

### *III. Clinical Manifestations and Management*

#### A. Mouth and Esophagus

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## CHAPTER XX

# GASTROESOPHAGEAL REFLUX

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**G**astroesophageal reflux (GER) is the movement of gastric contents retrograde into the esophagus; in addition to indicating such individual events, the term is also used to signify a benign but symptomatic condition. Gastroesophageal reflux disease (GERD) comprises the objective pathologic sequelae of such retrograde movement of gastric contents, but the term has also been used more recently to denote symptoms affecting quality of life, without regard to objective evidence of disease.<sup>1</sup> GERD now comprises the most common esophageal disorder, as well as one of the most common disorders of any kind affecting infants and children; in adults, it has been documented to be the most costly gastrointestinal disease, estimated to consume more than \$9 billion each year in direct costs.<sup>2</sup> The sparser data available in children indicate similar prevalence and cost issues. Therefore, in both children and adults, the promulgation of guidelines for the diagnosis and therapy of various diseases was applied early to GERD, albeit with awareness of the degree to which the current relative dearth of rigorous pediatric data impairs their reliability for children.<sup>3-6</sup>

### PRESENTATIONS AND SYMPTOMS

#### ESOPHAGEAL VERSUS EXTRAESOPHAGEAL

GERD may present as regurgitation, particularly in younger children; as esophageal symptoms, including chest pain, odynophagia, or dysphagia; as respiratory disease; or as diverse other symptoms or signs, including dental and neurologic manifestations.

#### AGE RELATED

GERD manifests differently in infants than in older children. Although the pathophysiologic underpinnings of this difference are not completely understood, it is likely that the large

nutritional demands for growth and the immaturity of neuromuscular and other systems conspire with dietary and postural provocations to generate the infantile forms, whereas the chronicity of the insults plays an increasingly important role in older children and adults.<sup>7</sup> Thus, regurgitation, crying presumed owing to the pain of esophagitis, and malnutrition in the infant transform into symptoms more predominantly centered on the pain and sequelae of esophagitis in the older child. Similarly, the respiratory presentations of GERD may be more centered on the upper airway and apnea in the infant, whereas in the older child, the lower airway and asthma become more important.

#### REGURGITATION

Regurgitation may produce malnutrition or may be associated with pain. If it is unassociated with objective signs of disease, including malnutrition, pain, or respiratory symptoms, it is generally considered benign GER. Regurgitating infants, without other signs of disease, are generally considered "happy spitters" and are managed nonpharmacologically. Regurgitation may persist in toddlers with GERD, and regurgitation into the mouth with reswallowing is sometimes evident in older children, and adolescents with GERD.<sup>8</sup> Regurgitation should be differentiated from vomiting, which has a distinct pathogenesis, including retrograde duodenal peristalsis, but, in practice, this differentiation is commonly ignored, and vomiting is used less specifically to encompass regurgitation. Regurgitation in young infants with GERD is often sufficiently projectile to further complicate this distinction.

#### PAIN

Pain has long been considered the primary symptom of esophagitis, represented by crying in young infants, but the correlation of pain with objective manifestations of endo-

scopic or even histologic esophagitis is incomplete.<sup>9,10</sup> Infant crying is associated with reflux episodes during video and esophageal pH probe monitoring.<sup>11</sup> On investigation, the esophageal pain symptoms may be disclosed to be associated with erosive changes visualized endoscopically, with histologic changes visualized microscopically, or with no evident changes. Recent awareness of differences in visceral sensitivity among individuals with irritable bowel syndrome and dyspepsia has begun to be applied to those with GERD, although, as yet, this concept has not been widely developed or applied to therapeutic strategies.<sup>10</sup> The differential diagnosis of chest pain in children encompasses esophageal motility disorders and eosinophilic esophagitis.<sup>12-14</sup> The differential diagnosis widens in the youngest children, who have the least ability to communicate discriminatory information.<sup>15</sup> Distinctions between odynophagia (painful swallowing) and dysphagia (difficulty swallowing) may be challenging in nonverbal children but can be useful in focusing the differential diagnosis between inflammatory conditions and motor abnormalities of the esophagus.

### OTHER

Esophageal inflammation caused by refluxed acid may result in erosive esophagitis and produce occult blood loss or hematemesis. Such inflammation, if protracted, can also cause strictures that obstruct the esophagus. Barrett's esophagus may be asymptomatic until a stricture, or even adenocarcinoma, causes obstructive dysphagia.

Respiratory symptoms and neurologic symptoms may be the presenting signs of GERD (see below). A variety of other symptoms (such as hiccups, sneezing, drooling, or mouthing) have been described.<sup>11,16</sup>

## EPIDEMIOLOGY AND NATURAL HISTORY

### EPIDEMIOLOGY

The challenges in identifying the epidemiology of GERD are exacerbated by an evolving definition of the disease, unclear demarcation between physiologic and pathologic reflux, lack of a diagnostic gold standard, and a paucity of incidence and prevalence data.<sup>17</sup> For symptoms of GERD, the general population prevalence in infants and children has been estimated to range from 1 to 8%, queried.<sup>18-20</sup> These estimates are further supported by earlier estimates of the proportion of children and adults presenting for evaluation of, or receiving therapy for, GERD.<sup>21</sup> Similarly, 7% of adults experience daily heartburn.

GERD is associated with many other disorders; these associations devolve from provocations of the pathogenic mechanisms of reflux. Thus, neuromuscular disorders can generate GERD by direct effects on upper gastrointestinal tract motility or indirectly by effects on intra-abdominal pressure and posture. Respiratory diseases can affect abdominal-thoracic pressure gradients and so predispose the patient to GERD.

### NATURAL HISTORY

Although regurgitation resolves in most symptomatic infants by 12 to 24 months of age, unselected infants with

frequent regurgitation may develop feeding problems in the subsequent year of follow-up.<sup>22</sup> By 9 years of age, children with frequent regurgitation during infancy may be more likely to develop persisting reflux symptoms, a phenomenon exacerbated by maternal smoking and maternal reflux symptoms.<sup>23</sup> Children over 1 year of age without neurologic 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.<sup>24</sup> However, half of older children with GERD have a chronic relapsing course.<sup>25</sup> Adults with reflux disease are nearly twice as likely as adults without reflux disease to recall having had symptoms of GERD during childhood.<sup>26</sup>

More severe pediatric GERD, the form detected by the earliest investigators, also persists in a minority beyond a year or two of age, but without therapy leads to definite morbidity and mortality.<sup>27</sup> Although strictures, Barrett's esophagus, and adenocarcinoma are rare in childhood, it is likely that GERD, beginning in childhood, predisposes the patient to these complications in adulthood.<sup>28</sup>

## PATHOPHYSIOLOGY

Understanding of the mechanisms underlying GER has expanded from the primitive conceptualization of the lower esophageal sphincter (LES) as hypotonic to the more complicated and accurate current model (Figure 24-1).<sup>29,30</sup> This current model incorporates dynamic changes at the gastroesophageal junction (GEJ) involving transient LES relaxations (TLESRs) of a sphincter supported actively by the hiatal crura. These motor mechanisms at the GEJ are impacted by more distal motor mechanisms related to gastric volume-pressure relationships promoting TLESRs and reflux and by more proximal motor mechanisms related to 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. The genetic and environmental factors that modulate all of these pathophysiologic mechanisms and thus underlie the determination of who becomes diseased are currently receiving attention.

