectrum, lack of a diagnostic gold standard, and scarcity of incidence and prevalence data. Estimates of GERD prevalence are based on data analyzed from interviews with patients and parents of children with GERD, and vary according to the symptom frequency and severity queried. The prevalence of GERD symptoms in the general population of infants and children is in the range of 1–10%, in contrast to a prevalence of 15–20% in adults [2], [3]. In a cross sectional study of 798 infants with regurgitation but without neurological or respiratory diseases, pathologic GER was diagnosed in 11% using Rome II criteria [4]. On a cross sectional survey of 566 unselected children aged 3 to 9 years, parents reported heartburn, epigastric pain, and regurgitation in 1.8%, 7.2%, and 2.3% of them, respectively [5]. In the same study, 615 children between 10 and 17 years of age reported the symptoms 5.2%, 5%, and 8.2% of the time, suggesting that parents may underestimate their children's experiences.

Gastroesophageal reflux disease is one of the most prevalent gastrointestinal disorders in children with neurologic and chronic respiratory disorders. This association is thought to arise as a result of the provocations of the mechanisms of reflux. In neuromuscular disorders, spasticity and prolonged recumbency, and in respiratory disorders, increased abdominal to thoracic pressure gradients and decreased tone of the lower esophageal sphincter (LES) due to some of the therapies, are all predispositions to GERD.

Very low birth-weight infants with chronic lung disease are diagnosed and treated for GERD more frequently than those without lung disease [6].

Natural history

Infantile GERD is generally regarded to have a favorable natural history, with persistent symptoms in about 5% of infants by one year of age, following a peak at 4 months, and resolving in the large majority between 12 and 24 months of age [7], [8]. Epidemiological studies of the natural history of GERD and its complications in older children are scarce [9]. Unselected infants with frequent regurgitation may develop feeding problems in the subsequent year of follow-up [10]. Children with chronic respiratory and neurological diseases commonly exhibit recurrent or chronic GERD symptoms. By nine years of age, children with frequent regurgitation during infancy may be more likely to develop persistent reflux symptoms,

a phenomenon exacerbated by maternal smoking and maternal reflux symptoms [8]. Children over one year of age without neurological impairment most commonly have "endoscopy-negative GERD", and their esophageal inflammation, even if present, is unlikely to deteriorate during a mean of 28 months of follow-up [11]. However, half of older children with GERD have a chronic relapsing course [12]. Adults with GERD were twice as likely to recall having at least one childhood symptom of GERD as adults without GERD, in a survey of 400 adults [13]. In an uncontrolled study of a cohort of 80 children with GERD followed up as adolescents and young adults at an average of 15 years later, 80% reported monthly reflux symptoms, and at least one third of the individuals reported use of anti-reflux medications [14]. Erosive esophagitis was present in 3 of the 14 individuals who were evaluated by an upper endoscopy.

The increasing diagnosis of GERD in older children and adolescents is a cause for speculating that GERD beginning in infancy or childhood may persist into adult years, thus predisposing to the complications of peptic strictures, Barrett's esophagus, and adenocarcinomas.

Genetics

GERD and its complications are recognized as clustering within families, suggesting a genetic background for GERD phenotypes. A gene mapped for "severe pediatric GERD" with prominent respiratory symptoms in five kindreds was localized to chromosome 13q14 [15]. Later, a genetic linkage for "infantile esophagitis" was identified at a separate locus [16]. A candidate gene approach to screen for mutations that might be causally associated with reflux suggests that a GERD1 gene on chromosome 13q14 might be located within 20 kb of SNP160 or SNP168 [17]. Due to the heterogeneity in GERD phenotypes, more than one genetic locus may be involved and might influence various of the pathophysiologic factors.

Pathophysiology

Understanding of the mechanisms underlying reflux episodes has expanded from the primitive conceptualization of the lower esophageal sphincter (LES) as hyptonic to the more complicated and accurate current model. This current model incorporates dynamic changes at the gastroesophageal junction involving transient LES relaxations (TLESRs) of a sphincter supported actively by hiatal crura which are intricately coordinated with the LES. These motor mechanisms at the gastroesophageal junction are impacted by more distal motor mechanisms, involving gastric volume–pressure relationships promoting TLESRs and reflux, and by more proximal motor mechanisms, involving esophageal clearance of the refluxed material. Sensory phenomena have been appreciated recently, both for their role in the pain symptoms of reflux (with or without esophageal inflammation) and for their role as the gastric afferent limb to the TLESR. Whether reflux produces esophagitis depends not only on the frequency and duration of the reflux episodes produced by the above mechanisms, but also on the balance between the noxiousness of the refluxate and the counteracting esophageal mucosal protective mechanisms. Current attention focuses on the genetic and environmental factors that modulate all of these pathophysiologic mechanisms and thus underlie the determination of who becomes diseased.

Anti-reflux barrier

Transient lower esophageal sphincter relaxation

Very low pressure of the LES is a prerequisite for reflux of gastric contents into the esophagus. Most reflux in infants and children, as in adults, occurs primarily in association with transient lower esophageal sphincter relaxation (TLESR), defined as an abrupt decrease in LES pressure to the level of the intragastric pressure unrelated to swallowing [18]. Premature infants as young as 26 weeks of gestational age who were diagnosed with GERD exhibited more acid reflux during TLESRs, compared with healthy controls [19]. TLESRs may be triggered by gastric distention and by increased intra-abdominal pressure [20], as occurs with straining, obesity, tight clothing, cough, and increased respiratory effort. In infants, extrinsic abdominal compression in semi-seated postures in the post-prandial period is an important factor contributing to the pathogenesis of reflux. Also important are the influences of the meal

size, intragastric secretory volume, and osmolarity on the occurrence of TLESRs.

The TLESR is primarily a vagal reflex with neural pathways in the brainstem, and may be triggered by mechanoreceptor afferents upon stretching of the gastric fundus. The neuroenteric mediators responsible for inducing TLESRs include nitric oxide, vasoactive intestinal polypeptide, and cholecystokinin A, while somatostatin, gamma-amino butyric acid B ($GABA_B$), and opiates have the opposite effect. Increasing proximal gastric volumes increases the rate of TLESRs [21].

