

# Gastroesophageal Reflux Disease



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## KEYWORDS

- Gastroesophageal reflux • Endoscopy • Impedance • Proton pump inhibitors
- Lifestyle changes • Extraesophageal symptoms • Pediatrics

## KEY POINTS

- Gastroesophageal reflux is a normal physiologic process that does not require treatment.
- In infants, reducing feeding volumes, offering smaller, more frequent meals, thickening feeds, and positioning can reduce reflux episodes; these infants should not be placed on acid suppression.
- Gastroesophageal reflux disease (GERD) occurs when reflux of gastric contents causes troublesome symptoms or complications. First-line treatment in children and adolescents includes lifestyle modification and acid suppression.
- GERD can have atypical presentations, such as recurrent pneumonia, upper airway symptoms, nocturnal or difficult to control asthma, dental erosions, and Sandifer syndrome.
- Diagnosis of GERD is largely based upon history and physical, but endoscopy and pH impedance can be used to help support the diagnosis in atypical presentations.

## INTRODUCTION

Gastroesophageal reflux (GER) is a normal physiologic process. It is defined as the involuntary flow of stomach content back into the esophagus.<sup>1</sup> Most episodes of reflux are into the distal esophagus, brief, and asymptomatic. GER disease (GERD) occurs when reflux causes troublesome symptoms or complications.<sup>2</sup>

## PHYSIOLOGY

Multiple mechanisms are in place to protect from reflux: the antireflux barrier, esophageal clearance, and esophageal mucosal resistance. The antireflux barrier is composed of the lower esophageal sphincter (LES), the angle of His, the crural

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diaphragm, and the phrenoesophageal ligament.<sup>3</sup> The LES consists of tonically contracted circular smooth muscles, composed of the intrinsic muscles of the distal esophagus and the sling fibers of the proximal stomach.<sup>4</sup> The crural diaphragm forms the esophageal hiatus and encircles the proximal LES. The phrenoesophageal ligament anchors the distal esophagus to the crural diaphragm. A small portion of the LES, up to 2 cm in adults, is intraabdominal. The LES resting pressure is higher than the intraabdominal pressure, and this prevents reflux of gastric contents into the distal esophagus. The angle of His is an acute angle between the great curvature of the stomach and the esophagus, and acts as an antireflux barrier by functioning like a valve. Esophageal clearance limits the duration of contact between luminal contents and esophageal epithelium.<sup>1</sup> Gravity and esophageal peristalsis remove volume from the esophageal lumen, and salivary and esophageal secretions neutralize acid. Esophageal mucosal resistance comes into play when acid contact time is prolonged, and this is determined genetically.

### **MECHANISMS OF GASTROESOPHAGEAL REFLUX**

Anything that interferes with these lines of defense can lead to GER. Inappropriate transient LES relaxation is among the most important causes of GERD in children.<sup>5,6</sup> Increased intraabdominal pressure relative to LES resting pressure permits the reflux of gastric contents into the distal esophagus.<sup>6</sup> Increased intraabdominal pressure can be caused by medications, the Valsalva maneuver, the Trendelenburg position, or lifting. Position and posture influence the angle of His, with esophageal acid exposure greater in the right side sleeping position than in the left position. Esophageal clearance is also delayed in the right position.<sup>1</sup> Although little is known about the angle of His in infants, it is hypothesized that this angle is less acute in young infants and becomes acute after 1 year of age; this would predispose their stomach to a more vertical lie and therefore increased ease of reflux.<sup>1</sup> In sliding hiatal hernias, there is a weakness of the phrenoesophageal ligament leading to an upward displacement of the LES into the lower mediastinum. As a result, the defense of the LES, angle of His, and the diaphragm are compromised.<sup>3</sup> The LES and crural diaphragm no longer overlap, and the LES length and pressure are reduced. Another proposed mechanism by which hiatal hernia leads to GER is by creating a hernia sac between the LES proximally and the crural diaphragm distally.<sup>7</sup> This sac has increased acid exposure and impaired clearance, and can reflux during subsequent swallow relaxations of the LES.<sup>7</sup>