### MOTOR ASPECTS

Tonic LES pressure is maintained above 4 mm Hg, a level adequate to prevent reflux, in most children, even those with GERD. Most reflux occurs when the LES relaxes transiently in a TLESR; the characteristics and provocations of TLESRs have been reviewed.<sup>31,32</sup> The TLESR can be viewed as an "aborted swallow," with afferents in the gastrointestinal tract proximal to the LES, or, more commonly, as a "belch equivalent" venting gastric pressure, with afferents in the stomach, distal to the LES. The TLESR is mediated primarily through vagal pathways via

the brainstem. Acting on either the sensory or the motor arm of the arc or on the central pattern generator, nitric oxide and cholecystokinin A seem to play a positive role in TLESR generation because their antagonists reduce the rate of TLESRs; somatostatin,  $\beta$ -aminobutyric acid B (GABA<sub>B</sub>), and opiates have the opposite effect. Agents affecting these sites, such as the GABA<sub>B</sub> agonist baclofen, have begun to be explored as therapies for GERD, but with ambiguous results. The central role of TLESRs in GERD is challenged by some reports that indicate that TLESR frequency is equivalent in those with and without GERD; the similar frequencies of TLESRs were accompanied by more frequent acid reflux episodes in the GERD patients in contrast to more gaseous or nonacid liquid reflux in the non-GERD patients, differences postulated as attributable to posture or other factors.<sup>33</sup>

The crural diaphragm that surrounds the LES bolsters its tone, particularly during straining; intricate neural connections ensure that TLESRs are physiologically accompanied by coordinated crural relaxation. This fact underlies the important role of hiatal hernia, particularly in more severe GERD, when the LES pressure can be overcome by gastric pressure, especially during straining (abdominal wall and diaphragm contraction), even in the absence of a TLESR.<sup>34</sup> In adults, hiatal hernia size correlated with

esophagitis severity to a greater extent than did manometric LES pressure or esophageal pH probe-monitored (EpHM) esophageal acid exposure, and hiatal hernia size is one risk factor for esophageal adenocarcinoma.<sup>35,36</sup> The etiology of hiatal hernia is unclear, however. It has been proposed either to cause or to be caused by GERD, and both increased abdominal pressure and esophageal traction have been implicated in generating a hiatal hernia.<sup>37</sup> Although hiatal hernia ("partial thoracic stomach") was the earliest identified pathologic correlate of pediatric GERD, a recent retrospective study identified hiatal hernia in only 6% of 718 children with GERD.<sup>38,39</sup> That study found that children with hiatal hernia manifested more delayed esophageal clearance than those without hiatal hernia. Nearly one-fourth of those with hiatal hernia were neurologically impaired, most of whom were treated with surgical therapy initially; nonoperative treatment resulted in an appreciable failure rate (25%) even in neurologically normal patients.<sup>33</sup> Although it is likely that many children do not manifest symptoms with a hiatal hernia, GERD symptoms that are refractory to medical management in patients with hiatal hernia should be treated surgically.<sup>40</sup>

Aspects of gastric function also provoke or impede reflux by affecting the gastric pressure-volume relationship. The volume of gastric material (ingested, secreted by

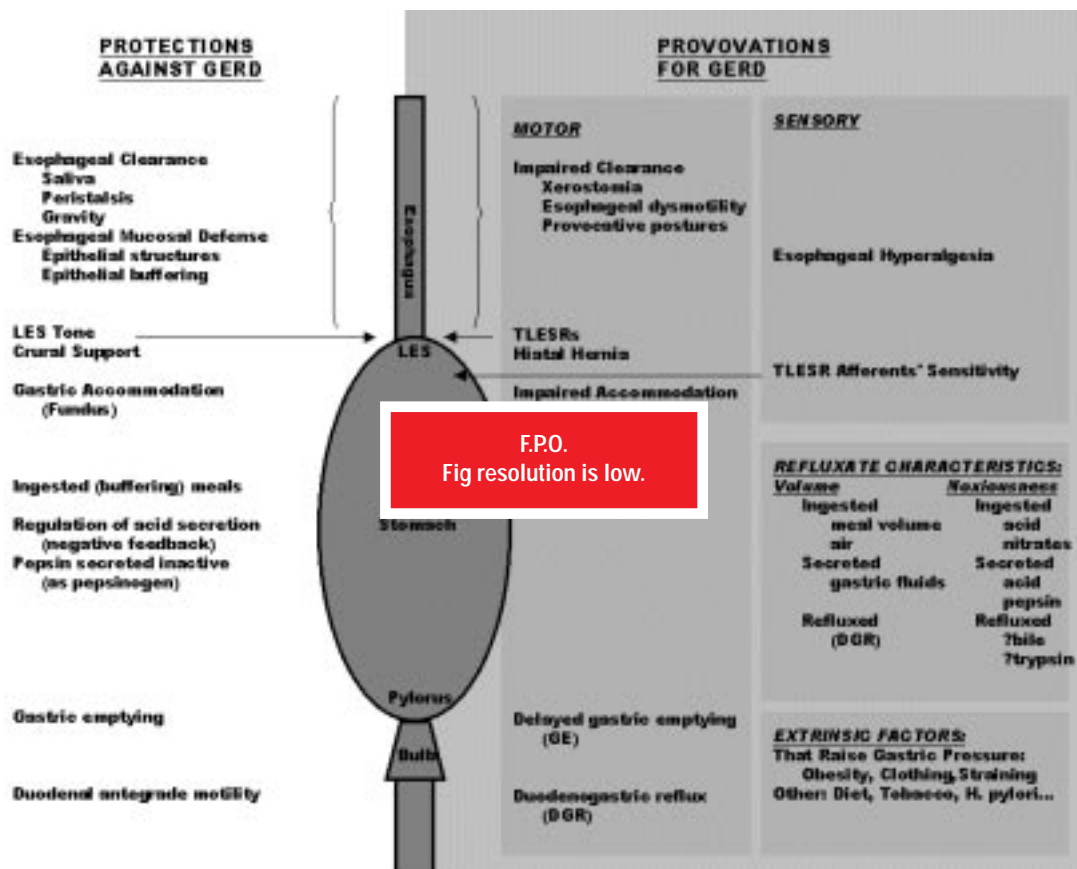


FIGURE 24-1 Physiologic reflux: range of normal values (mean  $\pm$  2 SD) in children of various ages ( $n = 285$ ) and adults ( $n = 15$ ). Total duration of esophageal acidification throughout the day, during normal activities and diet. Reproduced with permission from Orenstein SR: Gastroesophageal reflux. In: Stockman J, Winter R, editors. Current problems in pediatrics. Chicago: Mosby Year Book; 1991. p. 193–241.

the stomach, or refluxed from the duodenum) is, in turn, modulated by gastric emptying. Gastric accommodation, the stomach's ability to relax to accommodate increased volume, is a further modifying factor.<sup>41</sup>

Increased meal volume increases the frequency of TLESRs in children, consistent with the mechanisms postulated to underlie TLESRs.<sup>42</sup> By slowing gastric emptying, increased meal osmolality increases the rate of reflux episodes when the sphincter does relax.<sup>42</sup> Delayed gastric emptying per se accentuates the volume refluxed per episode in the postprandial period in children and seems to be associated with more severe GERD.<sup>43</sup> Gastric accommodation, measured by barostat or scintigraphically, likely impacts the occurrence of TLESRs as a response to a given intragastric volume; the stiffer stomachs (lesser accommodation) of infants than of adults may underlie some of the physiologic reflux of babies.<sup>7</sup> Intragastric pressures are also impacted by extragastrintestinal phenomena: chronically by obesity, tight clothing, or provocative postures; episodically by straining, coughing, or wheezing.<sup>44,45</sup>

