Pediatric Esophageal Disorders: Diagnosis and Treatment of Reflux and Eosinophilic Esophagitis

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Education Gaps

Gastroesophageal reflux (GER) occurs frequently in infants, with gastroesophageal reflux disease (GERD) representing only a small fraction of affected patients. The number of prescriptions for proton pump inhibitors (PPIs) has significantly increased. Clinicians need to be aware of the paucity of data supporting the effectiveness of PPIs for treating infants with reflux, and possible adverse effects of PPIs. Clinicians should also be able to recognize the potentially similar clinical presentation of GER and eosinophilic esophagitis.

Objectives   After completing this article, readers should be able to:

1. Differentiate physiologic reflux from gastroesophageal reflux disease (GERD).

2. Understand that an upper gastrointestinal (UGI) study should not be ordered for diagnosing reflux.

3. Recognize the limitations of PPI medications.

4. Know possible clinical presentations of eosinophilic esophagitis (EoE).

5. Identify dietary and medication treatment options for EoE.

6. Be cognizant of other esophageal disorders that can cause esophageal dysfunction.

ABBREVIATIONS

BRUE	brief resolved unexplained event
EoE	eosinophilic esophagitis
FDA	Food and Drug Administration
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
H2RA	histamine-2 receptor antagonists
PPIs	proton pump inhibitors
TLESR	transient lower esophageal sphincter relaxations
UGI	upper gastrointestinal

Abstract

Gastroesophageal reflux (GER) occurs frequently in infants, generally at its worst at 4 months of age, with approximately two-thirds of infants spitting up daily. GER typically improves after 7 months of age, with only ∼5% of infants continuing to have reflux at 1 year of age. The diagnosis can often be made based on clinical symptoms. Upper GI (UGI) study has low sensitivity and specificity and should not be ordered as a diagnostic test for reflux. UGI study is best for evaluating other anatomic causes of vomiting. GER becomes problematic

gastroesophageal reflux disease (GERD) when complications are present, including feeding difficulties and poor weight gain. Conservative treatment and thickened formula can be helpful for treating GERD. Proton pump inhibitors (PPIs) are frequently prescribed for treating reflux. However, studies do not show a definite benefit in infants, and there are potential side effects. Older children with GERD may present with regurgitation, heartburn, chest discomfort, dysphagia, abdominal pain, vomiting, poor appetite, or poor weight gain. Upper endoscopy is considered for children with concerning symptoms, persistent symptoms despite treatment, and relapse of symptoms after treatment. Other esophageal disorders can have a similar clinical presentation as GERD, notably eosinophilic esophagitis (EoE). EoE is a chronic immune-mediated disorder of the esophagus, which may present as dysphagia, food impaction, heartburn, vomiting, abdominal pain, feeding difficulties, or failure to thrive. Diagnosis is made histologically by the presence of esophageal eosinophilia on endoscopic biopsies in the correct clinical setting.

GASTROESOPHAGEAL REFLUX IN INFANTS

Definitions
Gastroesophageal reflux (GER), also referred to as spitting up, regurgitation, and spilling, is defined as the passage of contents from the stomach up into the esophagus. When GER causes troublesome symptoms or complications, including significant irritability, feeding difficulties, or poor weight gain, it is named *GERD*.

Prevalence and Natural History
GER is a normal physiologic process that occurs in healthy infants and children. A cross-sectional survey of 948 parents of healthy children found that reflux is at its worst at 4 months of age; at this time, about two-thirds of infants are spitting up at least once a day. (1) Similarly, another study reported that 41% of 3- to 4-month-old infants are spitting up at least half of their feeds every day. (2) Reflux improved after 7 months of age, at which time the percentage of infants spitting up on a daily basis dropped to ~20%, which further improved to ~5% or less by 1 year of age. (1)(2) This improvement is likely related to a combination of factors, including starting infant foods, spending more time in the upright and sitting positions, and decreased number of lower esophageal sphincter relaxations.

Certain pediatric populations are at higher risk for reflux, including children with hiatal hernia, neuromuscular disorders, chronic respiratory disorders, prematurity, history of esophageal atresia, achalasia or other reason for esophageal dysmotility, and obesity. There also appears to be a genetic component to reflux, as noted by an increase in reflux symptoms and reflux-associated diseases within families. (3)(4)

Pathophysiology
GER occurs secondary to transient lower esophageal sphincter relaxations (TLESR). These TLESR occur more often in the postprandial period, in response to gastric distention. Gastric distention and increases in intragastric pressure increase the number of TLESR, allowing GER to occur more frequently after eating and after eating larger meals. (5)

The antireflux barrier consists of the diaphragmatic crural support, the intra-abdominal segment of the esophagus, and the angle of His. In patients with a sliding hiatal hernia, these protective barriers are compromised. In these patients, the gastric cardia is displaced upward above the diaphragmatic hiatus. This interferes with the crural diaphragm support to the lower esophageal sphincter, thus increasing the potential for reflux. (6) An abnormal esophageal peristalsis response to refluxed material can lead to impaired clearance and reflux-related complications. (7)

Clinical Signs and Symptoms
GER often presents as effortless spitting up after feeds and in between feeds. At times, reflux can trigger more forceful vomiting, probably due to refluxed gastric contents stimulating pharyngeal sensory afferents. (8) Infants with GER

may be "happy spitters," and others may be fussy. Both reflux and fussiness occur commonly in infants; however, a double-blind placebo-controlled crossover trial of omeprazole in irritable infants with GER failed to demonstrate a correlation. Compared with placebo, omeprazole treatment resulted in improvement in the reflux index on pH study, but "there was no significant difference in the cry/fuss time while taking either omeprazole or placebo." Both groups showed improvement in irritability with time, regardless of treatment. (9)