### **DISTINGUISHING GASTROESOPHAGEAL REFLUX FROM GASTROESOPHAGEAL REFLUX DISEASE**

Whereas GER is a normal physiologic process, GERD occurs when reflux of gastric contents causes troublesome symptoms or complications.<sup>2</sup> In infants, crying and fussiness are often attributed to GERD, but are nonspecific and difficult to distinguish from other causes. GERD can cause infants to associate feeding with pain, and as a result feeding aversion, anorexia, and failure to thrive can develop.<sup>2</sup> Respiratory complications are less common, but recurrent pneumonia and interstitial lung disease secondary to reflux can occur owing to aspiration of gastric contents.<sup>8</sup> Reflux worsening asthma symptoms has also been reported.<sup>9,10</sup> Histologic changes can also help distinguish the two, with esophageal biopsies in GERD typically showing findings of basal zone hyperplasia, papillary lengthening, and neutrophil infiltration.<sup>11,12</sup>

## EPIDEMIOLOGY

There are few pediatric-specific data on GER and GERD epidemiology with incidence and prevalence based on questionnaires. The incidence of GERD in pediatrics was estimated to be 0.84 per 1000 person-years.<sup>13</sup> After 1 year of age, the incidence of GERD decreases with until age 12, and then reaches a maximum at age 16 to 17. The prevalence varies by study and age. It is estimated that 10% of all children have GER<sup>14</sup> and 1.8% to 8.2% have GERD.<sup>14,15</sup> The estimated prevalence of GERD in infants 0 to 23 months, children 2 to 11 years old, and adolescents 12 to 17 years old is 2.2% to 12.6%, 0.6% to 4.1%, and 0.8% to 7.6%, respectively.

## PRESENTING SYMPTOMS

### *Infancy*

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Daily regurgitation in healthy infants is physiologic and common, with the prevalence being highest in the first 3 to 4 months of life, at between 41% and 73%.<sup>16–18</sup> A large proportion of these infants regurgitate more than 4 times a day. Prevalence decreases to 14% at 7 months of age,<sup>17</sup> and to less than 5% after 12 months of age.<sup>16,18</sup> GERD can be difficult to diagnose in infants because they present with nonspecific symptoms that can be difficult to distinguish from other conditions (**Box 1**).<sup>19,20</sup> These symptoms include choking, gagging, irritability, regurgitation, refusal to feed, and poor weight gain. Crying, irritability, and vomiting are often attributed to GERD,<sup>18</sup> but can be indistinguishable from milk protein allergy<sup>21,22</sup> and do not correlate well with reflux on pH impedance studies,<sup>23,24</sup> or improve after trials of proton pump inhibitors (PPIs).<sup>25,26</sup> A history and physical examination should be done to rule out warning signals that require further investigation (**Box 2**),<sup>19</sup> before attributing them to GERD.

### *Childhood*

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GERD is often diagnosed in adults based on a history of substernal, burning pain, with or without regurgitation.<sup>2</sup> The diagnosis of GERD can similarly be made in adolescents.<sup>27</sup> However, history is unreliable in children under the age of 12, and these children can also present with different symptoms. In addition to the aforementioned typical GERD symptoms, 21% of children reported nausea or vomiting.<sup>13</sup> Abdominal pain and cough are also reported frequently.<sup>28</sup> In children with erosive esophagitis, cough, anorexia, and feeding refusal were found to be more frequent and severe in children ages 1 to 5 years of age, as compared with older children, while heartburn was less severe. Symptoms have not been found to be predictive of mucosal damage.

Children with certain underlying disorders are at high risk for developing severe and chronic GERD (**Table 1**).<sup>19</sup>

### *Atypical Presentations*

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An association between asthma and reflux measured by pH or impedance has been reported,<sup>29</sup> although the etiology is not established. Proposed mechanisms of GERD contributing to asthma include aspiration of gastric acid resulting in airway inflammation and causing vagally mediated bronchial or laryngeal spasm.<sup>30</sup> Alternatively, asthma may contribute to GERD. Pulmonary hyperinflation occurs as a result of chronic asthma. This hyperinflation causes the diaphragm to flatten, displacing the LES into the thoracic cavity, which has a negative atmosphere pressure, and thereby reduces the LES resting pressure and eliminates the angle of His. Studies have shown that the majority of children with asthma have an abnormal pH impedance study<sup>31</sup>; however, the use of a PPI in unselected patients with wheezing or asthma is of