Aspects of esophageal motor function determine the clearance from the esophagus of refluxed material.<sup>46</sup> Gravity provides the crude initial component of clearance in upright individuals; infants, who are recumbent for a greater proportion of the day, often lack this component. Esophageal peristalsis clears volumetric reflux not cleared by gravity. Primary peristalsis, peristalsis initiated by swallowing, comprises 90% of all esophageal responses to reflux. Esophageal distention stimulates secondary peristalsis, a backup function that may be particularly important when reflux occurs during sleep.<sup>47</sup> Esophagitis impairs peristaltic function, promoting vicious cycles of worsening esophagitis: 20% of adults with mild and 50% with severe esophagitis manifest failed or hypotensive peristalsis.<sup>48,49</sup> Saliva propelled the length of the esophagus provides a final "wash-down" and neutralizes residual acid. Methods of increasing salivary wash-down of the esophagus have been proposed as therapeutic, and cholinergic prokinetic agents may affect their clearance function by increasing salivation rather than by any change in gastrointestinal motor function.<sup>50,51</sup>

### SENSORY ASPECTS

The pain of reflux disease has long been associated with esophageal inflammation in the form of erosive (macroscopic, endoscopic) esophagitis or of histologic (microscopic) esophagitis. Nonerosive reflux disease (dubbed NERD by some) may thus manifest histologic inflammation or regeneration despite the absence of macroscopic changes. Esophageal pain unaccompanied by even microscopic abnormalities suggests mechanisms unassociated with inflammation. Contact of epithelial nerve endings with acid, in the absence of inflammation or regenerative changes, is one potential explanation. Another is that, in some individuals, chest pain is due to visceral hyperalgesia in the esophagus, analogous to the functional pain associated with irritable bowel syndrome or dyspepsia.<sup>52,53</sup>

Although esophageal sensory variations underlie some of the individual differences in the esophageal symptoms of GERD, differences among individuals in the sensitivity

of the gastric afferent limb of TLESRs might also produce differences in the frequency of actual reflux episodes in other individuals.

### REFLUX NOXIOUSNESS AND ESOPHAGEAL DEFENSE

The components of the refluxate determine its pathogenicity for the esophageal mucosa (and for more proximal sites). An important study in adults found that gastric acid, gastric pepsin, and bile salts transported to the stomach by duodenogastric reflux were important intrinsic components of refluxate, whereas trypsin was seldom found.<sup>54</sup> The study also demonstrated that acid was increased in the esophagus in patients with esophagitis, strictures, and Barrett's esophagus; that pepsin was increased in patients with strictures and Barrett's esophagus (particularly during the night); and that bile acids were found in the esophagus of 75% of their patients (particularly during the night) but were at cytotoxic concentrations in only 2% of them. Pepsin, when acidified, produces an early, irreversible lesion in the esophageal squamous epithelium, probably by damaging the junctional complex, thus allowing luminal acid greater access to the acid-permeable basolateral membrane and thereby promoting erosive esophagitis.<sup>55</sup> Elevated serum pepsinogen values in neonates with upper gastrointestinal bleeding and esophageal lesions provide further evidence for an important role of pepsin in erosive lesions in children.<sup>56</sup> Because acidity is important in rendering the other components (pepsin and bile salts or trypsin if implicated) pathogenic, therapies directed against acidity are generally effective.

In addition to the intrinsic components, gastric contents are also composed of extrinsic (ingested) material, particularly in the hour or two following a meal. The buffering character of infant milk feeds makes them far less provocative for esophagitis than the acidic liquids consumed by most older children and adults.<sup>7,57</sup> However, adult studies using dual pH probes to analyze the components of refluxate have documented a pocket of acid at the GEJ that escapes the buffering effect of meals, remaining highly acidic (median pH 1.6) compared with the gastric body (median pH 4.7,  $p < .001$ ), and readily traverses the squamocolumnar junction.<sup>58</sup> Of further concern are recent data suggesting that dietary nitrate (commonly derived from green leafy vegetables, particularly when grown with nitrate-based fertilizers) is absorbed, secreted in saliva, reduced by buccal bacteria to nitrite, and further reduced to nitric oxide by acidic gastric juice and ascorbic acid at the GEJ, potentially provoking mutagenesis.<sup>59</sup>

Esophageal defense against noxious refluxate is provided by luminal (pre-epithelial), epithelial, and vascular (postepithelial) factors.<sup>60</sup> Lacking a well-defined surface mucous layer (except possibly in Barrett's esophagus) and bicarbonate-secreting surface cells, the luminal defenses of the esophagus are quite limited. The more important epithelial defenses are both structural (apical cell membranes and intercellular junctional structures—both tight junctions and an intercellular glycoprotein material) and functional (acid-buffering mechanisms and two acid-extruding mechanisms—a Na/H exchanger and a Na-

dependent Cl/HCO<sub>3</sub> exchanger). The vascular defense is the removal by the blood supply of the excess H<sup>+</sup> that entered the epithelium from the lumen.

### GENETIC

Familial clustering of hiatal hernia, GERD, and Barrett's esophagus and adenocarcinoma has suggested a genetic predisposition.<sup>61</sup> Genetic linkage analysis identified a locus for a "severe pediatric GERD" phenotype in a group of five kindreds on chromosome 13q14 but excluded the locus in five other kindreds with an "infantile esophagitis" phenotype. It is likely that a disorder as common and as phenotypically diverse as pediatric GERD will be determined or modified at more than one genetic locus and that responsible genes may affect various aspects of the complex pathophysiology outlined above.

### ENVIRONMENTAL

Many aspects of the pathophysiology are rather obviously affected by environmental factors, such as dietary factors, habitual postures and activity, or clothing. Increased volume, osmolality, and acidity of the diet are provocative.<sup>42</sup> Supine and seated positions are provocative in infants, compared with the flat prone position, but similar results have not been found in older children and adults.<sup>62</sup> There is some ambiguity regarding whether one lateral position is more provocative than the other; the results are likely affected by meal volume and time postprandial. Increased straining, objectified as rectus abdominis contraction, makes reflux more likely to be propelled from the mouth as regurgitation.<sup>63</sup>

An environmental factor receiving particular attention recently is *Helicobacter pylori*. *H. pylori* gastritis, more common in less developed and less sanitary settings, may progress to atrophic gastritis, thus decreasing the acidity and volume of refluxate.<sup>64</sup> As such, it could be somewhat protective against GERD. Likewise, GERD symptoms and esophagitis may occur after eradication of the organism.<sup>65</sup> *H. pylori* genotypes predisposing the patient to more severe gastric disease may be most protective against GERD.<sup>66</sup>

### SPECIAL SITUATIONS

Nocturnal reflux and reflux in premature infants illustrate some aspects of the pathophysiology of GERD.

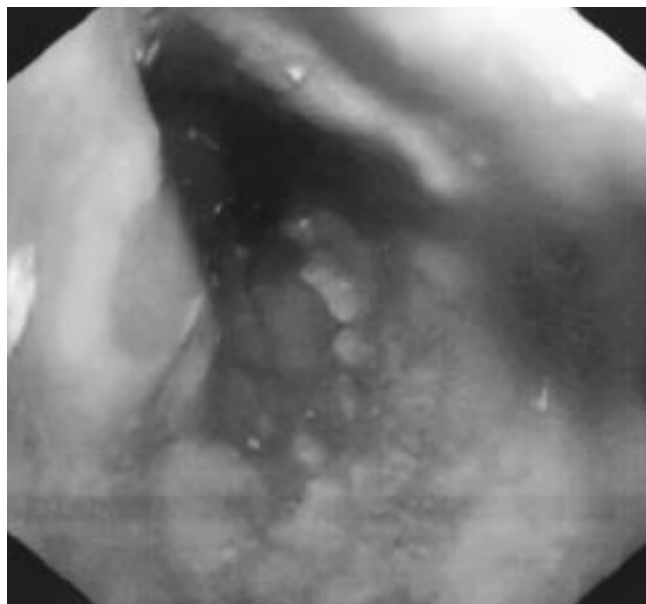
In normal children, reflux is uncommon during sleep. Nocturnal reflux does occur in children with GERD, at a time when protective clearance functions, gravitational clearance, swallowing, and salivation are less active.<sup>67,68</sup> Perhaps because of the absence of these protections, nocturnal GERD is associated with increased incidence of complications of GERD: extraesophageal manifestations, Barrett's esophagus, and adenocarcinoma. Nocturnal heartburn is associated with sleep disorders, reflux-associated respiratory disorders, and decreased health-related quality of life scores.<sup>69,70</sup>