Sandifer syndrome is an uncommon, but specific manifestation that has been associated with GERD. Sandifer syndrome is described as dystonic spasmodic movements with head, neck, and back posturing. The etiology is not entirely clear, but may be related to shared innervation of the diaphragm and muscles associated with movements of the head and neck, with diaphragmatic stimulation then causing reflex contraction of these muscles. (10) Another possible explanation could be that these movements result in symptomatic relief, perhaps related to improvement in esophageal motility. (11)

Infants with GERD may have associated feeding problems. These infants may associate reflux-related discomfort with feeding times, possibly progressing to feeding aversion. They may not gain weight well, due to both poor intake and regurgitation of consumed feeds.

GERD as a cause of brief resolved unexplained events (BRUEs) has been studied; these events were previously referred to as *apparent life-threatening events*. Data to support an association of reflux with BRUEs are limited. In a prospective infant study, simultaneous pneumogram and impedance pH study showed that only ∼15% of 527 apneic episodes were temporally linked with reflux.(12) "The available evidence suggests that in the vast majority of infants, GER is not related to pathologic apnea or to apparent life-threatening events, although a clear temporal relation based on history, observation, or testing occurs in individual infants."(8) In select infants who do have GERD-associated apnea or BRUE, this could be explained as an exaggeration of the normal protective reflexes that inhibit breathing when there is fluid in the pharynx. In the cases in which reflux is the cause of BRUE, this is more likely when the event occurred in close proximity to a feed, the infant was awake, and obstructive apnea was present. (8)

Diagnosis and Evaluation

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition published updated clinical practice guidelines in March 2018, to provide recommendations for the diagnosis and management of GER and GERD in infants and children. (13) Most often, GER can be diagnosed based on clinical history, without any additional testing. Concerning signs and symptoms that would warrant evaluation for other causes of vomiting include bilious vomiting, consistently forceful vomiting, failure to thrive, hematemesis or hematochezia, fever, lethargy, hepatosplenomegaly, bulging fontanelle, macro/microcephaly, hypo/hypertonia, seizures, suspected metabolic syndrome, and onset of vomiting after 6 months of age, among others. (8) Other diagnoses can present with refluxlike symptoms, including milk protein intolerance and EoE. Infants with milk protein intolerance improve with protein hydrolysate or elemental formula, or with exclusion of milk from the maternal diet if breastfed. EoE is discussed in further detail herein.

It is important to understand that although a UGI study may show episodes of reflux, this study should not be ordered as a diagnostic test. (13) The sensitivity, specificity, and positive predictive value of a UGI study, using pH monitoring as the reference, ranges from 29% to 86%, 21% to 83%, and 80% to 82%, respectively. (8) The low sensitivity and specificity could be due to the brief fluoroscopy time, the higher density of barium contrast compared with normal gastric contents, and/or the high occurrence of physiologic reflux. Instead, the indication for a UGI study is to evaluate for hiatal hernia or other anatomic abnormality as the cause of vomiting, such as malrotation, stenosis, web, annular pancreas, etc. UGI study can also identify tracheoesophageal fistula, vascular rings, achalasia, and motility abnormalities.

Twenty-four–hour impedance pH study is a test that can evaluate for reflux, including the frequency of reflux episodes, acid versus nonacid reflux, the extent of reflux (episodes that reach the proximal esophagus), and correlation of reflux episodes with symptoms. This test detects intraluminal bolus movement between electrodes positioned in the esophagus. GER is characterized by a drop in impedance progressing distally to proximally as liquid advances from the stomach to esophagus. Impedance testing is typically combined with pH monitoring to determine if the GER is acidic or nonacidic. The study can be conducted with or without reflux medications and patients should receive their usual oral/bottle feeds and/or tube feedings during the study. This study requires special equipment and training, and may not be available at all medical centers.

Endoscopy is reserved for those patients who have a more concerning history or examination findings and/or fail to respond to usual treatments. Endoscopy may also be considered for persistent reflux symptoms after 18 to 24 months of age. Endoscopy can evaluate for reflux esophagitis and other causes of refluxlike symptoms, including EoE.

Studies that have not been found to be useful for diagnosing reflux include gastrointestinal scintigraphy (milk scan) and bronchoalveolar lavage to check for lipid-laden macrophages and pepsin. These tests have low sensitivity and specificity for diagnosing reflux. (8)(13)

Management

In otherwise healthy infants with reflux, lifestyle modifications, caregiver education, and reassurance may be all that is needed until the reflux improves on its own with time. Lifestyle modifications include smaller, more frequent feeds, frequent burping, keeping the infant upright after feeds, avoiding vigorous handling after feeds, elevating the head of the bed when sleeping, and avoiding tobacco smoke exposure. Reflux is less likely to occur in the prone position and left side down position (14); however, because of the instability of a side-lying position and the risk of sudden infant death syndrome in the prone position, the only recommended sleeping position is on the back. Although a car seat does help keep infants in a more inclined position, this could actually exacerbate reflux due to increases in intra-abdominal pressure. (15)