**Box 1****Differential diagnosis for emesis in an infant or child***Gastrointestinal obstruction*

- Esophageal web
- Esophageal stricture
- Tracheoesophageal fistula
- Pyloric stenosis
- Duodenal atresia
- Malrotation with intermittent volvulus
- Intestinal duplication
- Antral/duodenal web
- Hirschsprung disease
- Foreign body/bezoar
- Incarcerated hernia
- Imperforate anus

*Other gastrointestinal disorders*

- Celiac disease
- Milk/soy protein allergy
- Achalasia
- Gastroparesis
- Peptic ulcer
- Eosinophilic esophagitis/gastroenteritis
- Inflammatory bowel disease
- Appendicitis
- Pancreatitis
- Cholecystitis/choledocholithiasis

*Neurologic*

- Intracranial mass
- Hydrocephalus
- Subdural hematoma
- Intracranial hemorrhage
- Infant migraine
- Chiari malformation

*Infectious*

- Meningitis
- Gastroenteritis
- Sinusitis
- Urinary tract infection
- Pneumonia
- Otitis media

- Hepatitis

- Sepsis

#### *Metabolic/endocrine*

- Galactosemia
- Hereditary fructosemia
- Urea cycle defects
- Amino and organic acidemias
- Fatty acid oxidation disorders
- Lysosomal storage disorders
- Congenital adrenal hyperplasia
- Diabetic ketoacidosis

#### *Renal*

- Obstructive uropathy
- Nephrolithiasis
- Renal tubular acidosis
- Renal insufficiency

#### *Other*

- Self-induced vomiting
- Cyclic vomiting syndrome
- Rumination
- Overfeeding
- Autonomic dysfunction
- Munchausen syndrome by proxy
- Medication/vitamin/drug toxicity
- Child abuse

*Adapted from* Vandeplass Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49(4):498–547; and Chandran L, Chitkara M. Vomiting in children: reassurance, red flag, or referral? *Pediatr Rev* 2008;29(6):183–92.

limited benefit.<sup>32</sup> Patients who may benefit from GERD treatment include those with heartburn, nocturnal asthma symptoms, or steroid-dependent and difficult-to-control asthma.<sup>9,10</sup>

Recurrent pneumonia and interstitial lung disease may be complications of GERD owing to aspiration of gastric contents.<sup>8</sup> Although an abnormal esophageal pH study may increase the probability of GERD causing recurrent aspirations, there is no definitive test that can prove GERD's causal role.<sup>33</sup>

Upper airway symptoms attributed to GERD include hoarseness, chronic cough, or a sensation of a lump in the throat,<sup>34</sup> although there are no strong data to support this claim.<sup>35</sup> Laryngoscopic findings attributed to reflux include erythema, edema, cobblestoning, and nodularity, although with low sensitivity and specificity<sup>36,37</sup> and poor correlation with pH probe studies.<sup>38</sup>

**Box 2****Warning signals that require investigation in infants with vomiting**

Bilious emesis  
 Gastrointestinal bleeding: hematemesis, coffee ground emesis, hematochezia  
 Choking, gagging, coughing with feeds  
 Forceful emesis  
 Onset of emesis after 6 months of life  
 Failure to thrive  
 Diarrhea/constipation  
 Fever  
 Lethargy  
 Hepatosplenomegaly  
 Bulging fontanelle  
 Microcephaly or macrocephaly  
 Seizures  
 Abdominal tenderness or distention  
 Suspected genetic syndrome

Studies revealed a cause and effect relationship between GERD and dental erosions,<sup>39</sup> with worse dental erosions when GERD symptoms are present. Other contributing factors to dental erosions include drinking juice, bulimia, racial and genetic factors affecting the characteristic of enamel and saliva, and children with neurologic impairment.

**Table 1****Medical conditions at high risk for gastroesophageal reflux disease**

<b>Condition</b>	<b>Contributing Factors</b>
Neurologic impairment	Decreased esophageal clearance <ul style="list-style-type: none"> <li>• Supine position</li> <li>• Abnormal swallow</li> <li>• Abnormal muscle tone</li> </ul> Increased reflux episodes <ul style="list-style-type: none"> <li>• Heightened gag reflex</li> <li>• Delayed gastric emptying</li> <li>• Constipation</li> <li>• Skeletal abnormalities</li> <li>• Medication side effects</li> </ul>
Obesity	
Esophageal atresia	Esophagus is congenitally dysmotile After surgery, a hiatal hernia is often present
Chronic respiratory disorders <ul style="list-style-type: none"> <li>• Bronchopulmonary dysplasia</li> <li>• Cystic fibrosis</li> <li>• Idiopathic interstitial fibrosis</li> </ul>	Unknown
Lung transplantation	Pneumonectomy contributes to esophageal and gastric motor dysfunction