GER in premature and full-term neonates is particularly challenging because of the dearth of data on which to base management.<sup>71,72</sup> Premature infants have an especially great need for caloric intake for adequate growth contrasted with

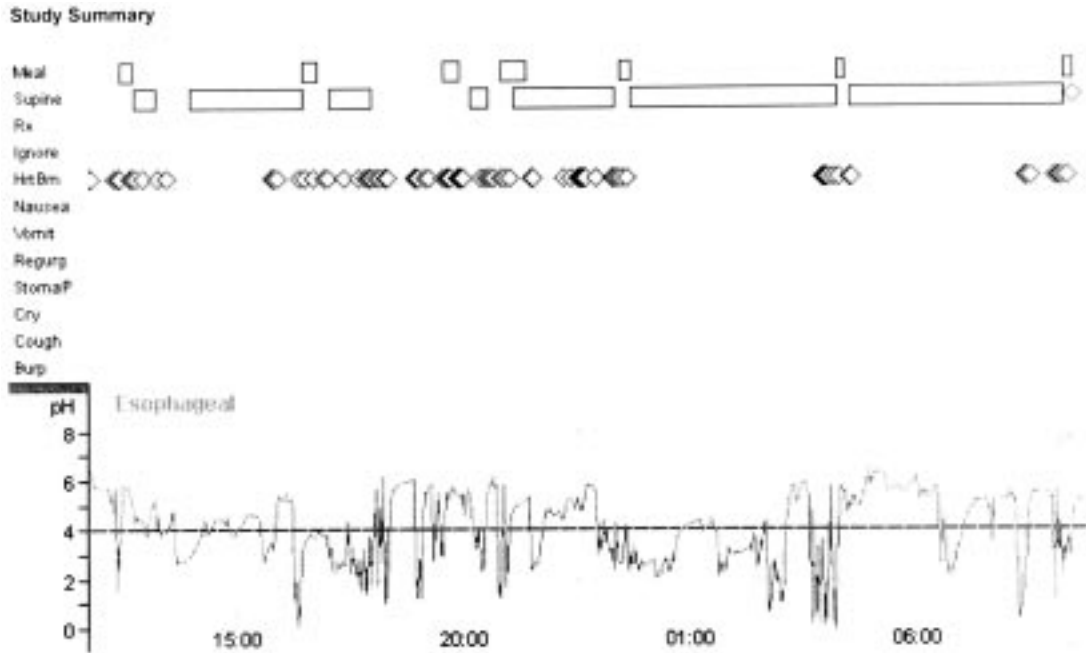
limited gastric capacity. The relatively large-volume refluxate thus reaches the upper esophageal sphincter frequently. The response to such refluxate has been described in infants: effective primary and secondary peristalsis and an increase or relaxation in upper esophageal sphincter pressure.<sup>72</sup> The UES responses can be conceptualized as protecting the airway from refluxate by increased sphincter pressure but relaxing to allow refluxate to escape the esophagus when excessive esophageal pressure is generated by the refluxate. Gravitational provocations to reflux caused by the low torso tone are marked in these young children. Nasogastric tubes, often used to feed premature infants before suck-swallow and gag maturation, may impair refluxate clearance if the tubes are large bore.<sup>73</sup> Reflux is often nonacid at this age because of the very frequent buffering feedings. Chronic lower respiratory disease related to prematurity produces vicious cycles with GERD pathophysiology, to make both worse. Coughing is an uncommon respiratory clearance mechanism in neonates. The limited cross-sectional area of the larynx and upper airway, combined with immature reflexes predisposing the patient to apnea, make upper airway obstruction a particularly hazardous manifestation of GERD at this age, and there are suggestions that nonacid reflux may be pathogenic for this manifestation in young infants.<sup>74</sup>

### DIAGNOSIS

Historically, diagnostic evaluation of GERD emphasized radiography, then EpHM, and then endoscopy, usually supplemented by histology in children. Nuclear scintigraphy and esophageal impedance measurement provided the ability to evaluate nonacid reflux that EpHM missed. More recently, considerations of cost and invasiveness have moti-



**FIGURE 24-2** An endoscopic appearance of Barrett's esophagus: salmon-colored patches of columnar mucosa extending proximal to the lower esophageal sphincter as tongue like projections with surface exudate.



**FIGURE 24-3** An intraesophageal pH probe study demonstrating gastroesophageal reflux episodes and relation to meals, position and symptoms. In this study reflux index (total time pH <4) is 29.6%, longest reflux episode is 64 minutes and 54 episodes (31.5%) are associated with heartburn. StomaP=stomach pain

vated less technologic investigations, using validated questionnaires and trials of empiric medical therapy.

### ENDOSCOPY

Endoscopy, particularly when supplemented by histology, is the most accurate method of demonstrating esophageal damage by reflux. In a retrospective analysis of 402 neurologically normal children, between 18 months and 25 years of age and without congenital esophageal disease, who were diagnosed to have GERD, erosive esophagitis was reported at endoscopy in more than one-third.<sup>75</sup> The prevalence of erosions increased with age. Strictures were found in 1 to 2%; Barrett's esophagus (Figure 24-2) was suspected endoscopically in nearly 3% but was not substantiated histologically by intestinal metaplasia. Optimization and standardization of practice and reporting of endoscopy are unrealized goals in pediatrics; a clinical outcomes research initiative developed in adults is currently being expanded in pediatric practices.<sup>76</sup>

### HISTOLOGY

Microscopic evaluation of biopsy samples from the distal esophagus, but avoiding the most distal area to minimize the false-positive findings at the GEJ, demonstrates abnormalities in many patients who have symptoms but no endoscopically visualized erosions. Infiltration of the epithelium with inflammatory cells, the changes recognizable in esophageal epithelium regardless of orientation of the specimen, received early attention. Neutrophils and eosinophils are not normally present in the epithelium of young children and can be indicators of GERD when found but are fairly insensitive indicators.<sup>77</sup> Furthermore, eosinophils concentrated above 20/high-power field (or perhaps even above 5/high-power field) are likely to repre-

sent eosinophilic esophagitis (see Chapter 25, "Esophagitis"), making them nonspecific for GERD. Intraepithelial lymphocytes ("squiggle cells") are more sensitive than other inflammatory cells but are fairly common; their specificity for GERD is unclear.

Morphometric histologic parameters require adequate size and proper orientation of the biopsy specimens but seem more reliable for diagnosis of GERD.<sup>77</sup> They correlate with EpHM documentation of esophageal acid exposure in both adults and infants.<sup>78</sup> The upper limit of normal basal layer thickness and papillary height in infants is 25% and 53%, respectively.