Hiatal hernia

Hiatal hernia is a fairly common finding in adults, with estimates of its prevalence ranging from 10–80%. Although widely believed to be a predisposition for reflux, it may be also be an incidental finding in asymptomatic persons [22]. Hiatal hernias have affected family members across multiple generations, leading some to suggest an autosomal dominant pattern of inheritance [23]. The diaphragmatic crura normally reinforce the LES as an anti-reflux barrier, and relax when a TLESR occurs. The lack of this reinforcement assumes significance when abrupt changes in abdominal pressure, such as during straining, overcome the LES pressure in a person with a hiatal hernia. Hiatal hernias are more prevalent in severe reflux disease, and have also been reported to be common in conditions associated with severe reflux, such as cystic fibrosis and neurological impairments [24]. Of 718 children with reflux, 6% were identified to have a hiatal hernia, and nearly a fourth of them were neurologically impaired [25]. Severe esophageal damage may occur during the prolonged esophageal acid exposure that can result from the trapping of acid in a hiatal hernia. The risk for reflux is considered to be greater with increasing size of a hiatal hernia, and complications of reflux like Barrett's esophagus are also associated with hiatal hernias [22].

Delayed gastric emptying

Delayed gastric emptying has been associated with more severe GERD in children [26]. Delayed emptying leads to gastric distention, more triggering of TLESRs, and accentuation of the volume and frequency of post-prandial reflux. Gastric emptying is influenced by the volume and osmolarity of the meal consumed; thus overeating and ingestion of fatty foods further provoke reflux. Children with cerebral palsy are considered to be more prone to reflux, due to disturbed motility, particularly gastroparesis. However, gastric emptying, measured by scintigraphy in 28 children with cerebral palsy, was not significantly different from that in a control group, and the emptying times did not correlate with GERD severity on pH monitoring [27]. Gastric fundic accommodation, the increase in gastric fundic volume in response to a meal, measured by barostat or scintigraphically, also likely impacts the occurrence of TLESRs, with greater accommodation allowing acceptance of greater volumes without provoking TLESRs. Other factors affecting intragastric pressure include obesity, tight clothing, provocative postures, straining, coughing, or wheezing.

Gastric sensorimotor aspects

In many patients including children, reflux symptoms of heartburn and chest pain correlate poorly with endoscopy findings. In the absence of erosive esophagitis, these symptoms are referred to as non-erosive reflux disease. In some of these cases, the pain of reflux disease may be associated with histologic esophagitis. In those patients lacking even microscopic inflammation, other potential explanations for the pain sensation include increased sensitivity of esophageal receptors to both nociceptive (painful) and non-painful stimuli, akin to visceral hyperalgesia causing functional pain in irritable bowel syndrome or dyspepsia. Such sensitization is proposed to be due to activation of the prostaglandin (PG) E receptor, and this may be an attractive target for treatment [28]. Studies conducted in adults with reflux demonstrate that acid infusion promotes esophageal pain hypersensitivity that is reduced by proton pump inhibition [29]. Symptoms elicited during acid infusion are also associated with increased esophageal contractility, postulated to be due to peripheral sensitization [30]. In support of a mechanism involving central sensitization of spinal afferents is the report of esophageal hypersensitivity upon duodenal acid exposure [31].

Refluxate

The pathogenicity of the refluxate is determined by the noxiousness of its constituents namely, acid, pepsin, trypsin, and bile salts. Acid in combination with pepsin has been found to be the most injurious to the esophageal mucosa. Most patients with reflux have normal gastric pH, and it has been suggested that volume rather than acidity of the refluxate may be more important in the pathogenesis of reflux. Infants, including premature infants of 24 weeks gestation, maintain that basal gastric pH below 4 from day one of life, but acid secretion is modified by neurocrine, endocrine, and paracrine pathways [32]. Severe reflux, defined by reflux index scores and esophagitis grade, in a small number of children correlated with gastric acid hypersecretion [33]. Pepsin and trypsin, being proteolytic enzymes, are directly damaging to the surface epithelium in their usual milieu, which is pH less than 4 for pepsin, and between 5 and 8 for trypsin. Increased serum pepsinogen values in neonates with upper gastrointestinal bleeding and esophageal lesions further support a pathogenetic role for pepsin [22]. Bile reflux may cause esophageal mucosal damage by rendering the membrane more permeable to acid. Simultaneous pH and bilirubin monitoring demonstrated bile and acid reflux in 9 of 13 children with severe esophagitis as graded by endoscopy [34]. Another report suggests a pathogenetic role for duodenogastric reflux, which was found to be higher in 10 patients with cystic fibrosis compared with 7 healthy controls [35]. Alterations in amino acid metabolism leading to increased esophageal mucosal taurine to serine ratio in patients with increased esophageal mucosal acid exposure may represent adaptive responses to acid reflux, and may precede esophageal inflammation [36]. Polyunsaturated fatty acids, precursors of eicosanoids, are also proposed to have a role in the pathogenesis of esophagitis [37]. In children, increased esophageal mucosal polyunsaturated fatty acids correlate positively with esophageal acid exposure but not with esophageal mucosal damage [37].

Esophageal clearance and mucosal resistance

An important line of defense against reflux is provided by effective peristalsis in coordination with swallowing; sucking appears as an integral part of this complex act in infants as early as 35 weeks of gestation. A disruption of the normal swallowing function particularly threatens the airways of fragile and physiologically immature infants with aspiration, apnea, cyanosis, and bradycardia. In older children, as in adults, upright posture confers an advantage in clearing refluxed material by the action of gravity, but this advantage is lacking in infants, who are generally recumbent in supine and semi-seated positions. Esophageal motor responses were nearly normal in response to infusion of saline in piglets with reflux, including those with esophagitis, but were impaired in response to acid infusion and influenced by acid volumes as well [38]. Primary esophageal peristalsis, initiated by swallowing, comprises 83% of all esophageal responses to reflux in infants [39]. Secondary peristalsis is induced by reflux and esophageal distention, and plays an important role in clearance during active sleep, thereby being crucial to infants who spend a great portion of time asleep. Peristaltic abnormalities may develop secondary to esophagitis; evidence for failed or hypotensive peristalsis is present in 20% of adults with mild, and 50% with severe esophagitis [40], [41]. Long lasting reflux episodes, those greater than 5 minutes, were reported to be more frequent in children with severe reflux than in those with mild reflux and controls [42]. Salivary functions include stimulation of wet swallows and the wash-down and neutralization of refluxed acid secretions. Other protective components proposed in the mucosal defense against acid reflux are prostaglandin E2 and nitric oxide, in low concentrations, but their contributions in children are poorly understood [43].

Helicobacter pylori

The role of H. pylori in relation to GERD symptoms and pathogenesis remains controversial. A recent prospective study compared symptoms before and after H. pylori eradication in 95 children. Symptoms remained unchanged, and were independent of H. pylori status [44]. Another study found that neither the diagnosis nor the severity of peptic esophagitis in H. pylori-infected, neurologically-impaired children was influenced by H. pylori eradication [45].