Sandifer syndrome, in which there is spasmodic torsional dystonia with arching of the back and rigid opisthotonic posturing of the neck and back, is an uncommon but specific presentation of GERD.<sup>2</sup> It must be distinguished from seizures, dystonia, or infantile spasms.<sup>40</sup> When related to GERD, it improves with antireflux treatment.

An apparent life-threatening event (ALTE) was first defined in 1986 as an episode that is frightening to the observer and that is characterized by some combination of apnea, color change, marked change in muscle tone, choking, or gagging.<sup>41</sup> The term ALTE was recently replaced by the term “brief resolved unexplained event,” which is characterized by a sudden, brief, and resolved episode occurring in an infant under 1 year of age that consists of one or more of the following: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone; and altered level of responsiveness. Because the change was recently made, published studies have evaluated GERD association with the ALTE definition. The results are conflicting. Although most series fail to demonstrate a temporal relationship between the two,<sup>29,42</sup> multiple studies do show that there is an association.<sup>43–45</sup> If other causes have been ruled out and GER is suspected, the diagnosis can be better evaluated by recording synchronous symptoms on multichannel intraluminal impedance (MII)/pH esophageal monitoring in combination with cardiorespiratory monitoring. When using esophageal manometry in conjunction with cardiorespiratory monitoring, infants with ALTE were found to have swallowing as the most frequent esophageal event associated with spontaneous respiratory events. This suggests a dysfunctional regulation of the swallow–respiratory interactions, and needs to be investigated further.<sup>46</sup> When using polysomnography with esophageal pH and impedance monitoring, apnea was seldom associated with reflux. When it was, the predominant sequence of events was obstructive or mixed apnea followed by reflux, suggesting against reflux as a cause of apnea.<sup>47</sup>

Apnea and sleep quality have similarly been evaluated by a combination of polysomnography with esophageal pH and impedance monitoring. The data, again, are conflicting. In some, GER was found unlikely to be related to apneic events and rarely seemed to cause sleep awakening.<sup>48,49</sup> Instead, awakening and arousal was precipitating GER. Another group has shown that acid and non-acid reflux was associated with sleep interruption in infants,<sup>50</sup> and acid reflux was associated with sleep interruption in obese children.<sup>51</sup>

## DIAGNOSIS

The diagnosis of GERD can largely be based on history and physical examination alone. There are several tools, however, to help make the diagnosis when there is an atypical presentation and to assess the severity and consequence of GERD.

### **Endoscopy**

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On endoscopy, visualizing endoscopic breaks in the mucosa is the most reliable evidence of reflux esophagitis.<sup>19</sup> The classic histologic findings of GERD are basal zone hyperplasia, papillary lengthening, and neutrophilic infiltration.<sup>12</sup> Although the histologic findings are not specific to GERD alone and have not correlated well with symptom severity of GERD in children,<sup>52</sup> they can help to support the diagnosis. The sensitivity of histology increases if multiple biopsies are taken, sampling in the mid and distal esophagus.<sup>11,53</sup> If using this method, the sensitivity of histology was 96% in patients with erosive esophagitis and 76% with nonerosive reflux disease.<sup>53</sup> The additional usefulness of pursuing endoscopy includes ruling out other disorders that can masquerade as GERD, such as eosinophilic esophagitis; identifying complications of reflux disease; and evaluating for empirical treatment failure.<sup>54</sup>