### ESOPHAGEAL pH PROBE MONITORING

EpHM (Figure 24-3) has helped to clarify the important role of esophageal acid exposure in GERD. However, many factors contribute to the variability of results in a given patient: technical variability owing to the type of recording equipment or probes, probe placement (methods include radiography, manometry, or regression equations related to patient height), number and placement level of probes (more proximal ones used for airway manifestations of GERD),<sup>79</sup> or duration of recording; patient variexposure; and scoring systems used (including pH threshold and reflux duration required for an "episode" and the pH data and calculations employed).<sup>80,81</sup> Some scoring systems emphasize early postprandial periods, whereas others emphasize fasting periods. Most analyses place some emphasis on clearance parameters by detailing prolonged acid reflux episodes. Conceptually, one of the most compelling is a method quantifying "area under the curve," such that degrees of acidity, as well as duration of acid exposure, are taken into account; computerized systems could make this scoring system more practical.<sup>80,82</sup>



**FIGURE 24-4** Upper gastrointestinal series illustrating mid and distal esophageal strictures in a patient with a history of vomiting and dysphagia for solids.

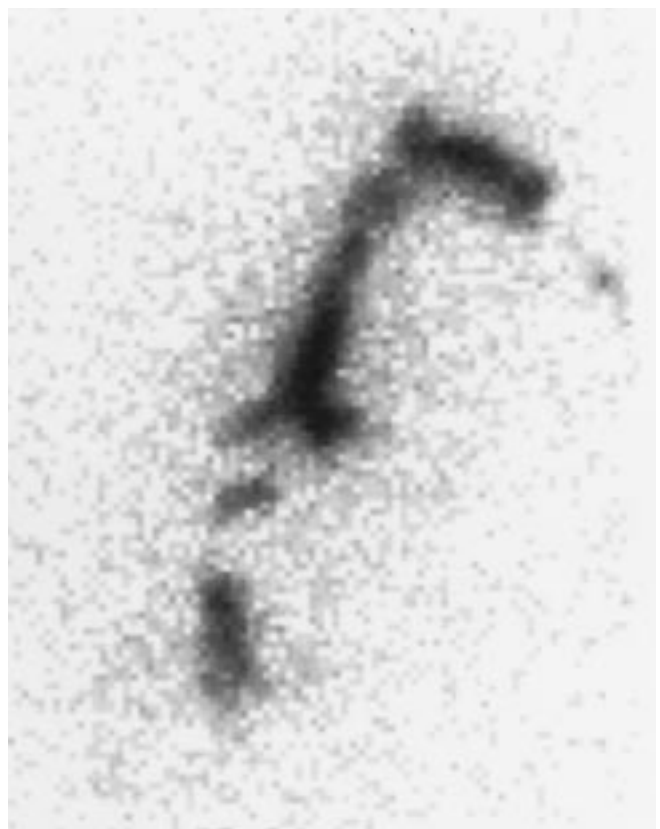
Although ambulatory and computerized monitoring now simplifies EpHM, the invasiveness and economic and temporal costs of the 24-hour test have prompted more limited and thoughtful use currently. One of the most useful indications is to identify whether acid reflux persists during acid suppression treatment when symptoms have not resolved; therapy can then be augmented or another diagnosis entertained depending on the results. Another particular use is the temporal correlation of symptoms with acid reflux events.<sup>83</sup>

### **RADIOGRAPHY**

Fluoroscopic evaluation of swallowing and of the upper gastrointestinal tract is often important in the evaluation of the child suspected to have GERD, but radiography is neither sensitive nor specific for diagnosing GERD per se. Fluoroscopy may disclose gastrointestinal obstructions (pyloric stenosis, malrotation with intermittent volvulus) or motor abnormalities (achalasia) that present with symptoms similar to GERD or may demonstrate complications of GERD (strictures—Figure 24-4). Barium esophagography or specialized swallowing studies may be useful in identifying abnormalities of pharyngeal, laryngeal, or upper esophageal function that may prompt aspiration during swallowing and during reflux.

### **NUCLEAR SCINTIGRAPHY**

Scintigraphy, sometimes crudely termed a “milk scan” because of one type of liquid meal used, employs solid or liquid meals labeled with technetium 99m—for its short (6 hour) half-life and limited radiation burden—to assess for delayed gastric emptying, a potential component of the pathophysiology (Figure 24-5). A second use, based on scintigraphy’s ability to demonstrate reflux optimally in the postprandial period (in contrast to EpHM, which is most sensitive during fasting, when gastric acidity is unbuffered), made it potentially complementary to EpHM evaluation.<sup>84</sup> Use in this way, however, requires prolonged



**FIGURE 24-5** Salivagram using Tc-99m sulfur colloid labeled small volume fluid introduced into the oropharynx produces prompt aspiration extending to the right and left main stem bronchi as seen on posterior imaging of the thorax.

restraint of the child and careful, technically demanding analysis and is thus impractical for clinical purposes. The third way in which scintigraphy has been used is to evaluate for aspiration, either with routine upper gastrointestinal scintigraphy or with salivagraphy.<sup>85</sup>

### IMPEDANCE

Esophageal intraluminal impedance represents another method of demonstrating bolus reflux, without regard for the acidity of the refluxate (see Figure 24-4). Like scintigraphy, it has been shown to be complementary to EpHM: in one study of 50 children monitored with impedance and EpHM simultaneously for about 6 hours, about 15% of impedance-detected episodes were identified by EpHM and about half of EpHM-detected acid episodes were identified by impedance.<sup>86,87</sup> These two tests may be complementary when performed simultaneously, but cumbersome performance and analysis may limit their effective use to research studies.

### MISCELLANEOUS TECHNIQUES

Esophageal manometry (particularly using Dent “sleeve” components to monitor sphincters) uses an esophageal catheter to demonstrate many of the pathophysiologic components of GERD, such as reduced lower esophageal sphincter tone, frequent TLESRs, and defective esophageal peristalsis. It also can demonstrate volumetric reflux, without regard for acidity, in the form of “common cavity” pressure elevations that are manifest first in the distal esophageal ports and may progress cephalad. However, this technique is cumbersome and of most use investigationaly.

Bilirubin monitoring in the esophageal lumen was developed because of the potential pathogenicity of duodenogastric reflux (particularly bile salts) in GER.<sup>88</sup> However, duodenogastric refluxate does not cause esophagitis except in the presence of acid, so focus on acid reflux remains most useful, and bilirubin monitoring is of most potential interest for research studies.

Surface electrogastrigraphy is a noninvasive technique to detect gastric myoelectrical activity, particularly that generated by the pacemaker interstitial cells of Cajal. It may be useful in identifying gastric myoelectrical abnormalities predisposing some children to GERD, but its use thus far is investigational, and it is predominantly used for functional symptoms such as nausea, anorexia, and dyspepsia.<sup>89</sup>

### RESPIRATORY TECHNIQUES

Laryngobronchoscopy allows visualization of abnormalities of the upper airway that may be predisposing patients to aspiration during reflux or swallowing (eg, laryngeal clefts) or that may suggest acid reflux-mediated damage to the airway (eg, vocal cord erythema or nodules).<sup>90</sup> Bronchoalveolar lavage may be accomplished concurrently to quantify lipid-laden macrophages (suggesting aspiration of lipid-containing material).<sup>91</sup> Flexible endoscopic evaluation of swallowing with sensory testing uses a small nasopharyngeal endoscope to visualize the larynx during swallowing and to test for appropriate reflexes to tactile stimulation of the larynx.<sup>92</sup> This technique has been minimally evaluated in children but can identify abnormalities

that may predispose patients to aspiration. Most of these techniques do not distinguish well between aspiration during swallowing and during reflux. The “sleep study” employs EpHM concurrently with polysomnography (usually including electrocardiography, nasal airflow by thermistor or end-tidal CO<sub>2</sub>, and respiratory efforts by chest wall impedance) to identify apneic episodes (particularly obstructive ones) that are temporally associated with acid reflux episodes.