Clinical presentations

Esophageal presentations attributed to GERD vary according to the age of the patient, and include regurgitation, irritability, arching, and feeding aversion in infants, and vomiting, chest pain, heartburn, and abdominal pain in older children. Circumstantial evidence strongly suggests a relationship between reflux and a variety of extraesophageal presentations. These extraesophageal manifestations involve the airways or dental erosions. The former are best appreciated in light of the intricate coordination of the intimately related human respiratory and the digestive tracts, especially in fragile infants [46]. The relationship between reflux and respiratory symptoms is bi-directional; reflux may precipitate or exacerbate respiratory disease, and vice versa.

Esophageal

Vomiting and regurgitation

Regurgitation and vomiting are the most easily recognizable symptoms of pediatric reflux. Episodes are usually effortless, non-bilious and post-prandial. It is usually the quantity and type of emesis that differentiates physiologic reflux in "happy spitters" from symptomatic reflux in infantile GERD. Some children have persistent or intermittent symptoms beyond the first year of life. Projectile non-bilious emesis in the first few weeks of life may mimic hypertrophic pyloric stenosis but simply represent reflux, whereas bilious emesis mandates evaluation for intestinal obstruction.

Irritability and pain

Irritability coupled with arching in infants is thought to be a nonverbal equivalent of heartburn and chest pain reported by older children with reflux, and strongly believed to be clinical manifestations of esophagitis. However, these symptoms may correlate poorly with gross and microscopic findings in the esophageal mucosa. Infant crying has been demonstrated in association with reflux episodes during video and esophageal pH probe monitoring [47]. In patients with non-erosive reflux disease and normal esophageal histology, these symptoms are speculated to represent heightened sensory perception or visceral hyperalgesia. An important presentation overlapping with GERD, particularly in infants, is cow's milk allergy; studies report the two conditions co-existing in 42–58% children [48], [49]. Generally, in all children with the aforementioned symptoms, other causes of esophagitis, such as eosinophilic or infectious esophagitis, and esophageal motility disorders, warrant consideration.

Failure to thrive

Infants and older children with reflux are frequently reported to suffer from failure to thrive, but preterm infants are relatively protected, probably as a result of special care in intensive care units [50]. In a retrospective review of 295 children with clinical presentations suspicious for reflux, 72.5% (mean age four years) had at least one positive diagnostic test, and these children had a higher frequency of failure to thrive compared to those with negative testing for GERD [51]. Severe reflux may predispose to feeding refusal, and, in turn, to inadequate caloric intake, due to pain provoked by esophageal acid exposure during meals. In addition, loss of nutrients and calories due to emesis may predispose a child to poor growth. As an iatrogenic factor, the use of restricted diets to treat overlapping food sensitivities could also impair oral feeding abilities and contribute to poor growth.

Extra-esophageal

Apnea

Apnea is a frequently cited extraesophageal manifestation of reflux in infants, but the causal relationship is controversial, despite being examined by multiple investigators. Most episodes of apnea of prematurity occur in the post-prandial period, and likely follow bouts of regurgitation, and yet studies using impedance and monitoring cardiorespiratory events have been contradictory [52], [53]. In 21 infants with a history of intermittent reflux and apnea, 81% of apneic events did not follow episodes of reflux [52]. However, using pH and impedance testing in 22 infants with a history of irregular breathing and reflux, 29.7% (49 of 165) apneic episodes were associated with reflux, though only 22.4% of these were related to acid reflux [53], (*Fig. 1*) [54]. Apnea related to reflux has been explained on the basis of a

laryngeal chemoreflex causing respiratory pauses and laryngospasm [54], but might also be due to prolongation of normal mechanoreceptor-induced glottic closure [55], or to immaturity of pharyngo-esophageal clearance functions.

Otolaryngologic

Gastroesophageal reflux has been associated with several important otolaryngologic manifestations, including stridor, chronic cough, hoarseness, and "lump in the throat" [56]. Several laryngoscopic and bronchoscopic findings have been described as predictive of reflux. These include post glottic edema, vocal cord edema, nodules, arytenoid edema, tracheal cobblestoning, and sub-glottic stenosis [57]. Significant associations in adults may be limited to posterior commisure erythema (in 76% of GERD, 0% of normals), vocal cord erythema (in 70% of GERD, 2% of normals), and arytenoid medial wall erythema (in 82% of GERD, 30% of normals) [58]. Airway abnormalities such as tracheomalacia and laryngomalacia are often diagnosed in infants and children with stridor, and notably associated with laryngopharyngeal reflux [59], [60], though it is possible that the airway obstruction promotes the reflux. The prevalence of reflux as diagnosed by barium studies and pH metry was 70% in 54 children with laryngotracheomalacia compared with 39% in a control group. Gas reflux episodes with mild acidity have been demonstrated in adults with reflux laryngitis on concurrently performed impedance and pH studies, suggesting a contrast in the quality and quantity of refluxate involved in esophageal and extraesophageal presentations [61]. In 20 adults with laryngitis, a three month open label trial of high dose omeprazole (60 mg/day) resulted in significant improvement in laryngoscopic findings, including in all those patients who had a positive pharyngeal pH study. Symptoms of laryngitis and quality of voice as outcomes did not improve significantly [62]. In 90 of 100 children diagnosed with GERD based on the results of pH metry, the common laryngeal abnormalities were erythema and edema of the posterior laryngeal mucosa, vocal nodules and granulomas. A significant improvement in voice quality and laryngeal status occurred in those with laryngeal abnormalities in response to 12 weeks of anti-reflux therapy [63]. Possible mechanisms underlying these associations are neural reflexes mediated by intraesophageal acid, stimulation of laryngeal chemoreceptors, aspiration, and direct acid related inflammation [64]. Exacerbation of reflux possibly occurs as a consequence of negative intrapleural pressure and altered thoraco-abdominal pressures that allow acid to breach the anti-reflux barrier [65]. In a case-control study, neurologically normal children with GERD were found to be significantly more often affected by sinusitis, laryngitis, asthma, pneumonia, and