### ***pH and Impedance***

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Twenty-four-hour esophageal pH monitoring measures the frequency and duration of acid esophageal reflux. This test can be performed by either placing a nasal catheter, or by clipping a wireless sensor to the esophageal mucosa via endoscopy. A decrease in the intraesophageal pH to less than 4 is considered acidic exposure. For criteria to diagnose acid reflux, please refer to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition–European Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus paper from 2009.<sup>19</sup> The main indications for pH monitoring include evaluating endoscopy-negative patients for abnormal esophageal acid exposure if they are being considered for antireflux procedures and evaluating patients who are refractory to PPI therapy.<sup>55</sup> There are limitations to standard pH monitoring. It is a poor detector of weakly acidic (pH of 4-7) reflux<sup>56</sup> and can also overestimate acid exposure by picking up “pH-only” episodes, in which there is no reflux.<sup>57</sup> In infants and children, weakly acidic GER is more prevalent than in adults,<sup>57,58</sup> which can explain why abnormal esophageal pH monitoring does not correlate with symptom severity in infants.<sup>59</sup> Abnormal esophageal pH is observed more frequently in adults and children with erosive esophagitis.<sup>60,61</sup>

MII uses change in impedance to measure the anterograde and retrograde movement of fluid, solids, and air in the esophagus. Dual pH-MII is able to detect reflux regardless of pH value, detect anterograde versus retrograde flow thereby distinguishing between swallows and GER, determine the height of refluxate, and differentiate between liquid, gas, or mixed refluxate.<sup>62</sup> Nonacid pH is defined as a pH of greater than 4 and the reflux index is defined as the percentage of time the pH drops to less than 4. **Tables 2** and **3** provide the reflux parameter definitions and normal values for reflux per 24 hours in infant and children. Normal values for infants and children with nonacid and acid reflux were determined by Mousa and colleagues<sup>63</sup> in a multicenter study evaluating multiple parameters of reflux via pH/MII in a very clean population. The infant and children selected had no evidence of acid reflux or symptoms associated with regurgitation. They were also off antireflux medications at the time of the procedure and did not have a fundoplication. Based on the study, in infants, more than 48 acid reflux episodes or more than 67 nonacid reflux episodes in 24 hours are considered pathologic. With children, more than 55 acid reflux episodes or more than 34 nonacid reflux episodes in 24 hours is considered pathologic.

In infants and children, pH-MII optimizes the yield of the GER–symptom association.<sup>64</sup> Indications for pH-MII include (1) evaluating the efficacy of antireflux therapy, (2) endoscopy-negative patients with symptoms concerning for reflux despite PPI therapy in whom documentation of nonacid reflux will alter clinical management,<sup>55,62</sup> (3) evaluating tube fed patients for reflux, because the majority of refluxate during tube feeding is nonacidic,<sup>62</sup> and (4) differentiating aerophagia from GER.

### ***Motility Testing***

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Findings on esophageal manometry are not sensitive or specific enough to make the diagnosis of GERD, but can identify alternate motor disorders that may present similar to GERD.<sup>19,54</sup> Esophageal dysmotility is present in a proportion of patients with GERD,<sup>65</sup> with motor dysfunctions of both the LES and esophageal body being the major factors predicting medical refractoriness of reflux disease in children.<sup>66</sup> However, patients with gastroparesis are at increased risk for GERD,<sup>67</sup> and there are studies that show that infants and young children with delayed gastric emptying tend to be more symptomatic,<sup>68</sup> gastric emptying studies do not confirm the diagnosis of GERD<sup>69</sup> and are not recommended for its routine evaluation.

<b>Table 2</b> <b>Reflux parameters on pH-multichannel intraluminal impedance</b>	
<b>Definitions</b>	
Liquid reflux	Drop in impedance of $\leq 50\%$ of baseline value with subsequent recovery, in $\geq 2$ of the distal-most channels
Acid GER	pH decreases and remains $< 4$ for $\geq 5$ s; if pH was already $< 4$ , it decreases by $\geq 1$ pH unit for $\geq 5$ s; with or without a decrease in impedance of $\leq 50\%$ of baseline value
Nonacid GER	pH increases, remains unchanged, or decreases by $\geq 1$ pH unit while remaining $\geq 4$ , with a retrograde decrease in impedance of $\leq 50\%$ of baseline value in $\geq 2$ of the distal-most channels
Gas reflux	Simultaneous and rapid increases in impedance in $\geq 2$ channels ( $> 3000$ Ohms) of the distal-most channels
<b>Extent of reflux migration</b>	
Localized to distal esophagus	Height of reflux is confined to the 2 most distal impedance channels (channels 5 and 6)
Proximal	Height of refluxate reaches either or both of the most proximal channels (channels 1 and/or 2)
<b>Parameters of symptom association</b>	
Reflux index	Percent of time pH is $< 4$
Symptom index	Percent of symptoms episodes that are related to reflux ( $[\text{no. of reflux-related symptom episodes} \div \text{total no. of symptom episodes}] \times 100$ ) • Positive when $> 50\%$
Symptom sensitivity index	Percent of symptom associated reflux episodes ( $[\text{no. of reflux-related symptom episodes} \div \text{total no. of reflux episodes}] \times 100$ ) • positive when $> 10\%$
Symptoms associated probability	Statistical probability that symptoms and GER events are associated • Positive when $> 95\%$

Abbreviation: GER, gastroesophageal reflux.