### QUESTIONNAIRES

Questionnaires focus on symptoms and avoid costly and invasive diagnostic testing. They may be used to diagnose GERD or to categorize or stratify the disease. They may assess specific disease symptoms or may focus on quality of life (either generic or disease-specific), such that management strategies may be compared as to efficacy. After treatment or passage of time, they may be used to quantify improvement, stability, or worsening of disease. To be useful, questionnaires must be developed and validated using sophisticated methods to demonstrate the accuracy, reliability, and reproducibility (internal consistency, test-retest consistency, and interobserver consistency). Diagnostic questionnaires are tested for content validity, and questionnaires used for assessment of changes over time must be shown to be responsive to such changes.

The degree to which reflux is common and manifests as symptoms without objective damage makes GERD questionnaires particularly compelling. Questionnaires to assess GERD in adults<sup>93-96</sup> and infants<sup>97</sup> have been validated, and others are being developed.

### EMPIRIC TRIAL OF THERAPY

The availability of powerful acid-suppressing pharmacotherapy has prompted the use of a brief trial of the aforementioned therapy as a diagnostic test in adults, and this practice may reasonably be used in children.<sup>98,99</sup> Children whose symptoms clearly respond, particularly those whose symptoms do not recur after a course of some weeks of such therapy, are thus spared more invasive and costly diagnostic testing. Nonresponding or relapsing symptoms should undergo more definitive testing.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of GERD in children is large and may be categorized based on the presentation (Table 24-1 and 24-2). Of particular recent interest is eosinophilic esophagitis, which may overlap with GERD in presentation and in histopathology but which must be treated quite differently (see Chapter 25, “Esophagitis”).

### THERAPY

The risks and benefits of therapy are increasingly evaluated and compared in terms of cost-effectiveness, with particular focus on quality of life, especially health-related quality of life. Economic considerations are also increasingly invoked. Cost-effectiveness analysis in adult GERD indi-

**TABLE 24-1** DIFFERENTIAL DIAGNOSIS OF PEDIATRIC GERD: ESOPHAGEAL PRESENTATIONS

Vomiting, regurgitation	
GI obstruction	Malrotation/volvulus
Pyloric stenosis	
Stricture	
Annular pancreas	
Duodenal web/stenosis	
Intestinal duplication	
Bezoar	
Superior mesenteric artery syndrome	
Infections	Adhesions
Motility disorders	Gastroenteritis, parasites
Food intolerance	Achalasia
Gastroparesis	
Pseudo-obstruction	
Nonreflux GI inflammation	Dietary protein allergy
Functional GI disorders	Peptic ulcer disease/gastritis
Eosinophilic gastroenteritis	
Hepatobiliary disorders	
Pancreatitis	
Extragastrintestinal disorders	Rumination
Cyclic vomiting syndrome	
Metabolic disorders	
Increased intracranial pressure	
Uremia	
Ureteropelvic junction obstruction	
Infections	
Migraines	
Pregnancy	
Toxins	
Munchausen syndrome	
Adrenal insufficiency	
Esophagitis (pain and irritability)	“Colic”
Food intolerance	
Eosinophilic esophagitis	
Gastritis/peptic ulcer disease	
Infections	
Diffuse esophageal spasm	
Hepatobiliary disorders	
Pancreatitis	
Cardiac pain	
Costochondritis	
Visceral hyperalgesia	
Malingering	
Dysphagia	Eosinophilic esophagitis
Achalasia	
Other esophageal motility disorders	
Globus	
Vascular ring	
Failure to thrive	Feeding disorder
Malabsorption	
Metabolic disorder	
Chromosomal anomaly/genetic syndrome	
Underfeeding	

GI = gastrointestinal

cates that proton pump inhibitors (PPIs) are the most cost-effective initial and maintenance medical therapy in most situations, although, in some settings, the costs of drugs make histamine<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) preferred.<sup>100,101</sup> The situation is probably different in infants, for whom reflux is predominantly of relatively larger volumes of material that is less acidic, so that, theoretically, lifestyle measures and prokinetic agents could be more

**TABLE 24-2** DIFFERENTIAL DIAGNOSIS OF PEDIATRIC GERD: EXTRAESOPHAGEAL PRESENTATIONS

Apnea/ALTE	Prematurity
Bronchopulmonary disease	
RSV, pertussis	
Sepsis	
Seizure	
Cardiac disease	
Laryngotracheomalacia	
Choanal atresia	
Micrognathia	
Macroglossia	
Foreign body aspiration	
Adenoidal and tonsillar hypertrophy	
Otolaryngologic presentations	
Otitis	Infections
Sinusitis	Infections
Allergies	
Cystic fibrosis	
Immotile cilia syndrome	
Immune deficiency	
Stridor, hoarseness	Viral croup
Subglottic stenosis	
Laryngomalacia	
Tracheomalacia	
Laryngeal cyst	
Vascular ring	
Wheezing, chronic cough	Bronchial asthma
Cystic fibrosis	
Allergies	
Foreign body aspiration	
Immotile cilia syndrome	
Postnasal drip	
Pneumonia	
Bronchitis, bronchiectasis	
Cough tic	
Dental erosions	Acidic foods and drinks
Acidic medications (chewable vitamin C tablets, aspirin)	
Bulimia	
Rumination	

ALTE = apparent life threatening event ; GERD = gastroesophageal reflux disease; RSV = respiratory syncytial virus.

cost-effective in this age group, although this expectation has not been realized to date.<sup>7</sup>

### LIFESTYLE MEASURES (CONSERVATIVE THERAPY)

For infants, lifestyle measures have the clearest benefit.<sup>102</sup> Even telephone teaching of these measures may lead to symptom resolution for a sizeable proportion of infants.<sup>103</sup> The prone position clearly produces less reflux than the supine or seated position, but concerns about provocation of sudden infant death syndrome have significantly limited its use during ages when this syndrome is most common. Thickening of infant feeds reduces regurgitation, decreases crying, and increases sleep time.<sup>104</sup> Lower volume and lower osmolality feedings also decrease reflux.<sup>42</sup>

### PHARMACOLOGIC THERAPY

Pharmacotherapeutic agents encompass acid-lowering agents, barrier agents, and prokinetic agents (Table 24-3).

Acid-lowering agents are most useful for symptoms and complications that are acid related, such as heartburn

TABLE 24-3 PHARMACOTHERAPY FOR PEDIATRIC GERD

MEDICATIONS	DOSES	SIDE EFFECTS
ACID NEUTRALIZATION		
Antacids	1 mL/kg/dose, 3–8 times/d	Constipation, seizures, osteomalacia, hypophosphatemia (Al); diarrhea (Mg); fluid retention (Na); milk-alkali syndrome (Ca)
HISTAMINE <sub>2</sub> 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	Pediatric doses not defined	Headache, dizziness, constipation, diarrhea, nausea
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 divided doses: AC	Headache, rash, diarrhea, nausea, abdominal pain, vitamin B <sub>12</sub> deficiency
Lansoprazole	1.4 mg/kg/d, 1–2 divided doses: 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
PROKINETICS		
Metoclopramide	0.1 mg/kg/dose qid: AC, HS	Drowsiness, restlessness, dystonia, gynecomastia, galactorrhea
Cisapride*	0.2 mg/kg/dose qid: AC, HS	Diarrhea, cramps, cardiac arrhythmias
Erythromycin	3–5 mg/kg/dose tid-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 tid-qid: AC, HS	Hypotension, bronchospasm, salivation, cramps, blurred vision, bradycardia

AC = ante cibum; GERD = gastroesophageal reflux disease; HS = hour of sleep; PC = post cibum.