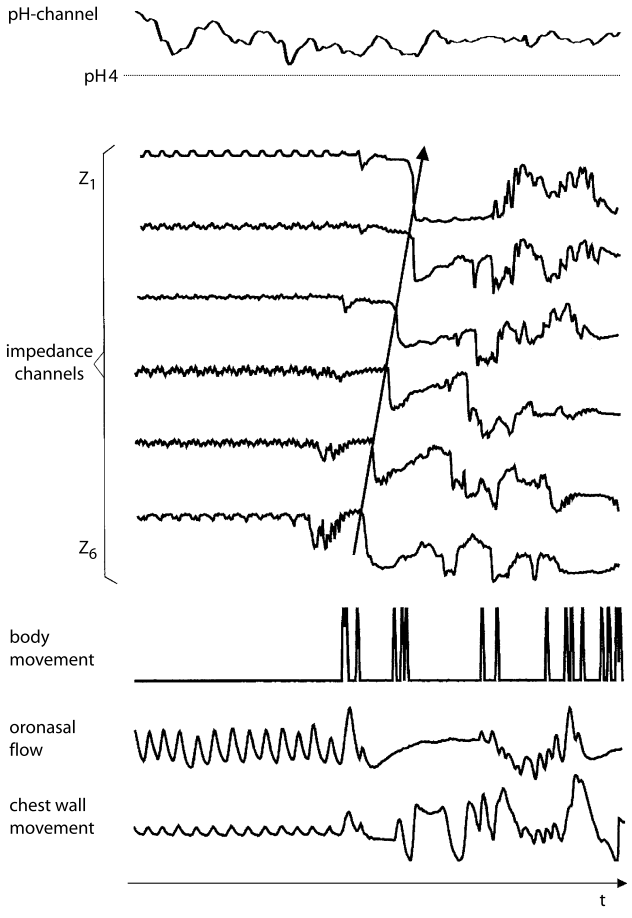


Fig. 1. Intraluminal impedance and simultaneous pH probe and pneumogram illustrating non-acid reflux: retrograde esophageal bolus passage with sequential decrease of impedance over time at pH $>$ 4. Temporal association with body movement and central breathing irregularity is apparent on the oronasal and chest wall movement sensors. [Wenzl TG (2202) Investigating esophageal reflux with the intraluminal impedance technique. J Pediatr Gastroenterol Nutr 34(3): 261–268]

bronchiectasis, but not by otitis media, than those without GERD [66]. Esophageal clearance was significantly delayed in 89 children with chronic respiratory symptoms when compared with those with primarily gastrointestinal symptoms (n = 83) or mixed symptoms (n = 64) in a study determining the severity of acid reflux by pH metry [67].

Asthma

Asthma and reflux commonly co-exist, but the contributions of each to the pathogenesis and symptoms of the other remain debatable, mainly due to differences in the selection criteria of study participants, and outcome measures evaluated [68]. Adult asthmatics report reflux symptoms more frequently than non-asthmatics, and experience more nocturnal awakening in relation to their late eating habits [69]. Children with asthma experience a high prevalence of reflux [70]–[72], but both are common conditions and thus could be associated by a chance in some children. One recent study described a 75% prevalence of reflux in 36 asthmatic children; reflux episodes were more frequent in upright versus supine positioning, but the overall reflux duration was not significantly different between positions [73]. Nuclear scintigraphy, used to detect clinical correlation between reflux symptoms and asthma episodes in asthmatic children, revealed scintigraphic evidence of reflux in 10 of 26 (38.5%) with GER symptoms, compared with 23 of 100 (23%) children without GER symptoms, but did not provide support for a direct causal effect of reflux on asthma [74]. A randomized controlled trial, rare in pediatric reflux-respiratory disease literature, evaluated asthma outcome in 37 children (10–20 years old, mean 14 years), using ranitidine for only four weeks as the intervention. A positive outcome was reported for nocturnal asthma symptoms but not for pulmonary functions [75]. Proposed mechanisms for reflux-induced asthma symptoms are acid-stimulated vagal nerve afferents triggering bronchospasm, or aspiration of gastric contents.

Dental erosions

A limited number of studies have examined the role of acid reflux in producing dental erosions in children [76], [77]. In 37 children evaluated for GERD, 20 of them were identified to have dental erosions, and all of them also had an endoscopic diagnosis of GERD [77]. As in adults, dental erosions in association with acid reflux affect the posterior dentition along the lingual surfaces. Ingestion of acidic (juices) and caffeinated beverages, consumption of ascorbic acid, and poor oral hygiene are other contributory factors.

Sandifer's syndrome

Sandifer's syndrome is characterized by hyperextended posturing involving the head, neck and upper torso. Originally the syndrome was thought to be a manifestation of reflux accompanied by hiatal herniation, but subsequent reports have identified cases in children without a diagnosis of a hiatal hernia [78], [79]. Many of these children are also diagnosed to have a neurological disorder. The majority of children with Sandifer's syndrome respond well to anti-reflux therapy.

Complicated GERD

The important esophageal complications of chronic reflux are strictures, Barrett's esophagus, and adenocarcinoma. Aggressive medical management, preferably with proton pump inhibitors, and close follow-up, using tests to assess symptoms and severity of reflux, are warranted in complicated GERD. Surgical management is contemplated in patients who remain unresponsive to medical therapy.

Strictures

Exposure of the esophagus to acid and perhaps to pepsin is crucial to the pathogenesis of reflux strictures; hiatal hernia and esophageal dysmotility are other risk factors [80]. Reflux strictures are typically located in the distal third of the esophagus, and should be distinguished from congenital esophageal stenosis and other types of strictures: caustic (generally more proximal), eosinophilic, postoperative/anastomotic, following radiation therapy or sclerotherapy, or (rarely in children) malignant. Esophageal mucosal biopsies obtained below the stricture help to confirm the diagnosis of reflux esophagitis and exclude eosinophilic esophagitis, Barrett's esophagus, or malignancy. Reflux strictures are treated with a series of dilations in conjunction with potent antireflux therapy [81]. Surgical resection or strictureplasty are reserved for recalcitrant strictures [82].

Barrett's esophagus
Barrett's esophagus, a rare diagnosis in children, is known to occur with long-standing acid exposure, and in association with cystic fibrosis, severe mental retardation, and repaired esophageal atresia [83], [84]. Genetic predispositions, prolonged duration of esophageal acid exposure, more severe nocturnal symptoms, and a reduced sensitivity to acid are implicated in the causation of Barrett's esophagus. Normal esophageal squamous epithelium is replaced by intestinal columnar metaplasia with goblet cells; the metaplasia is recognized in the distal esophagus as salmon-colored tongues of tissue projecting proximally into the paler pink esophagus. Guidelines for screening and surveillance have been proposed to help identify patients with Barrett's esophagus who may progress to develop dysplasia and adenocarcinoma [85].