### **Upper gastrointestinal studies**

Although GERD is reported commonly on upper gastrointestinal studies, the correlation between reflux reported on upper gastrointestinal studies and 24-h pH monitoring is poor.<sup>70,71</sup> Therefore, upper gastrointestinal studies should be reserved for defining anatomic abnormalities and not reflux.

### **Diagnostic Trial of Acid Suppression**

Because GERD is diagnosed primarily based on symptoms alone in older children and adolescents, responding to an empirical trial of PPI therapy helps to support, although it cannot confirm, a diagnosis of GERD.<sup>72</sup> In both children<sup>73</sup> and adolescent<sup>27</sup> patients with endoscopically proven GERD, a 4- to 8-week course of PPI improves symptoms significantly. There are limitations to performing a PPI trial to diagnose GERD. It does not control for placebo effect, spontaneous resolution of symptoms, and the possibility that other conditions may improve on PPI treatment. Additionally, it does not differentiate between healing esophagitis and reflux symptoms.<sup>54</sup> PPI therapy is more apt to resolve esophagitis than GERD symptoms, so a negative PPI trial does not exclude GERD as a diagnostic possibility. A trial of acid suppression in infants and young children is not warranted, because symptoms suggestive of GERD are less specific.<sup>26</sup>

**Table 3****Normal values for acid and nonacid reflux on pH/multichannel intraluminal impedance per 24 hours in infants and children**

	Infants		Children	
	Median (IQR)	95th Percentile	Median (IQR)	95th Percentile
Index of acid regurgitation (%)	0.6 (0.3–0.9)	1.4	0.4 (0.2–0.8)	1.3
No. of acid regurgitation episodes in 24 h	20 (11–26)	48	14 (11–15)	55
Index of nonacid regurgitation (%)	0.7 (0.5–1.2)	2.5	0.1 (0–0.3)	1.0
No. of nonacid regurgitation episodes in 24 h	32 (16–45)	67	6 (3–11)	34
Index of GER episodes (%)	1.4 (0.9–1.2)	2.9	0.6 (0.3–1.2)	2.4
No. of GER episodes in 24 h	54 (33–69)	93	21 (11–41)	71

*Abbreviations:* GER, gastroesophageal reflux; IQR, interquartile range.

*Adapted from* Mousa H, Machado R, Orsi M, et al. Combined multichannel intraluminal impedance-pH (MII-pH): multicenter report of normal values from 117 children. *Curr Gastroenterol Rep* 2014;16(8):400; and Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49(4):498–547.

### ***Bronchoalveolar Lavage and Pepsin (for Evidence of Microaspiration with Reflux or Swallowing Disorder)***

Evaluating pulmonary aspirates for pepsin has been investigated as a biomarker for GERD. Although studies support the association of the 2 conditions,<sup>74–76</sup> problems with prior studies include pepsin assays not being specific to pepsin A, the isoform found exclusively in the stomach.<sup>77</sup> Other pepsin isoforms, mainly pepsin C, are also produced in the lungs, pancreas, and seminal vesicles, thereby limiting specificity. Prospective studies evaluating children with chronic cough, asthma,<sup>78</sup> and GERD<sup>79</sup> have found that lung pepsin does not predict pathologic esophageal reflux, nor does it correlate with extraesophageal symptoms or quality of life score. Lung pepsin did, however, correlate with lung inflammation, suggesting a role for pepsin as a biomarker for reflux-related lung disease.<sup>78</sup>