Thickeners, like commercial powder thickeners or infant cereal, can be added to formula to help decrease reflux episodes. Because most reflux events in infants are already nonacidic because milk/formula neutralizes gastric acid, thickening formula is a practical consideration for treating reflux. A systematic review and meta-analysis of 14 randomized controlled trials assessing the effect of thickened formula for GER in infants, showed that thickened formula significantly reduced the number of episodes of regurgitation and vomiting. However, esophageal pH monitoring showed no change in the reflux index (percentage of time during which the pH was <4) or the number of episodes of acid reflux per hour. The authors stated that "although the differences were statistically significant, the reduction may be of questionable clinical significance (eg, reduction in regurgitation by 0.6 episode per day)." (16)

Infant cereal (rice cereal and oatmeal cereal) and commercial powder thickeners can be used to thicken formula. However, recent concerns have been raised about increased levels of arsenic in rice cereal. Nectar consistency equals 1.5 teaspoons of cereal per ounce of formula. Adding infant cereal or commercial thickener powder increases the calorie density of the formula. Thickening formula typically requires a faster flow bottle nipple because of the increased effort required to suck the thicker formula. Pulverizing the cereal can decrease the potential for cereal clogging the nipple. Powder thickeners and infant cereals do not work well to thicken breast milk, because the enzymes in breast milk break down the thickener. Although xanthum gum–based thickeners can thicken breast milk, they are not recommended for infants younger than 1 year because of the potential association with necrotizing enterocolitis. (17) In May 2011, the US Food and Drug Administration (FDA) advised against using a commercial xanthum gum gel thickener in infants born before 37 weeks. Another option to thicken breastmilk is a carob bean gum thickener. Carob bean gum thickener must be added to warmed breastmilk for it to dissolve completely and thicken. It is marketed for use in infants older than 42 weeks' corrected gestational age and weighing more than 6 pounds.

Specific commercial formulas are available, which will thicken when consumed. One advantage of these formulas is that they do not require increased effort to suck from the bottle, because they become thickened once in the stomach and exposed to gastric acid. Therefore, these formulas are not very effective in infants receiving an acid-blocker medication. Formulas with higher whey percentage could also be beneficial for infants with GERD, because whey empties faster from the stomach than casein, resulting in less formula in the stomach to be refluxed. As noted earlier, because of the potential for milk protein intolerance possibly presenting with similar refluxlike symptoms, a 2- to 4-week trial of a protein hydrolysate or elemental formula is reasonable. (13)

Medications are often prescribed to treat GERD, including histamine-2 receptor antagonists (H2RAs) and PPIs. However, a number of studies show no decrease in infant regurgitation of PPIs compared with placebo. (13) Multiple studies have shown no significant difference in PPIs over placebo in improving crying or irritability, making it uncertain whether PPIs provide a definite benefit. (13)

Antacids should be used with caution in infants, based on reports of increased plasma aluminum levels or milk alkali syndrome with repeated use. (18) H2RAs decrease acid secretion by inhibiting the H2 receptor on the gastric parietal cell. H2RAs work quickly, with gastric pH rising within 30 minutes and peak onset of action about 2.5 hours after dosing. PPIs suppress acid production by inhibiting the H+K+ ATPase on the gastric parietal cell, the final step in acid production. The onset of action of PPIs is 1 to 2 hours, with peak effect being seen after several days. Compared with H2RAs, PPIs have higher rates of improvement in healing erosive/ulcerative esophagitis. (19) PPIs are able to inhibit meal-induced acid secretion, with best bioavailability seen when administered 30 minutes before meals. Tachyphylaxis, or tolerance, can develop quickly with oral and intravenous H2RAs. (20)(21) PPIs have not been shown to develop tachyphylaxis.

The number of prescriptions for PPIs has significantly increased. "Use of PPIs increased 4-fold from 2000 to 2003" in infants younger than 12 months. (22) PPI options include omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, and dexlansoprazole. The FDA has approved omeprazole, lansoprazole, and rabeprazole for infants older than 1 year, pantoprazole for children older than 5 years, and dexlansoprazole for those older than 12 years. Only esomeprazole is approved for infants older than 1 month.

PPIs can be prescribed as liquid suspensions, packets, soluble tablets, or capsules. The capsules contain enteric-coated granules and can be opened up and sprinkled on a spoonful of soft food, like applesauce or yogurt, or added to 2 oz of apple juice. The soluble tablets can be placed on the tongue to dissolve or they can be dissolved in 5 to 10 mL of water before administration. Choice of PPI often depends on insurance formulary and ease of administration. Dosing for PPIs generally starts at 1 to 1.5 mg/kg per day. PPIs are dosed starting at once daily, though can be increased to twice daily if needed. Twice-daily dosing has shown faster improvement in symptoms at 1 week, but with a similar response at 2 weeks. (23)

Adverse effects of H2RAs and PPIs are uncommon and similar to placebo, including headache, diarrhea, abdominal pain, and nausea. (24)(25)(26)(27) A randomized double-blind placebo-controlled study of infants with GER treated with lansoprazole found that compared with placebo, there was no difference in the number of infants who responded to lansoprazole treatment; however, there was an increased number of adverse events in the lansoprazole-treated infants, including lower respiratory tract and lung infections. (28) A different prospective study showed that children with GERD who were treated with ranitidine or omeprazole had increased rates of acute gastroenteritis and community-acquired pneumonia compared with healthy controls. The increased risk of infections seen in children treated with acid-suppressing medications could be related to changes in intestinal flora, direct inhibitory effect of acid-suppressing medications on leukocyte functions, and/or absence of the low gastric pH limiting microbial survival. (29) Some adult studies have raised concern about PPIs causing increased risk for osteoporosis and fractures, but other studies have found no increased risk in patients without other major risk factors. (30) PPI use alone does not seem to be a risk factor for hypomagnesemia. (31)(32) Some studies show an association of PPIs with iron-deficiency anemia. (33)(34) However, many of these adult studies are confounded by other comorbidities. (13)