Adenocarcinoma
Adenocarcinoma is extremely rare in childhood, but it does occur and should be sought in those with Barrett's esophagus. In an 11 year-old patient, the diagnosis of Barrett's esophagus was reported to progress to adenocarcinoma [86]. The risk of developing esophageal adenocarcinoma increases with hiatal hernia size, Barrett's esophagus length, and acid reflux severity.

Diagnosis

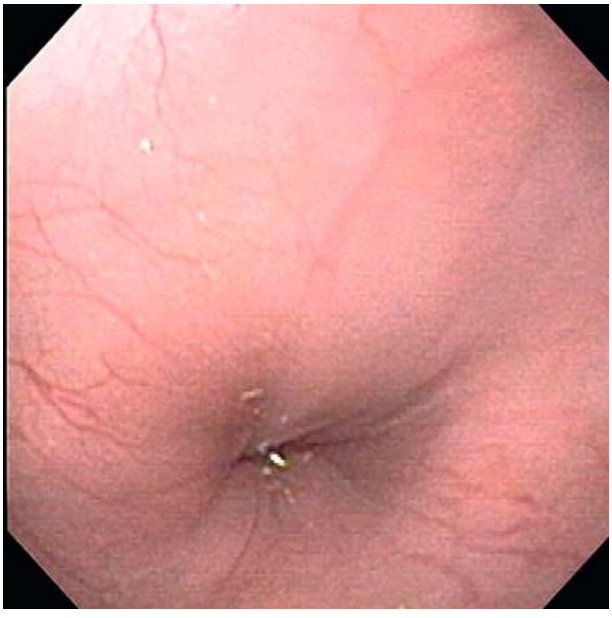
The diagnosis of uncomplicated esophageal reflux is usually established on the basis of a good history, and a thorough examination, with attention to the child's growth, nutritional, respiratory, neurological, and atopic status. A validated questionnaire has been developed for symptom assessment in infants and translated into multiple languages; others designed specifically for older children are now in use in epidemiological studies but must be further tested for reliability and validity [87], [88]. Complicated, unresponsive, and atypical presentations of GERD are indications for specialized investigations such as those discussed in the following section.

Endoscopy
An upper endoscopy, particularly when supplemented by histology, is the most accurate method of demonstrating esophageal damage by reflux, and for differentiating GERD from other diagnostic possibilities (*Fig. 2a–c*). It is performed as an outpatient procedure, and is less cumbersome than a 24-hour pH metry. Histologic abnormalities may be present in biopsies sampled from grossly normal esophageal mucosa. A review of endoscopic evaluation of reflux in 402 neurologically normal children, between 18 months and 25 years of age and without congenital esophageal disease, revealed erosive esophagitis in more than one-third, strictures in 1 to 2%, and suspected Barrett's esophagus (but without histologic confirmation) in nearly 3%.

Histology
A diagnostic upper endoscopy in children is almost always supplemented by distal esophageal biopsies. Biopsies at two levels are important to demonstrate differential eosinophilia in eosinophilic esophagitis. Histologic findings of reflux esophagitis are epithelial hyperplasia (the upper limit of normal basal layer thickness and papillary height in infants is 25% and 53%, respectively [89]), intraepithelial inflammation, vascular dilatation in papillae, balloon cells, and ulceration (*Fig. 3a–c*) [90]. Due to the often superficial, fragmented, and randomly oriented nature of biopsies in children, cellular inflammatory infiltrate may be the only recognizable finding [91]. Neutrophils are seen in about 20% or less of pediatric cases of reflux esophagitis, appearing in the most severe cases, and are hence not a sensitive marker. Eosinophils are not normally present in the epithelium of young children and can be indicators of GERD, but in concentrations greater than 20/high-power field (hpf) are likely to represent eosinophilic esophagitis, making them nonspecific for GERD. A few intraepithelial lymphocytes ("squiggle cells") are normally found, but $>$ 6 squiggle cells/hpf indicate reflux esophagitis [90].

Esophageal pH-probe monitoring
Esophageal pH monitoring (EpHM) is widely accepted as a safe and reliable method for detecting acid reflux. Perhaps its greatest utilities are in clarifying the relationship between reflux and discrete respiratory events such as apnea (with pneumogram), in quantifying acid reflux in extraesophageal GERD, and in assessing the efficacy of antisecretory therapy. In a retrospective analysis of children evaluated for GERD, EpHM detected reflux episodes at a higher rate com-

pared with barium examinations (83% versus 43%), and showed a lower false negative rate (7% versus 48%) [92]. Its utility in infants and children may be limited in the presence of structural upper airway or GI anomalies, and due to the buffering effect of non-acidic infant formula; probe placement, patient positioning, and dietary factors may contribute to day-to-day variability in pH-metry results [93]. Parents of children undergoing pH studies also perceive changes in their child's feeding pattern and activities during EpHM investigations, but the large majority regarded it as a well-tolerated test [94]. The utility of three different formulas to calculate pH probe placement based on patient height has been the subject of recent analyses [95], [96]. Fluoroscopy and, rarely in pediatrics, manometry are also used to verify probe positioning.



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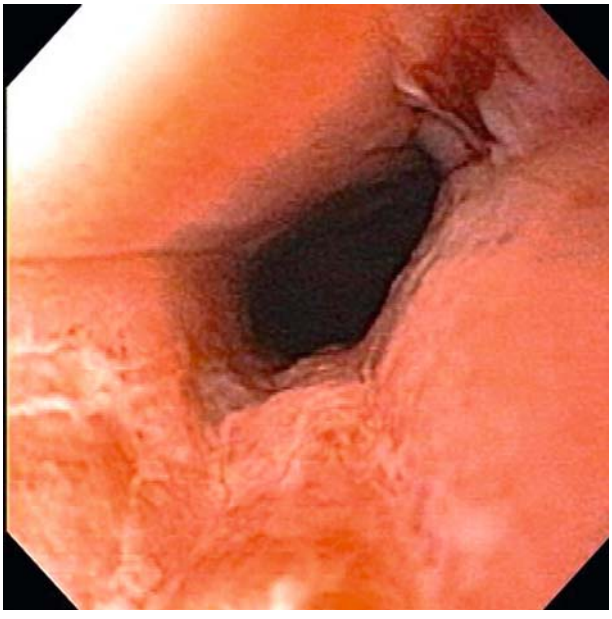