## **TREATMENT**

### ***Infant***

Infant regurgitation is common and largely physiologic, peaking at 3 to 4 months of age, and resolving by 12 to 13 months of age.<sup>18</sup> In thriving infants in whom symptoms of regurgitation are likely secondary to physiologic GER, management should focus on parental education and support.<sup>80</sup> For formula-fed infants, reducing feeding volumes in overfed infants, or offering smaller, more frequent meals, can decrease reflux episodes.<sup>19</sup> Changing the infant's body position while awake can be effective. The prone and left side down positions are associated with fewer reflux episodes,<sup>81,82</sup> but should be recommended only in awake infants under the age of 1 to decrease the risk of sudden infant death syndrome. Thickening feeds helps to reduce the visual symptoms of GER,<sup>83,84</sup> although it does not esophageal reflux frequency, as shown by pH monitoring.<sup>85,86</sup>

PPI use has been increasing steadily in infants with the most common reasons for use being identified as GER (59%) and poor feeding (23%).<sup>87</sup> The mean age of use, between 4 and 8 months of age, correlates with the timing of physiologic reflux. The

majority of infants who are being placed on antireflux drugs do not meet the criteria for GERD.<sup>88</sup> PPIs have not been shown to benefit infant symptoms attributed to GER over placebo,<sup>25,26</sup> and discontinuing antireflux medications in this age group has not shown to cause a significant difference in symptoms. Therefore, antireflux medications are not recommended for infants with GER.

Milk protein sensitivity can be difficult to differentiate from GER symptoms with no diagnostic tools to differentiate between the 2 entities.<sup>89</sup> A prospective study found that 85 of 204 patients with documented GER by pH impedance testing had milk protein sensitivity.<sup>21</sup> Therefore, infants with recurrent vomiting and persistent symptoms may benefit from a 2- to 4-week trial of an extensively hydrolyzed protein formula.<sup>22,90</sup>

### **Children and Adolescents**

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#### **Lifestyle changes**

Recommendations for lifestyle changes are derived from adult data. Although there is some physiologic evidence that various foods as well as alcohol and tobacco affect the pressure of the LES, targeted interventions have not shown any benefit in clinical trials.<sup>91,92</sup> Patients should avoid foods and beverages that trigger their personal GERD symptoms. The only beneficial measures documented are weight loss in obese patients,<sup>93</sup> avoidance of late night eating,<sup>94</sup> elevation of the head of the bed, and prone or left-sided sleeping position.<sup>95</sup>

#### **Acid suppression**

**Histamine-2 receptor antagonists** Parietal cells secrete acid in response to 3 stimuli: histamine at the H<sub>2</sub> histamine receptor, acetylcholine, and gastrin. Histamine 2 receptor agonists (H<sub>2</sub>RAs) suppress gastric acid secretion by competitively inhibiting histamine at the parietal cell's H<sub>2</sub> receptor. In adequate doses, H<sub>2</sub>RAs are effective in the treatment of peptic disease<sup>96</sup> and healing erosive esophagitis compared with placebo.<sup>97,98</sup> However, patients requiring more than occasional use can develop to rapid tachyphylaxis.<sup>99</sup> Dosage requirements vary by age, but children require a relative higher dose than adults.<sup>96</sup>

**Proton pump inhibitors** PPIs are the most potent acid suppressants. They work by blocking the final step in acid secretion: the gastric H<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatase (ATPase), which causes resorption of K<sup>+</sup> ions and secretion of H<sup>+</sup> ions. Compared with H<sub>2</sub>RAs and placebo, PPIs provide faster and increased relief of symptoms and are more effective in healing erosive esophagitis.<sup>97,100,101</sup> After erosive esophagitis is healed, there is a low rate of relapse and recurrence of GERD symptoms.<sup>102</sup> Thus, prolonged courses of PPI are not recommended without continued diagnosis.

There is increasing evidence of side effects from prolonged acid suppression, resulting from hypochlorhydria. For this reason, the smallest effective dose of acid suppression for only the necessary period of time should be used.<sup>54</sup> Hypochlorhydria impairs vitamin B<sub>12</sub>, calcium, and iron absorption. PPI therapy has been associated with fractures in adults with osteoporosis, as well as fractures in young adults.<sup>103</sup> This same association has not been seen in children younger than 18 years of age. Long-term acid suppression also has increased infectious risks. In neonates, H<sub>2</sub>RA therapy is associated with higher rates of necrotizing enterocolitis.<sup>104</sup> Long-term hypochlorhydria is hypothesized to alter the intraluminal environment, promoting the growth of small bowel bacteria.<sup>105</sup> This leads to small bowel bacterial overgrowth, a condition in which the bacteria cause excessive fermentation, resulting in symptoms of bloating, abdominal pain, and diarrhea. The reduction in gastric acid secretion allows pathogen colonization from the upper gastrointestinal tract. In PPI users, a significant positive dose–response relationship has been observed between PPI use