Erythromycin and metoclopramide are prokinetic medications that can increase gastric emptying, thereby potentially decreasing reflux episodes. However, data supporting the use of prokinetic medications for treatment of reflux are insufficient, and also these medications carry the potential for adverse effects and drug-drug interactions. (35) There is a black box warning for metoclopramide for tardive dyskinesia, characterized by repetitive potentially irreversible involuntary movements of the body, most often the face. Other side effects of metoclopramide include restlessness, irritability, lethargy, headache, confusion, difficulty sleeping, gynecomastia, and galactorrhea. Erythromycin has the potential to cause gastrointestinal symptoms, including abdominal pain, nausea, vomiting, diarrhea, and loss of appetite. Also, an association has been found between erythromycin and prolongation of the QT interval and torsade de pointe arrhythmia. Erythromycin should not be given with other drugs that can prolong the QT interval or drugs that are metabolized by P450 enzymes. Given the lack of strong data and the potential for adverse effects, prokinetic medications are not recommended for routine treatment of children with reflux. (8)(13)

Ultimately, for patients with life-threatening complications proven to be related to GERD, surgical treatment with Nissen fundoplication can be considered. Nissen fundoplication is not indicated in infants with frequent spitting up who are otherwise feeding well and gaining weight well, because infants with uncomplicated GER are expected to improve on their own with time. In these patients, potential complications of Nissen fundoplication outweigh the benefits. Possible post-Nissen complications include dumping syndrome, gas bloat syndrome, early satiety, and postoperative retching and gagging. One study reported ∼75% of 233 pediatric patients were restarted on antireflux medications within 1 year after a Nissen procedure. (36)

Prognosis

Infants with GER should improve with time. There is often a dramatic improvement in reflux symptoms after 7 months of age, with only a small percentage of infants still having problems with reflux at 1 year of age. Referral to a pediatric gastroenterologist should be considered if concerning symptoms are present, like hematemesis, feeding difficulties, poor weight gain, and respiratory symptoms, and/or the reflux does not improve with time.

Reflux in Older Children

Reflux and heartburn symptoms are reported to occur weekly in ∼2% of 3- to 9-year-old children and 5% to 8% of 10- to 17-year-old children. (37) Children with more frequent spitting up episodes during infancy were 2.3 times more likely to have 1 or more reflux symptoms at 9 years of age. (2) Older children with reflux may present with regurgitation, heartburn, vomiting, poor appetite, poor weight

gain, chest discomfort, dysphagia, and/or abdominal pain, often after mealtimes. Less commonly, respiratory and ear-nose-throat symptoms, like wheezing, hoarseness, or cough, could be a presentation of reflux.

There does appear to be an association between GER and asthma. The number of abnormal esophageal pH studies is increased in children with asthma. (38)(39)(40) Reflux could worsen asthma symptoms, but asthma could also worsen reflux symptoms. Mechanisms by which asthma could worsen reflux includes cough-induced increases in intra-abdominal pressure, lung hyperinflation changing the relation between the crural diaphragm and the gastroesophageal junction, airway obstruction causing negative intrathoracic pressure, and asthma medications decreasing the lower esophageal sphincter pressure. Reflux as the cause of worsening asthma symptoms could be secondary to aspiration of gastric contents resulting in airway inflammation and airway hyperresponsiveness. Respiratory and gastrointestinal systems also have a common embryologic origin, resulting in shared innervation by the vagus nerve and shared autonomic reflexes. Reflux could stimulate receptors in the distal esophagus and lead to vagal reflex and bronchial constriction. The association of reflux with asthma appears to be greater when the asthma is difficult to control, when reflux symptoms have an onset before respiratory symptoms, and when there are nocturnal asthma symptoms. It is recommended that asthmatic children with these specific symptoms be considered for baseline pulmonary function tests followed by a 3-month trial of empiric acid suppression medication. (41)

Although some studies have shown an association of reflux with specific respiratory and ear-nose-throat diagnoses, others have not shown such an association. (40)(42)(43)(44) Pneumonia is not often caused by aspiration of refluxed contents. Recurrent pneumonia could be related to abnormal swallowing; therefore, these children should undergo a video swallow study to evaluate for aspiration of swallowed liquids, rather than assuming that the pneumonia is secondary to reflux and only initiating reflux treatments. Ultimately, neither the association of respiratory symptoms with reflux nor the response to reflux medications has been established by controlled studies, and other causes of these symptoms should be assessed. Although some studies have shown an association of dental erosions with GERD, other studies have not shown such an association. (45)(46) Recommendations for specific evaluation and length of treatment are unclear. Close follow-up with a pediatric dentist is important.