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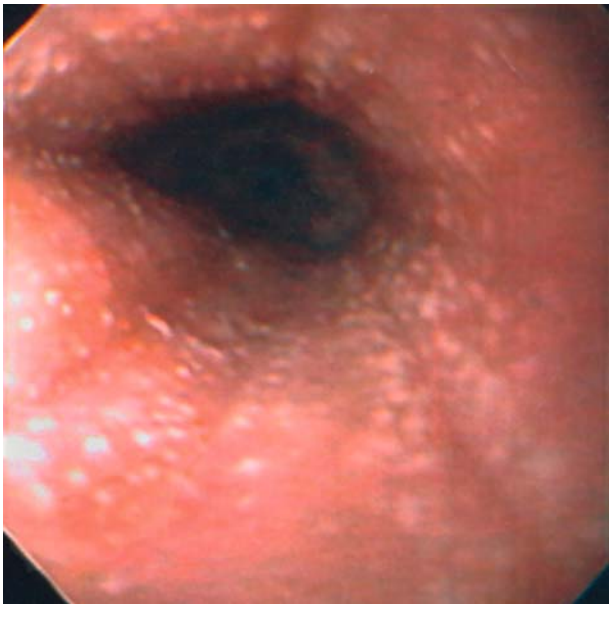

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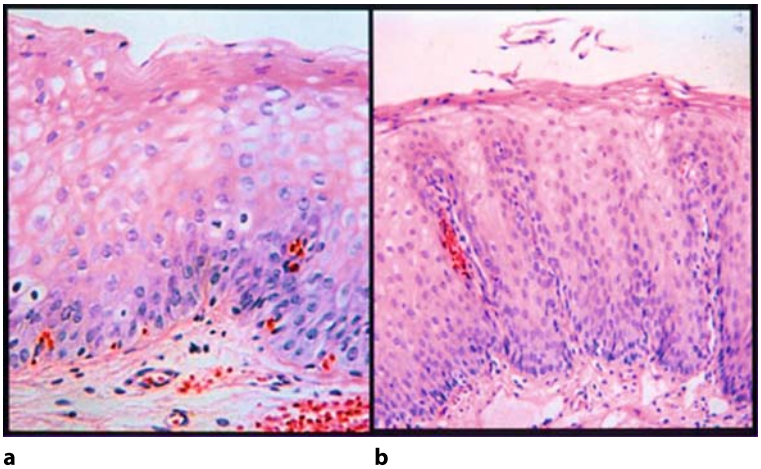
Fig. 2a–c. Endoscopic images from children with (**a**) a normal esophagus, (**b**) an esophagus with erosive reflux esophagitis, and (**c**) an esophagus affected by eosinophilic esophagitis. Eosinophilic esophagitis, distinct from GERD, often appears as in this image, with furrowing of the esophageal mucosa, and white specks on the surface resembling candidiasis

Conventional pH metry normative data includes reflux index (the percentage of time during a 24-hour day that the esophageal pH is <4), number of episodes and number of episodes longer than five minutes. Scores have been developed to associate reflux with respiratory disease, but are not widely used currently [97], [98]. Symptom association with reflux episodes comprises a frequently used function of EpHM [99], [100]. Dual pH monitoring, with the upper probe in upper esophagus, pharynx, or even the airways, is suggested as a potentially useful technique in patients with reflux and airway symptoms, but the limited pediatric data are conflicting and warrant further validation [101], [102]. The value of combining pH metry with impedance to improve the diagnostic yield and to clarify the pathogenetic role of non-acid reflux is now being explored in infants and children. [103], [104]. An exciting development is the application of the Bravo pH capsule system in children with GERD, sparing the patient the discomfort of an indwelling transnasal probe; this technique has the potential for higher quality data acquisition than conventional pH metry [105].

Fluoroscopy

Fluoroscopic evaluation of swallowing and of the upper gastrointestinal tract is often important in the evaluation of the child presenting with obstructive gastrointestinal symptoms or chronic respiratory symptoms. It may also disclose other diagnoses: pyloric stenosis, malrotation, achalasia, and strictures. It has a low sensitivity and specificity for diagnosing reflux and is only a brief snapshot of overall reflux [92]. Barium esophagography or specialized swallowing studies may be useful in identifying abnormalities of pharyngeal, laryngeal, or upper esophageal



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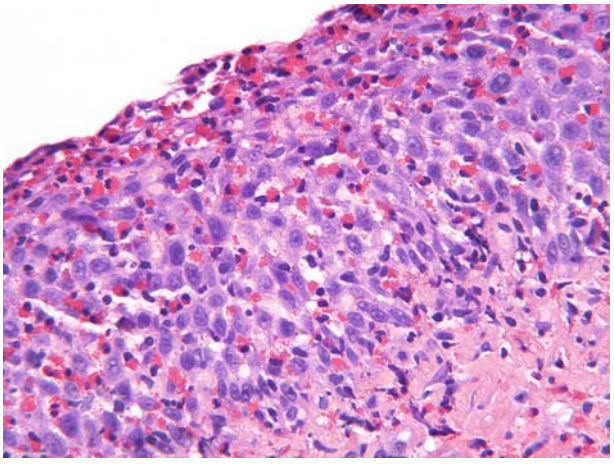

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Fig. 3a–c. Biopsies of the esophagus from children with (**a**) normal histology, (**b**) morphometric changes of reflux manifest in papillary lengthening and basal layer thickening, and (**c**) eosinophilic esophagitis. Extensive esophageal epithelial eosinophilia, as shown in this image (>20eos/hpf), along with papillary elongation and basal layer hyperplasia, constitute the histological features of eosinophilic esophagitis.

function that may prompt aspiration during swallowing and during reflux.

Nuclear scintigraphy
Scintigraphy, also referred to as "a milk scan", is generally performed in infants and children suspected of reflux to gather information regarding reflux-associated aspiration, and to quantify gastric emptying times. The study employs liquid (generally in infants) or solid meals labeled with technetium 99m – for its short (6 hour) half-life and limited radiation burden. It offers the advantage of detecting non-acid reflux in the post-prandial period, but is technically demanding and restrictive for a child. Scintigraphy has a sensitivity of 79% and specificity of 93%, when pH metry is used to define reflux [106]–[108].

Impedance
The multiple intraluminal impedance technique is a valuable tool for diagnosing reflux, and its relationship to respiratory events, particularly in infants, in whom post-prandial reflux is non-acidic (*Fig. 1*) [54]; it also evaluates esophageal clearance and swallowing. In an early report of its use in infants, the sensitivity of impedance was 98.7%, compared with 18.9% for pH metry in identifying all reflux [109]. Despite time-consuming and visually complex analysis, impedance studies are gradually being applied to the evaluation of pediatric GERD, and its therapies [53], [104], [110].