\*Use in the United States restricted through a limited access program supervised by a pediatric gastroenterologist.

and esophagitis. Acid-lowering agents, listed in order of increasing potency, are acid-neutralizing antacids, H<sub>2</sub>RAs, and PPIs. In a review of adult studies without regard to dosing or duration of therapy, PPIs were found to produce more patients free of heartburn, more patients healed, than H<sub>2</sub>RAs or barrier agents.<sup>105</sup> Such comparisons are unavailable for children; it is likely that similar conclusions would be reached for older children, but it is unlikely that most infants require powerful acid suppression.

“Step-up” and “step-down” strategies signify those that start with H<sub>2</sub>RA and “step up” to PPI for those who fail to respond adequately versus those that start with PPI and respond adequately versus those that start with PPI and “step down” to H<sub>2</sub>RA when patients have responded adequately to the PPI. Optimal strategies for children are unclear. Recommended H<sub>2</sub>RA dosing for children has probably generally been too low but is undergoing re-evaluation.

Nocturnal acid breakthrough for patients on PPIs has been treated with bedtime doses of H<sub>2</sub>RA, but there is evidence for tachyphylaxis to daily H<sub>2</sub>RAs within a week.<sup>106</sup> Considerations include incorrect diagnosis, improper administration (should be given just before a meal and not in hepatic cytochrome P-450-2C19 that results in more rapid metabolism of PPIs. Studies that compare several different PPIs at different doses should be critically evaluated in light of the fact that, for most PPIs, similar doses seem to have similar efficacies (except that esomeprazole, the S-isomer of omeprazole, is considerably more potent than omeprazole on a weight basis). For children unable to take

PPI capsules, granules can be administered orally or into the stomach in weakly acidic material such as apple juice or yogurt or into the intestine dissolved in sodium bicarbonate. Pantoprazole is currently the only PPI available in the United States in intravenous formulation.<sup>107–109</sup>

Barrier agents include sucralfate, which complexes with the base of ulcers or erosions, so it is most effective in settings in which the esophageal epithelium is broached. Gaviscon forms a different sort of barrier, floating on top of the gastric contents and potentially reducing reflux in that way.

Prokinetic agents have tremendous theoretical benefit in reflux, particularly in young children, but that theoretical benefit has been challenging to demonstrate objectively, and potential side effects and toxicity have limited their use. Bethanechol is without clear benefit and is currently rarely used. Metoclopramide has a narrow therapeutic range, and extrapyramidal side effects are not uncommon. Cisapride and domperidone are generally unavailable in the United States. Low-dose erythromycin may improve gastric emptying by activating motilin receptors, but the potential effects of widespread use of this antibiotic on antimicrobial resistance are of concern.<sup>110</sup> Baclofen, a GABA<sub>B</sub> agonist, is being studied as an antireflux agent because of its inhibition of TLESRs.<sup>111</sup>

## SURGICAL THERAPY

Fundoplication, the wrapping of the gastric fundus around the GEJ, has been used for decades to treat refractory

GERD. Although it is efficacious in many children, complications are common and distressing. Cost-effectiveness analyses suggest that fundoplication is most likely to be favored in patients with anticipated prolonged duration of requirement for therapy: younger patients with GERD. However, its long-term effectiveness is ambiguous; many individuals treated with fundoplication nonetheless require ongoing pharmacotherapy for symptom relief.

Complications are most common in those most likely to require it, that is, those with chronic neurologic or respiratory disease. Complications include persistence of the symptoms prompting surgery (often owing to a loose wrap) or the side effects of the surgery (often owing to a tight wrap).<sup>112,113</sup> More broadly, persistence of the symptoms may be due to a “bad diagnosis,” wherein the symptoms prompting surgery were incorrectly attributed to GERD; a “bad patient,” whose challenging physiology makes a successful fundoplication difficult; or a “bad therapy” (incompetent to prevent reflux) performed by a surgeon with deficient or inappropriate technique. Side effects of the surgery, in contrast to ineffective surgery, are usually due to a wrap’s excessive tightness: an antegrade obstruction that produces dysphagia or a retrograde obstruction that produces gas-bloat. Other complications may be due to vagal injury, producing nausea and vomiting owing to gastroparesis or diarrhea or hypoglycemic symptoms owing to dumping (rapid gastric emptying).

Gas-bloat is common and a particularly challenging side effect of fundoplication because understanding of its pathophysiology is limited, and the management options are limited and often experimental. Its symptoms include inability to belch or vomit when needed, retching, gagging, nausea, early satiety, postprandial fullness, and abdominal distention. The pathophysiology of gas-bloat in an individual patient may include gastric hyperalgesia, abnormal gastric emptying, impaired accommodation, or impaired vagal function. These various causes require different types of pharmacotherapy.

Methods to prevent complications prior to performing fundoplication include (1) careful elimination of nonreflux causes of the symptoms prompting surgery; (2) awareness that failure of aggressive PPI pharmacotherapy to control symptoms suggests a nonreflux cause; (3) careful tailoring of the operation in those predisposed to complications by neurologic or respiratory disease, delayed gastric emptying or retching, short esophagus (from esophageal atresia, stricture, or large hiatal hernia), or esophageal dysmotility (eg, from esophageal atresia); (4) choice of an experienced or closely mentored surgeon; (5) optimal “tightness” of the fundoplication to prevent reflux but avoid dysphagia (eg, looser in those with defective peristalsis); and (6) use of a venting gastrostomy for those predisposed to problems because of lower gastric compliance or volume (eg, infants). Some surgeons have used preoperative gastric emptying studies to select patients for concurrent pyloroplasty, but, currently, data argue against that practice because fundoplication itself promotes more rapid gastric emptying.

When complications do occur following fundoplication, the diagnosis and competence of the wrap may be re-evaluated with barium fluoroscopy, endoscopy with histology, and

pH probe using other modalities (eg, esophageal or antroduodenal manometry, gastric emptying scintigraphy) as indicated and treating any other diagnosis if found. Conservative management of complications often includes dietary and feeding modifications. Pharmacotherapy is often required for postfundoplication complications, either directed at the recurrent reflux or directed at the specific side effect of fundoplication if one is present. Fundoplication revision, or dilation of a persistently tight wrap, is sometimes needed.<sup>112,113</sup>

Laparoscopic fundoplication can be as effective as open fundoplication in children and associated with more rapid postoperative recovery but requires a surgeon experienced in performing the technique in these small patients.<sup>114</sup>

Endoscopic therapies aimed at the gastroesophageal junction in patients with reflux may prove useful enough to be applied to children.<sup>115</sup>

## COMPLICATED GERD

### ESOPHAGEAL COMPLICATIONS: STRICTURES, BARRETT’S ESOPHAGUS, AND ADENOCARCINOMA

Chronic reflux may result in scarring of the esophagus, producing a stricture. This scarring appears to depend on acid and perhaps on pepsin.<sup>54</sup> These peptic strictures are generally located in the distal third of the esophagus (see Figure 24-5). Rarely in children, these strictures may be accompanied by Barrett’s esophagus. They should be distinguished from other types of strictures: caustic (generally more proximal), eosinophilic, postoperative/anastomotic, following radiation therapy or sclerotherapy, or (rarely in children) malignant. Peptic strictures should be biopsied below the stricture to confirm the diagnosis of reflux esophagitis and exclude eosinophilic esophagitis, Barrett’s esophagus, or malignancy. They are treated with a course of endoscopic dilations at increasing intervals, supplemented by aggressive antireflux therapy. Injection of corticosteroids into the stricture at the time of dilation has been used for resistant strictures. Resection or strictureplasty may be required for those strictures not amenable to dilation or that perforate during dilation. The relative merits of chronic antireflux pharmacotherapy versus fundoplication are debated. A coexisting large hiatal hernia may encourage surgical treatment.