It is important to also consider unrecognized constipation contributing to reflux symptoms. This could be explained by the cologastric brake, where stool loading in the rectum activates a rectogastric inhibitory reflex. (47) Constipation can cause delayed gastric emptying and this gastroparesis can result in reflux. Studies show that gastric emptying improves after starting treatment with stool softeners. Treatment of constipation has the potential to quickly resolve chronic upper gastrointestinal symptoms, including reflux. (48)

Treatment for reflux in older children includes lifestyle modifications and weight management, if overweight. Sleeping with the head of the bed elevated and not lying down right after eating can be helpful; avoiding caffeinated beverages, chocolate, peppermint, and spicy foods can also be beneficial. Ideally patients should limit fatty foods, because fat can slow gastric emptying, thereby increasing the possibility for reflux. It is also better to eat smaller portions, because smaller meals decrease TLESR. Avoiding tobacco exposure and alcohol is important, as these can decrease lower esophageal sphincter pressure, increasing the risk for reflux events. Several studies have shown that chewing sugarless gum can increase salivary flow and neutralize acid, thus helping with reflux symptoms (49)(50)(51); however, the sorbitol sweetener in excessive amounts of sugarless gum could contribute to abdominal pain and diarrhea.

Antacid medications neutralize acid and are appropriate for short-term relief of occasional reflux symptoms. They work within 5 minutes and have a short duration of effect. PPI medications can be used to empirically treat classic reflux symptoms in older children, starting at a dose of 1 to 1.5 mg/kg per day. Patients who do not respond to once-daily dosing can be given twice-daily dosing (generally 1 mg/kg per dose twice a day up to 40 mg twice a day). If symptoms improve with acid-suppressing medications, recommendations are to continue treatment for 4 to 8 weeks and then wean. (13) It is better to wean the medication rather than stop suddenly, to avoid rebound hyperacidity caused by increased serum gastrin levels associated with longer-term PPI use. If concerning symptoms are noted at the time of presentation, symptoms persist despite empiric PPI treatment, or a quick relapse of symptoms is seen after PPI treatment, endoscopy should be considered for further evaluation, including reflux esophagitis and EoE.

EOE IN CHILDREN

Definition
EoE belongs to a group of disorders known as eosinophilic gastrointestinal disorders. EoE is a chronic immune-mediated disorder of the esophagus characterized by clinical symptoms of esophageal dysfunction and the histologic presence of more than or equal to 15 eosinophils per high-powered field in the esophageal mucosa, in the absence of other eosinophilic syndromes. (52)

Prevalence

EoE is a relatively recently identified disease with the first adult report in 1978 (53) and the first pediatric report in 1983. (54) Although some studies have suggested an increase in the prevalence of EoE, a review of esophageal biopsies from 1980 to 1988 compared with 2001 to 2002 showed that the prevalence of EoE was unchanged. (55) Recently, the incidence and prevalence of EoE in children was found to range from 0.7 to 10 in 100,000 per person-year and 0.2 to 43 in 100,000, respectively. (56) Prevalence of disease was highest in those children with dysphagia or food impaction, at 63% to 88%. (56) EoE affects male patients disproportionately, with a male-to-female ratio of approximately 3 to 1. (57) Historically, EoE was thought to preferentially affect white patients; however, recent studies suggest similar frequency in white and black children. (58) EoE has been reported in male and female patients of all age groups and of most ethnicities and races. The overall risk for first-degree relatives of a patient with EoE is 1.8%, increasing to 2.3% for sex-matched first-degree relatives. (59)

Clinical Signs and Symptoms

Clinical symptoms of EoE are variable and often age dependent. Symptoms in the younger child may include regurgitation, nausea, vomiting, or feeding difficulties, and may be severe enough to cause failure to thrive. In the older child and adolescent, symptoms of dysphagia, heartburn, food impaction, nighttime cough, and epigastric abdominal pain are more common. Other possible symptoms of EoE in both age groups include malnutrition, growth failure, esophageal dysmotility, and rarely, hematemesis. Asking the key questions of whether the child chews food excessively or uses liquid chasers during meals may help identify clinical symptoms of EoE, which parents may mistakenly attribute to simply "eating too fast." It is also necessary to consider EoE in the child with chronic heartburn or GERD given its potentially similar clinical presentation. A personal history of atopy manifesting as asthma, eczema, allergic rhinitis, and/or food allergies is reported in up to 60% of children with EoE, and can be another clue to the underlying diagnosis. (60)(61) Children with symptoms of possible EoE should be referred to a pediatric gastroenterologist for evaluation, particularly those who have dysphagia, food impaction, reflux symptoms unresponsive to PPI, longstanding reflux symptoms, or inability to withdraw PPI therapy without recurrence of symptoms.

Pathophysiology

Both genetic and environmental factors are implicated in the pathogenesis of EoE. EoE is believed to be caused by non–immunoglobulin E allergic response to allergen(s). Allergens are most frequently foods, though some research supports environmental aeroallergens as potentially causative. (62) An EoE genetic susceptibility locus has been identified at 5q22, demonstrating a genetic basis to this disorder. (63) More recently, 2 genome-wide association studies have discovered an association of the 2p23 locus with EoE. (64)(65) It is believed that when a food allergen enters the body through a disrupted epithelial barrier, esophageal antigen–presenting cells interact with the allergen, releasing a cascade of proinflammatory cytokines and chemokines, leading to the recruitment of eosinophils to the esophagus. (66)

Diagnosis

EoE is an endoscopic diagnosis in the correct clinical setting. Ideally, when a diagnosis of EoE is being entertained, the patient should be started and maintained on a PPI for a period of 6 to 8 weeks before endoscopy. Endoscopic visual clues to diagnosis include linear furrows, concentric rings, loss of the typical esophageal vascular pattern, and/or the presence of white patches on the mucosal surface (Figs 1–3). However, up to 30% of patients may have a visually normal-appearing esophagus, highlighting the importance of a biopsy in making the diagnosis of EoE. (67)