Tests for reflux aspiration
The identification of lipid-laden macrophages in tracheal aspirates is generally considered a useful marker for aspiration but lacks the sensitivity or specificity for it to be considered a highly reliable test [111], [112]. Scores are computed, based on the number of lipid-laden macrophages in a given sample, and used to grade the probability of aspiration. Moderate to large number of macrophages may imply aspiration but does not differentiate between reflux- and swallow-related aspiration. Pepsin in tracheal aspirates, sputum, and saliva has been proposed as a more reliable and specific test of reflux aspiration. A strong association has been reported between positive tracheal pepsin assays in children with reflux or respiratory symptoms, particularly in those with coexisting symptoms [113], [114].

Management

Conservative anti-reflux therapy
Aspects of anti-reflux conservative therapy recommended for adults may also be applied to older children and adolescents with GERD, but must be tailored to infants because of unique developmental and maturational factors.

For infants, who are mostly supine, the gastroesophageal junction is constantly "under water," and accessible to reflux of gastric contents. Although prone position has been shown to reduce reflux compared with supine or seated infant positions, support for instituting such measures has been less than enthusiastic due to the link between prone position and sudden infant death syndrome. Efforts to minimize physically engaging and excitable situations in the post-prandial period may also help in reducing reflux, because of the increase in regurgitant reflux promoted by abdominal contractions [115]. Effective parental reassurance and telephone conversations aimed at educating parents regarding reflux go a long way in symptom resolution for a large number of infants [116]. Thickening of feeds is a first line anti-reflux therapy in infants [104], [117], [118]. Formula viscosity may be increased either by adding rice cereal to feeds or by using commercially available pre-thickened (with rice starch or locust bean gum) anti-regurgitant formulas. This intervention reduces regurgitation, decreases crying, and increases sleep time [118], [119]. Adding 15 mL rice cereal per 30 ml of milk formula increases the caloric density by 50% and may induce constipation. Pre thickened or home thickened formulas are comparable in their anti-regurgitation efficacy, but the former may be better tolerated [119]. Frequent and small volume feedings, as well as lower osmolality feedings, have all been advocated as beneficial to infants with reflux [120].

Pharmacotherapy
Pharmacotherapeutic agents encompass anti-secretory agents, antacids, barrier agents, and prokinetic agents (Table 1). Anti-secretory agents are the first line of pharmacotherapy because they are most efficacious in treating acid related symptoms and complications of reflux. Anti-secretory agents include histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). PPIs have assumed a significant position in management of severe, complicated and extraesoph-

ageal reflux presentations, and have the potential for obviating the need for anti-reflux surgical procedures. Data on the efficacy, safety, tolerability, and dosage for omeprazole and lansoprazole in children are available [121], [122]. Important developments pertaining to the subject include approval of PPIs for pediatric use, as well as the availability of new formulations of both these drugs that are expected to simplify treatment options and compliance. Further information on safety and efficacy of H2RAs is also being gleaned in children, which may prove useful because of their efficacy in fasting and nocturnal reflux, despite their generally lower potency and tendency toward tachyphylaxis [123]. Most studies, at least in older children, have found PPIs to be more efficacious in symptom relief and healing of esophagitis compared with H2RAs, antacids, or barrier agents [121], [122]. The daily doses of PPIs administered to children are higher on a weight basis than the standard adult dosages.

A failure to respond to optimal doses of PPIs should raise considerations of incorrect diagnosis, improper administration (should be given just before

Table 1. Anti-reflux pharmacotherapy, oral dosages, and side-effects. AC = ante-cibum; PC = post-cibum; HS = hour of sleep

Prokinetics		
Metoclopramide	0.1 mg/kg/dose qid: AC, HS	Drowsiness, restlessness, dystonia, gynecomastia, galactorrhea
Erythromycin	3–5 mg/kg/dose qid: AC, HS	Diarrhea,vomiting, cramps, antibiotic effect, pyloric stenosis
Domperidone	Pediatric doses not defined	Hyperprolactinemia, dry mouth, rash, headache, diarrhea, nervousness
Bethanechol	0.1–0.3 mg/kg/dose qid: AC, HS	Hypotension, bronchospasm, salivation, cramps, blurred vision, bradycarida
H2-receptor antagonists		
Cimetidine	10–15 mg/kg/dose qid: AC, HS	Headache, confusion, pancytopenia, gynecomastia
Ranitidine	3–5 mg/kg/dose bid-tid: AC, HS	Headache, rash, constipation, diarrhea, malaise, elevated transaminases, dizziness, thrombocytopenia
Famotidine	0.5 mg/kg/dose bid: AC	Headache, dizziness, constipation, nausea, diarrhea
Nizatidine	Pediatric doses not defined	Headache, dizziness, constipation, diarrhea nausea, anemia, urticaria,
Proton pump inhibitors		
Omeprazole	0.7–3.3 mg/kg/d, 1–2 div doses: AC	Headache, rash, diarrhea, nausea, abdominal pain, vitamin B 12 deficiency
Lansoprazole	15 mg/d ($\leq$ 30 kg); 30 mg/d ($>$30 kg): AC	Headache, diarrhea, abdominal pain, nausea
Pantoprazole	Pediatric doses not defined	Headache, diarrhea, abdominal pain, nausea, flatulence
Rabeprazole	Pediatric doses not defined	Headache, diarrhea, abdominal pain, nausea
Esomeprazole	Pediatric doses not defined	Headache, diarrhea, nausea, abdominal pain, flatulence, dry mouth, constipation
Barrier agents		
Sucralfate	40–80 mg/kg/d qid: AC, HS	Vertigo, constipation, dry mouth, aluminum toxicity, decreases absorption of concurrently administered drugs
Sodium alginate	0.2–0.5 mL/kg/dose 3–8 times/d PC	Same as antacids
Antacids		
	1 mL/kg/dose, 3–8 times/d	Constipation, seizures, osteomalacia, hypophosphatemia (Al), diarrhea (Mg), fluid retention (Na), milk-alkali syndrome (Ca)

a meal and not in the presence of antacids or H_2RAs), or genetic variation in hepatic cytochrome P-450-2C19, which results in more rapid metabolism of PPIs. For children unable to swallow PPI capsules, granules can be administered orally in a weakly acidic material such as apple juice or yogurt, or in a solution of sodium bicarbonate for administration through jejunal tubes.

Antacids neutralize already-secreted acid, must be given in relatively large doses to compare with anti-secretory therapies, and convey potential side effects. Nonetheless, their immediate neutralization of refluxed acid may be useful for occasional instantaneous relief, and thus also as a rapid diagnostic test for the cause of pain.