and increased risk of community-acquired pneumonia.<sup>106,107</sup> There was a similar increased risk, although no dose–response relationship, seen with H2RA use. With both PPI and H2RA use, there is an increased risk of gastroenteritis<sup>107</sup> as well as community-acquired *Clostridium difficile* infection.<sup>108</sup> Gastric polyps and nodules can be noted after prolonged PPI therapy, but these changes are benign.<sup>54</sup>

**Antacids** Antacids are compounds containing different combinations, such as calcium carbonate, sodium bicarbonate, aluminum, and magnesium hydroxide. They provide rapid but short-term symptom relief by buffering gastric acid, and in high doses are as effective as H2RAs.<sup>109,110</sup> These drugs have no efficacy in healing erosive esophagitis.<sup>111</sup> Dosing of these medications is based on age and weight (Table 4).

## SURGICAL MANAGEMENT

Fundoplication is an antireflux surgery that may benefit children with confirmed GERD who have failed optimal medical therapy, who are dependent on medical therapy over a long period of time, or who have life-threatening complications of GERD.<sup>19</sup> Although studies are needed to confirm which cohort of GERD patients are most likely to benefit from a fundoplication, it is suggested for those with respiratory complications, including asthma or recurrent aspiration related to GERD.

Despite its value in preventing GERD, fundoplication has other consequences including gas bloat syndrome, impaired gastric accommodation, gastric hypersensitivity, rapid gastric emptying, retching, or dysphagia.<sup>112</sup> Children with neurologic

Table 4 Pharmacologic agents for the treatment of gastroesophageal reflux disease		
Medication	Dose	Age
Proton pump inhibitors		
Omeprazole	0.7–3.3 mg/kg/d, max 20 mg/d	≥2 y
Lansoprazole	0.7–3 mg/kg/d	≥1 y
Esomeprazole	<20 kg: 10 mg/d ≥20 kg: 10–20 mg/d	≥1 y
Pantoprazole	≥15 kg to <40 kg: 20 mg/d ≥40 kg: 40 mg/d	Pediatric indication for erosive esophagitis in ≥5 y
Histamine-2 receptor antagonists		
Famotidine	1 mg/kg/d divided in 2–3 doses, max 20 mg bid	≥1 mo
Ranitidine	5–10 mg/kg/d divided in 2–3 doses, max 300 mg/d	≥1 mo
Cimetidine	400 mg 4×/d	No pediatric indication
Antacids		
Calcium carbonate	2–5 yo: 375–400 mg PRN; max 1500 mg/d 6–11 yo: 750–800 mg PRN; max 3000 mg/d ≥12 yo: 500–3,000 mg PRN; max 7500 mg/d	≥2 y
Sucralfate		No pediatric indication for independent treatment of gastroesophageal reflux disease

Abbreviations: max, maximum; PRN, as needed; yo, years old.

impairments suffer from many conditions, such as scoliosis and epilepsy, which decrease the success rate of antireflux therapy. In this group of children, fundoplication is associated with an high recurrence rate and significant morbidity and mortality, with a 40% surgical failure rate, 12% to 30% rate of recurrent reflux, 59% experiencing postoperative complications, and a 1% to 3% mortality rate. Surgery done in early infancy also has a higher failure rate and greater risk for surgical mortality.<sup>113</sup>

Transpyloric feeds have been proposed as an alternative to fundoplication in patients with GERD who are medically complex. Reflux can still occur during transpyloric feeds, and is thought to be a result of increased transient LES relaxations when fat is instilled into the small bowel.<sup>114</sup> Despite this phenomenon, the number of reflux events and the percentage of full-column events during transpyloric feeds are lower when compared with gastric feeds. Studies comparing transpyloric feeds and fundoplication are few, but suggest that there is a trend toward more major complications with fundoplication compared with gastrojejunal feeds in neurologically impaired children.<sup>115</sup> The 2 therapies have comparable rates in decreasing aspiration pneumonia, although neither eliminates the risk completely.<sup>116</sup>

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