PPI use before endoscopy is recommended to rule out GERD as the cause of esophageal eosinophilia, and also attempt to identify those patients with an entity known as PPI-responsive esophageal eosinophilia. In these patients, esophageal eosinophils normalize after PPI use. PPI-responsive esophageal eosinophilia may represent a distinct clinical disorder, possible subtype of EoE, or severe GERD. (68)

Multiple biopsy specimens should be obtained from both the distal and proximal esophagus, because EoE can be a patchy disease. A count of more than or equal to 15 eosinophils per high-powered field must be present on and isolated to the esophageal biopsy specimen; biopsy specimens from
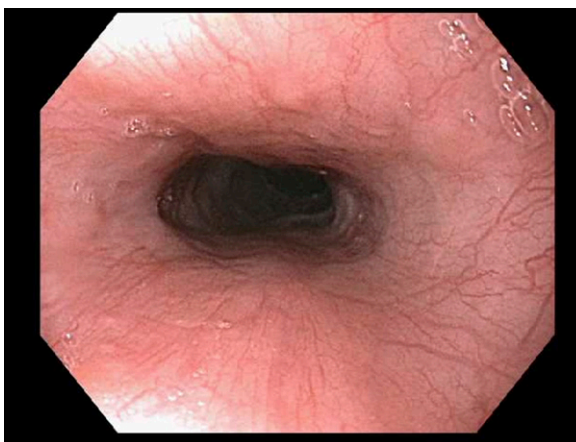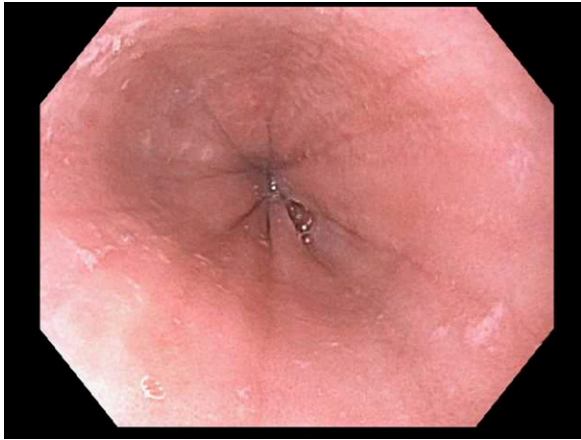

Figure 1. Endoscopic appearance of normal esophagus.

Figure 2. Mucosal edema, loss of vascular pattern, and linear furrows in a patient with eosinophilic esophagitis.

the stomach and duodenum should be devoid of excessive eosinophils. Excessive eosinophils in the stomach and/or duodenum would suggest the alternate diagnosis of eosinophilic gastritis or eosinophilic gastroenteritis. Currently, EoE remains an endoscopic diagnosis; there are no diagnostic radiologic, serologic, or stool studies.

Treatment

EoE is managed with dietary therapy, medical therapy, or combination of both. Systemic steroids such as prednisone should not be used routinely or long term in the treatment of EoE given their significant side effect profile. However, systemic steroids could be considered in the short-term management of the patient with acute conditions such as severe dysphagia, narrow esophagus, or poor growth. Current medical treatment of EoE includes the use of swallowed topical corticosteroids: fluticasone proprionate or oral viscous budesonide. Fluticasone is puffed into the mouth and
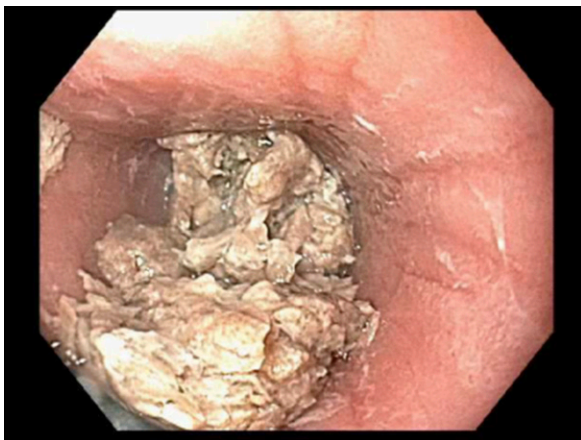
Figure 3. Food impaction in a patient with eosinophilic esophagitis.

then swallowed. Budesonide is often mixed with sucralose to make a viscous solution before swallowing; amino acid–based nutritional powders are another option to thicken budesonide. Instructions include not eating or drinking for 30 minutes after medication administration, and then rinsing the mouth with water. When swallowed, these topical corticosteroids are deposited along the surface of the esophageal mucosa, with the goal being symptom resolution and histologic improvement. Dosing for these medications is based on age and weight, and ranges from 88 to 440 μg twice daily for fluticasone proprionate and 0.5 to 1 mg twice daily for budesonide. Potential side effects include dry mouth, nosebleed, and oropharyngeal or esophageal candidiasis. Although previously no significant systemic side effects were seen with topical corticosteroids, newer studies have shown some evidence of adrenal suppression with the use of swallowed fluticasone and oral viscous budesonide. [69][70] Of patients treated with swallowed topical corticosteroids, 50% to 85% show improvement in their EoE symptoms. [71][72][73][74] However, multiple studies demonstrate that EoE almost always returns after discontinuation of therapy if no other interventions have been instituted. [60][75][76]

Dietary modification is an important treatment arm in the care of the patient with EoE. Dietary modifications include the use of an amino acid–based elemental diet, empiric elimination of the 6 most common food allergens (milk, soy, eggs, wheat, nuts/peanuts, fish/shellfish) referred to as the 6-food elimination diet, or the selective elimination of specific foods based on results of allergy testing and clinical symptoms. Elimination of dietary allergens has proven successful in improving clinical symptoms and histology.