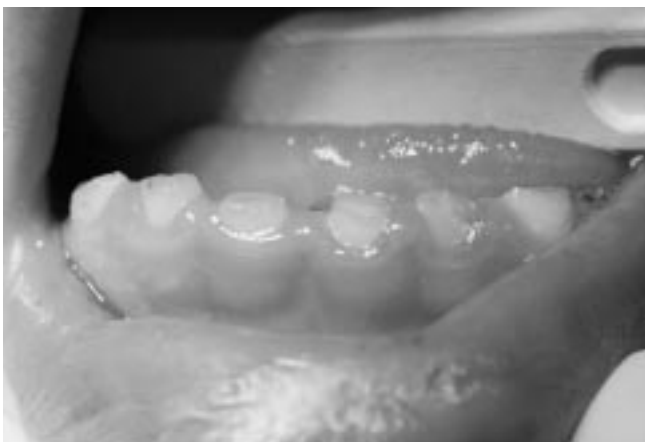
Barrett’s esophagus is uncommon in children but has been reported.<sup>116</sup> The intestinal metaplasia of the distal esophagus, manifesting endoscopically as salmon-colored tongues of tissue projecting proximally into the paler pink esophagus (see Figure 24-2), increases with age until about the fifth decade, and the density of goblet cells increases in parallel.<sup>28</sup> In children, associated conditions include neurologic disability, chronic respiratory disease, repaired esophageal atresia, chemotherapy for malignancies, and hiatal hernia.<sup>117</sup> Postulated pathogenesis of Barrett’s esophagus has included genetic influences, reflux of both acid and pepsin, and possibly a decreased sensitivity to reflux events that results in impaired clearance reflexes.<sup>54,61</sup> The importance of duodenogastric reflux of bile (and possibly trypsin) has been debated.<sup>54,118</sup>

Guidelines for the diagnosis of, therapy for, and surveillance for dysplasia and malignancy in Barrett’s esopha-

gus have been promulgated for adults and may be applicable to children.<sup>119-122</sup> Hiatal hernia size, length of the Barrett's esophagus, and severity of acid reflux are all risk factors for esophageal adenocarcinoma; surgical reduction of hiatal hernia and associated fundoplication thus may be indicated in those with hiatal hernia.<sup>36</sup> Because of the apparent insensitivity to reflux in many patients with Barrett's esophagus, it is worthwhile to assess the adequacy of therapy with EpHM and to evaluate periodically via endoscopy for regression or progression of the Barrett's epithelium and for dysplasia.<sup>123,124</sup> Successful attempts to ablate the specialized epithelium have been reported in adults. Adenocarcinoma is extremely rare in childhood, but it does occur and should be sought in those with Barrett's esophagus.<sup>123</sup>

## EXTRAESOPHAGEAL GERD

**Respiratory Complications and Interactions.** Embryonic relationships between the upper gastrointestinal tract and the airway lead to both luminal and neural connections between the two systems. Consequently, GERD provokes and worsens respiratory diseases, both otolaryngologic and lower respiratory tract disorders, and may do so either by aspiration of refluxate, producing inflammatory changes in the lumen, or by reflexive responses of the airway to refluxed material in the esophagus.<sup>125,126</sup> The respiratory diseases, in turn, may worsen GERD. Epidemiologic evidence suggests that GERD, particularly when reflux occurs recumbent and during sleep, is associated with a several-fold increase in sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis.<sup>70,127,128</sup> Data on otitis media are conflicting.<sup>127,129,130</sup> Laryngotracheomalacia and stridor often coexist with GERD; laryngoscopic changes in the posterior larynx suggest laryngeal irritation by GERD; and chronic hoarseness, chronic cough, and chronic sinusitis have apparently been effectively treated by GERD therapy in open-label trials.<sup>131-133</sup> Dental erosions on the lingual aspects of the posterior teeth also may represent extraesophageal GERD (Figure 24-6).<sup>134-136</sup>



**FIGURE 24-6** Dental imaging showing generalized enamel and dentin erosions at the incisal edges in a patient with gastroesophageal reflux disease. Some dental caries is also present.

Infantile apnea represents a prototypical upper airway response to reflux in the infant, whereas the bronchospasm of asthma represents a prototypical lower airway response to reflux in the older child.<sup>69,74,125,126,137-142</sup> Probable mechanisms for these phenomena have been reviewed.<sup>143,144</sup> Whether aspiration, esophageal airway reflexes, both, or neither is implicated in the pathophysiology of individual cases is challenging to determine, and it is likely that most infants with apnea and most older children with asthma do *not* have reflux-induced respiratory disease. Nonetheless, GERD may play an important role in selected cases, which will be resistant to management if GERD is not considered.<sup>137</sup>

Diagnosis of individual patients suspected of GERD-mediated extraesophageal disease is difficult. The presence of concurrent GERD symptoms makes GERD a more likely factor in respiratory disease. It is often important to distinguish aspiration during reflux from aspiration during primary swallowing because the therapeutic approach will be different. The diagnostic methods must be tailored to the particular questions raised by the presentation but may include upper esophageal EpHM,<sup>145</sup> fluoroscopy (particularly specialized upper esophageal swallowing studies, sometimes termed "cookie swallow"),<sup>146</sup> scintigraphy to diagnose aspiration (particularly the salivagram<sup>85</sup>), laryngobronchoscopy (to disclose posterior glottic edema, erythema, and nodules and including bronchoalveolar lavage for lipid-laden macrophages or trypsin to assess aspiration),<sup>91,147-149</sup> and flexible endoscopic evaluation of swallowing with sensory testing.<sup>92</sup> Laryngobronchoscopy may be coordinated with endoscopic and histologic evaluation of the upper gastrointestinal tract.<sup>150</sup> Impedance testing discloses nonacid reflux that may be important in infantile apnea.<sup>74</sup> An empiric trial of aggressive antireflux therapy may also be used.

Therapy for extraesophageal manifestations of GERD has been reviewed.<sup>151-153</sup> When GERD is responsible for extraesophageal presentations, it seems that the therapy must be aggressive in terms of both potency and duration to affect the respiratory symptoms. Twice-daily PPIs maintained for at least 3 months are often recommended. Fundoplication surgery seems to provide better results, and in adults, the best surgical results are obtained in patients with nocturnal asthma, onset of reflux symptoms before pulmonary symptoms, evidence of laryngeal inflammation, and a good response to medical treatment. However, the complication rate for fundoplication is greater in children with respiratory disease than in those without.

**Neurologic Presentations and Interactions.** Neurologically abnormal children have more GERD, and more complicated GERD, than neurologically normal children. Increased gastric pressure mediated by spasticity, chronic supine posturing impairing refluxate clearance, inability to communicate or move to ameliorate symptoms, and possibly other direct effects of neurologic abnormality all predispose patients to more severe GERD. Thus, erosive GERD, strictures, Barrett's esophagus, adenocarcinoma, and chronic respiratory manifestations of GERD are all more common in children with neurologic disability.

In addition to the impact of neurologic disorders on GERD, GERD may induce symptoms that mimic seizures

or neurologic disease. Torso hyperextension (“arching”) is a common manifestation of infantile reflux.<sup>11</sup> More unusual and severe manifestations in older children include Sandifer’s syndrome, a stereotypic torso, and nuchal hyperextension with unclear pathophysiology.<sup>16,154</sup>

GERD, one of the most common and costly disorders afflicting children, presents with a wide array of symptoms, overlaps in presentation with many non-GERD diseases, can be challenging to diagnose, and does not lend itself readily to simple curative therapy. The burgeoning incidence of adenocarcinoma related to chronic GERD in adults focuses attention on the possible initiation of this cancer in childhood GERD. Further clarifying the pathogenesis of this important disease would have important implications for prevention and treatment.

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