Sucralfate is the most widely used barrier agent, and acts by forming a complex with the base of ulcers or erosions. Its main use is in erosive and ulcerative esophagitis.

Prokinetic agents have theoretical benefit in reflux, particularly in young children, but their use has been limited due to lack of objective demonstration of benefit, and due to concerns about serious side effects and toxicity. Bethanechol, a non-selective cholinergic agonist, is without clear benefit and is currently rarely used. Metoclopramide is a dopamine-2 receptor antagonist, 5-HT3 antagonist, 5-HT4 agonist, and a slightly anticholinergic agent that acts by increasing the LES pressure and improving gastric emptying. It has a narrow therapeutic range; extrapyramidal side effects and drowsiness are the most common side effects [124]. Domperidone is a peripheral dopamine-D2 receptor antagonist that has a therapeutic potential for improving gastric emptying and esophageal motility, but clinical efficacy data are lacking [125]. A small number of studies investigating the effects of erythromycin in children with gastroparesis support a role for erythromycin as a prokinetic agent, but it has not been studied in children with reflux [126]. It exerts its prokinetic effects at low doses by direct activation of gastric motilin receptors on cholinergic neurons. Higher doses of erythromycin may stimulate the alternative pathway, activating the *muscular* motilin receptors, and producing prolonged, non-propagated antral contractions which will not improve gastric emptying. Potentially serious side effects are rare with low dose erythromycin; emergence of antimicrobial resistance has not been studied [126]. Cisapride is now generally unavailable for use in United States. A new motilin receptor agonist without antibacterial activity, ABT-229, was shown in a placebo controlled study to significantly reduce mean percentage of time esophageal pH was less than 4, but did not change the results of the esophageal manometry and gastric emptying studies [127].

The potential beneficial effects of baclofen, a GABA type-B receptor agonist, are attributed to its reducing the frequency of reflux episodes by its reduction of TLESRs. Pediatric experience with baclofen in neurologically impaired children was recently reported; administration of baclofen orally or via feeding tube three times daily for one week significantly reduced the frequency of emesis, as well as the pH parameters of total number of reflux episodes, and episodes longer than five minutes. However, baclofen did not positively impact the reflux index [128].

Anti-reflux surgery

Fundoplication remains an important, and perhaps the most definitive, technique for eliminating reflux. The most common indications for performing this surgery in children are GERD refractory to pharmacotherapy and life threatening respiratory complications associated with reflux, such as aspiration. [129]–[131]. The exact role of fundoplication in extraesophageal GERD and in those children with chronic lung diseases is unclear [130]. Symptoms and signs suggestive of reflux may persist or recur after surgery, and may prompt resumption of pharmacotherapy, despite lack of documentation of reflux. In a two-year post fundoplication follow-up of 176 children (two-thirds of whom also had other medical disorders, including neurodevelopmental delay, asthma, and cystic fibrosis), two thirds reported reflux-like symptoms necessitating therapy [132].

Laparoscopic Nissen fundoplication is being increasingly performed in infants and children. Reports cite it as well-tolerated, and associated with favorable early and late outcomes [133]–[135]. Forty-eight children with reflux and symptoms of airway disease had no recurrence of reflux during a one year follow-up post-procedure, and the overwhelming majority of parents perceived the outcome as positive [135]. During a median follow-up of three years after laparoscopic fundoplication in 38 children, 66% were completely asymptomatic and 26% were improved. In comparison with the open surgical technique, children undergoing laparoscopic Nissen fundoplication have a shorter hospital stay and a lower complication rate [136]. The

rate of complications in children with and without neurological diseases is reported as 2 and 3.4% in different studies [137], [138]. In one center's experience, almost all of the complications occurred in the first 50% of the cases, underscoring the effects of the learning curve and improved techniques [137].

Esophagogastric separation was performed with favorable results in 10 neurologically impaired children who had failed previous fundoplication; further experience and long-term outcomes with this technique are desirable [139]. Robotic laparoscopic anti-reflux surgery has also been added to the surgical armamentarium, but it has only been performed in a small number of children. The early reports are encouraging, provided instruments appropriate for pediatric cases are made available [140].

Endoscopic treatment

Endoscopic therapies against GERD that have been studied in adults include radiofrequency ablation, gastroplication, and injection of inert biopolymers. Experience with these techniques in children is limited.

Radiofrequency ablation procedure is a novel anti-reflux treatment strategy. A single published pediatric report describes 6 older children with an average age of 18 years, of whom five were asymptomatic at a three month follow-up; at six months follow-up mean GERD symptom scores were significantly better than before the procedure [141]. Endoluminal gastroplication and suturing in adults are reported to improve reflux index and symptom scores. A recent study of children (median age 12.4 years) with refractory GERD undergoing gastroplication reported a significant improvement in symptoms and quality of life scores [142]. At follow-up, 33 months later, 82% remained off anti-reflux medications, and at one year, six of nine patients had improved pH parameters including reflux index on a pH study. This procedure may be complicated by suture perforation, mucosal tear, and bleeding [143]. Early experience with the injection of a biochemically inert and bioabsorable polymer into the muscle of the gastric cardia is encouraging. Further data regarding the efficacy and safety of these three techniques in large controlled studies involving adults are needed before exploration of the precise role and clinical application of these endoluminal therapies can be defined in carefully selected pediatric GERD patients [143].

Conclusion

Gastroesophageal reflux is the most common esophageal disorder in children, and is responsible for heterogeneous presentations ranging from effortless regurgitation in "happy spitters" to complex esophageal and extra-esophageal GERD. The frequency and noxiousness of refluxate in proportion to the various esophageal defense mechanisms, and genetic, physiological and environmental influences ultimately determine the pathogenicity and complications of the disorder. While most children may be confidently diagnosed solely on the basis of a detailed history followed by appropriate response to therapy, diagnostic tools may be useful to clarify the role of reflux in extra-esophageal, and complicated GERD. Prompt identification and intervention for GERD in children is crucial to the prevention of strictures, Barrett's esophagus and adenocarcinoma that are associated with long-standing reflux exposure. The first line of anti-reflux therapy in children is conservative therapy emphasizing thickened feeds, smaller volume meals, proper positioning, and elimination of smoke exposure. Proton pump inhibitor therapy has an established role in the management of those with GERD sequelae, and as empiric therapy in those with extra-esophageal GERD. Fundoplication, reserved for children who are refractory to pharmacotherapy, is being performed successfully; results of laparoscopic surgery in children are favorable with respect to shorter hospital stay, and lower complication rate than open fundoplication.

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