More than 95% of patients treated with exclusive amino acid–based elemental formula demonstrate clinical and histologic improvement. [60][77] Endoscopy is repeated a minimum of 6 weeks after dietary or medication change. Clinical symptoms do not always correlate with histologic findings, making endoscopic surveillance important. Once endoscopic resolution of esophageal eosinophilia is noted, foods can be systematically reintroduced while monitoring for the redevelopment of clinical symptoms; endoscopy is used to ensure that there is no histologic evidence of disease recurrence in the absence of clinical symptoms. Although an elemental diet has excellent success in treating EoE, consuming the volume of formula needed to maintain nutrition may be a real challenge, and a nasogastric or gastrostomy tube may be required.

Approximately 75% of patients demonstrate improvement with empiric elimination of the 6 most common food

allergens. (78) This 6-food elimination diet does not require any food allergy testing. However, it has a number of potential drawbacks, including the unnecessary elimination of foods leading to more significant dietary restriction and the need for repeated endoscopies to ensure that the reintroduced foods did not cause relapse of the EoE. Empiric elimination of milk alone could be considered, because milk is the most common food identified as a cause of EoE, and studies have shown that eliminating milk can successfully treat EoE, even when food allergy test results are negative. (79) The guided food elimination diet, in which foods are eliminated based on allergy testing and clinical reactions, has success rates of 57% to 77%. (60)(80) Newer dietary approaches include the 4-food elimination diet (milk, wheat, eggs, and legumes), and the 2-food elimination diet (animal milk and gluten-containing cereals) with "step-up" to the 4-food elimination diet or 6-food elimination diet in nonresponders. (81)(82) The treatment of EoE, whether dietary elimination and/or swallowed topical corticosteroids, is a decision that must be individualized for the patient, taking into account the present symptoms and patient/family compliance.

Dilation therapy is reserved for patients with esophageal stricture. Dilation may be achieved via the passage of sequentially larger bougie dilators or endoscopic balloon dilators. Esophageal perforation is a possible and serious potential complication of dilation therapy. In pediatrics, medication or dietary treatment is typically the first treatment choice.

Other Esophageal Disorders

Esophageal dysfunction can also result from a myriad of anatomic, traumatic, iatrogenic, and motility causes. Congenital anatomic abnormalities of the esophagus include congenital esophageal stenosis, esophageal atresia with or without fistula, and vascular rings, among others. Caustic ingestions from household cleaners are particularly dangerous given their markedly alkaline nature; perforation, mediastinitis, and/or stricture may result. Pill esophagitis has been associated with a number of medications, including tetracycline and other acne medications, as well as nonsteroidal anti-inflammatory drugs. Ingestion of foreign bodies is a common problem in children, with more than 100,000 cases occurring annually; the cervical esophagus, the level of the aortic arch, and the lower esophageal sphincter are the 3 most likely areas of esophageal impaction. Esophageal damage from a button battery lodged in the esophagus can be very severe and burns may occur in as little as an hour after ingestion, necessitating prompt endoscopic removal. Achalasia is a motor disorder of the esophagus characterized by lack of esophageal peristalsis, increased lower esophageal sphincter pressure, and incomplete relaxation of the lower esophageal sphincter; it presents clinically as a functional obstruction in the region of the esophagogastric junction. Together, these diagnoses account for many of the other causes of esophageal dysfunction and disease. (83)

Summary

- Based on strong research evidence, upper gastrointestinal (UGI) study should not be ordered as a diagnostic test for reflux, because the sensitivity and specificity are low. UGI study is, however, helpful to evaluate for anatomic abnormalities that could cause vomiting. (8)(13)

- Based on some research evidence as well as consensus, proton pump inhibitors (PPIs) are not expected to improve reflux symptoms or fussiness in infants. There is also concern about possible adverse effects related to PPIs, including pneumonia and gastroenteritis. (8)(9)(13)(28)

- Based primarily on consensus due to lack of relevant clinical studies, eosinophilic esophagitis should be considered in the child with gastroesophageal reflux disease given its potentially similar clinical presentation.

- Based on strong research evidence, eosinophilic esophagitis should be managed with dietary therapy, medical therapy, or combination of both. (60)(71)(72)(73)(74)(77)(78)(79)(80)(81)(82)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/ content/39/8/392.supplemental.

Pediatric Esophageal Disorders: Diagnosis and Treatment of Reflux and Eosinophilic Esophagitis

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PIR Quiz

1. A 2-month-old boy is brought to the clinic by his parents because of persistent vomiting for the past 2 weeks. The mother thinks that the child might be vomiting green occasionally. The child has not had significant weight gain since the last time you saw him at 2 weeks of age. On physical examination, he is less than the 5th percentile for weight. You are concerned that the child may have some underlying anatomic condition. Which of the following is the most appropriate next step in diagnosis in this patient?

    A. 24-hour impedance pH study test.
    B. Surgery consultation.
    C. Ultrasonography of the abdomen.
    D. Upper gastrointestinal series.
    E. Radiography of the abdomen.

2. You are seeing a 3-month-old boy in your clinic. The mother reports that he has been "vomiting with every feed" and she is concerned that he is "not keeping down anything." He is taking a regular cow milk–based formula. On physical examination, he is an alert, active infant with stable and normal vital signs. The infant is growing well and has been at the 75th percentile for height and weight on the growth curve. The remainder of the physical examination findings is unremarkable. Which of the following is the most appropriate next step in management for this patient?

    A. Follow-up in 1 week for weight check.
    B. Prescribe acid suppressants.
    C. Pyloric ultrasonography.
    D. Reflux precautions.
    E. Switch to an elemental formula.

3. A 4-month-old girl is brought to your office with worsening spitting up symptoms. You previously had seen her 2 weeks ago and diagnosed her with reflux. At that time, you recommended small frequent feeds, thickening feeds with rice cereal, burping, and upright positioning. Despite these measures, the mother reports that the infant is feeding less and is irritable after feeding. You notice that the child has not gained much weight since the last visit. Which of the following is the most appropriate next step in management?

    A. Erythromycin.
    B. Histamine-2 receptor antagonists.
    C. Metoclopramide.
    D. Nissen fundoplication.
    E. Switch to a lactose-free formula.

4. You are seeing a 6-year-old boy who has repeated asthma exacerbations. He is taking an inhaled corticosteroid daily as a controller medication and is slightly overweight. The mother reports that the boy has heartburn, chest discomfort, and occasional vomiting. In addition to referring him to a pulmonologist for asthma management, which of the following is the most appropriate immediate next step in management?

    A. Follow-up in the office in a couple of weeks.
    B. Food allergy testing.
    C. Increase his dose of inhaled corticosteroids.
    D. Order lung function tests.
    E. Prescribe acid reflux suppressants.

5. A 14-month-old girl is brought to the office for follow-up. She has had reflux all her life and continues to be below the 5th percentile for weight. Proton pump inhibitors (PPIs) were tried which worked for a while but on tapering the medication, the symptoms return. The diagnosis of eosinophilic esophagitis is confirmed. Which of the following is the most appropriate next management step for this patient?

    A. Four-food elimination diet consisting of milk, wheat, nuts, and shellfish.
    B. Premedication with diphenhydramine prior to meals with no diet restriction.
    C. Six-food elimination diet and swallowed topical corticosteroid combination regimen.
    D. Six-food elimination diet consisting of milk, soy, eggs, wheat, nuts, and fish.
    E. Two-food elimination diet consisting of animal milk and gluten-containing cereals followed by a step up to 4- or 6-food elimination diet in nonresponders.

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Supplementary Material	Supplementary material can be found at: http://pedsinreview.aappublications.org/content/suppl/2018/07/31/39.8.392.DC1
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To begin with, pediatricians should screen for the social and economic risk factors that lead to homelessness in an effort to intercede before families are displaced. Children known to be in shelters or transient living conditions should be screened for mental health problems with standardized screening questionnaires such as the Screen for Child Anxiety Related Disorders (SCARED); the Ages & Stages Questionnaire: Social-Emotional (ASQ-SE); and the Patient Health Questionnaire (PHQ)-2 and PHQ-9.

Whether in an office setting or an emergency department, pediatricians should take advantage of acute care visits for homeless children to provide needed comprehensive care, for example, to update immunizations while dealing with the acute problem rather than scheduling a separate follow-up appointment.

As pediatricians, we care and advocate for our individual patients, but as citizens, recognizing the social underpinnings of homelessness, we can effect change in our communities through advocacy, political action, and work through various organizations, such as the American Academy of Pediatrics.

Any society is measured by how it cares for its most vulnerable members. To support our most vulnerable children we need programs that strengthen their families: through economic advancement by enhancing education and job skills; with agencies that support single-parent homes with subsidies for services such as after-school care; with early education available to every child. Social safety net programs (public assistance, WIC, SNAP, housing vouchers, and child care vouchers) enable young single parents to work while their children are in safe, positive environments. As always in pediatrics, prevention is preferable to treatment, and programs that address the social factors leading to homelessness can prevent the multitude of problems created for children who become homeless.

COMMENT: One hundred thousand or more children are homeless on any given night, and 2½ million children over the course of a year. This in "the land of the free," where, ironically, we call ourselves "the *home* of the brave"! Shame on us. And now, as I'm writing this in June 2018, we are fracturing families, separating children from their refugee parents at our borders—more than 2,000 children during the past 2 weeks, many of them not old enough to understand what is happening to them. What can we say? Shame on us.

Yes, advocacy is fundamental to the role of the pediatrician.

– Henry M. Adam, MD
Associate Editor, *In Brief*

CME Quiz Correction

An error appeared in the print version of the quiz accompanying the August 2018 review "Pediatric Esophageal Disorders: Diagnosis and Treatment of Reflux and Eosinophilic Esophagitis" (Adamiak T, Plati KF. *Pediatr Rev.* 2018; 39(8):392–402; DOI: 10.1542/pir.2017-0266). Question 5, answer option E should read "Two-food elimination diet consisting of animal milk and gluten-containing cereals followed by a step up to 4- or 6-food elimination diet in nonresponders." The online version of the quiz is correct, and a correction notice has been posted with the online version of the article. The journal regrets the error.

ANSWER KEY FOR OCTOBER 2018 PEDIATRICS IN REVIEW
Overall Approach to Trauma in the Emergency Department: 1. B; 2. C; 3. A; 4. E; 5. D.
Human and Animal Bites: 1. C; 2. C; 3. D; 4. D; 5. D.
Collagen Vascular Diseases: SLE, Dermatomyositis, Scleroderma, and MCTD: 1. A; 2. A; 3. C; 4. D; 5. A.

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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An erratum has been published regarding this article. Please see the attached page for:

http://pedsinreview.aappublications.org//content/39/10/532.full.pdf

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