



## Gastroesophageal reflux disease in children



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### ABSTRACT

Despite the frequency with which antireflux procedures are performed, decisions about gastroesophageal reflux disease treatment remain challenging. Several factors contribute to the difficulties in managing gastroesophageal reflux. First, the distinction between physiologic and pathologic gastroesophageal reflux (gastroesophageal reflux disease—GERD) is not always clear. Second, measures of the extent of gastroesophageal reflux often poorly correlate to symptoms or other complications attributed to reflux in infants and children. A third challenge is that the outcome of antireflux procedures, predominately fundoplications, are relatively poorly characterized. All of these factors contribute to difficulty in knowing when to recommend antireflux surgery. One of the manifestations of the uncertainties surrounding GERD is the high degree of variability in the utilization of pediatric antireflux procedures throughout the United States.

Pediatric surgeons are frequently consulted for GERD and fundoplication, uncertainties notwithstanding. Although retrospective series and anecdotal observations support fundoplication in some patients, there are many important questions for which sufficient high-quality data to provide a clear answer is lacking. In spite of this, surgeons need to provide guidance to patients and families while awaiting the development of improved evidence to aid in these recommendations. The purpose of this article is to define what is known and what is uncertain, with an emphasis on the most recent evidence.

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### Definitions and natural history

The definition of gastroesophageal reflux (GER) is *involuntary retrograde passage of gastric contents into the esophagus with or without regurgitation or vomiting*. In infancy, the incidence of GER is approximately 75%. Persistence and severity of symptoms distinguish GER from gastroesophageal reflux disease (GERD). However, the distinction is often blurred. Many studies document the natural history of GER in infants, with a peak incidence at 4–5 months of age.<sup>1</sup> The rate of cessation of symptoms by 1 year of age in the literature ranges between 80% and 95% of cases.<sup>2–4</sup> There are identifiable high-risk groups for GERD, including those with prematurity, esophageal atresia, congenital diaphragmatic hernia, neurologic impairment, obesity, and specific genetic disorders.<sup>1</sup>

### Physiology

Normally, the lower esophageal sphincter (LES) maintains a resting tone of about 12–25 mmHg. The LES normally relaxes briefly when there is a peristaltic wave. There are also longer

duration LES relaxations that last 5–30 s, during which the pressure in the esophagus is the same as that in the stomach. These are called transient lower esophageal sphincter relaxations (TLESRs), and they are the physiological cause of GER. TLESRs are independent of swallowing and of relatively longer duration than the relaxation triggered by a swallow.<sup>2,5</sup> They may not be clinically noticeable if reflux is in the lower esophagus and volume clearance and peristalsis are prompt. The LES tone in infants with GER is not different from normal but they do have more TLESRs and/or TLESRs of longer duration.<sup>6</sup>

### Clinical presentation

Clinical presentations vary with age, and the symptoms of GERD are familiar to pediatric surgeons. Clinical symptoms in infants are generally less reliable indicators of pathologic GERD and correlate poorly with pH monitoring results and endoscopy and endoscopic biopsy findings.<sup>6</sup> There is no symptom or constellation of symptoms that are diagnostic of GERD or that predict response to therapy in infants and toddlers. Although apnea and sudden infant death syndrome are a significant cause of neonatal mortality, there is little evidence of a cause and effect relationship between GER/GERD and infant apnea.<sup>7</sup>

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Effortless vomiting, epigastric pain and dyspepsia, anemia, failure to thrive, and strictures may be the presentation of GERD in older children. Airway problems such as laryngeal irritation, chronic cough, or recurrent pneumonia may be seen. GERD and reactive airway disease are both common, and may occur in the same patients (they are correlated). However, the degree to which GERD causes or exacerbates asthma is a subject of controversy. Recent publications have downplayed the impact of GERD on asthma control.<sup>8–10</sup>

### Diagnostic evaluation

A 2013 review of the literature found poor data and low levels of evidence for the accuracy of diagnostic tests for GERD in children.<sup>7</sup> Routine upper GI radiography (UGI) in the evaluation of GERD has been shown to have a low yield,<sup>11,12</sup> and the 2009 consensus recommendations from the North American and European societies, discussed in detail below, state that routine UGI is not indicated for the diagnosis of GERD—the false-positive rate is high due to non-pathologic reflux, and episodes of reflux are often infrequent, brief and easily missed.<sup>13</sup> UGI may be used to rule out other anatomic abnormalities mimicking GERD, but the yield is low if obtained for screening purposes.<sup>11</sup>

More invasive studies include continuous pH monitoring via a probe in the distal esophagus. The pH study has historically been the most accurate test for GERD; a variety of scoring systems are used, but the common elements include the number of significant pH drops (below 4 and longer than 15 s duration), time required for the pH to return to normal (clearance), and the number of reflux episodes with a clearance time of more than 5 min (longer episodes). Other parameters may be measured to attempt to differentiate normal patients from those with GERD. The correlation between clinical symptoms and reflux is often poor, even if the pH score is “abnormal”. In addition, the test is expensive (requiring hospitalization in children), invasive, and often impractical or impossible in complex patients. pH studies do not, of course, demonstrate alkaline or neutral reflux, and the advent of multichannel intraluminal impedance (MII) studies addresses this failing. There is some evidence that combined MII/pH studies may better correlate with duration of GERD symptoms and provide prognostic information.<sup>14–16</sup> In older children with respiratory and laryngeal problems, addition of MII to standard pH studies can increase the sensitivity of detecting GERD correlation with symptoms.<sup>16–18</sup> Combined MII/pH studies are widely used, but as yet high-quality evidence for the sensitivity, specificity and utility in many clinical scenarios is lacking.<sup>19</sup>

### *Pediatric gastroesophageal reflux clinical practice guidelines*

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) along with its European counterpart ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) published clinical practice guidelines in 2009.<sup>13</sup> This article provides an extensive review of available evidence on gastroesophageal reflux in children and infants. It is important for pediatric surgeons to be aware of its contents, since it is a consensus document from two large pediatric gastroenterology societies and provides a systematic assessment of the evidence. The review is quite extensive, and the details of its conclusions are beyond the scope of this article. However, a brief summary will be valuable for surgeons.

To create the guidelines, nine pediatric gastroenterologists and two pediatric epidemiologists were selected from the two participating societies. They then performed a systematic review of the available literature. This review included 377 articles related to

therapy and 195 additional articles related to etiology, diagnosis, and prognosis. Articles were evaluated using Oxford Center for Evidence-Based Medicine Levels of Evidence and Oxford Grades of Recommendation.<sup>20</sup> All recommendations were based on consensus, and feedback from society members was considered prior to finalization of the recommendations. It is reasonable to believe that these recommendations represent the best evidence in 2009.

As mentioned, the extent of these recommendations is beyond the scope of this article but it is worth mentioning items that are included in the guidelines. These include a discussion of definitions and mechanisms. Discussion of diagnostic methods included history and physical examination, esophageal pH monitoring, combined MII, motility studies, endoscopy and biopsy, barium contrast radiography, nuclear scintigraphy, esophageal and gastric ultrasonography tests on fluids from the ear, lung and esophagus, and empiric trials of acid suppression.

Treatment modalities considered included lifestyle changes, pharmacologic therapies [histamine-2 receptor (H-2) antagonists, proton pump inhibitors, and prokinetic agents] and surgical therapy. While it is of particular interest to surgeons, the discussion of surgical therapy is relatively limited. Guidelines were then provided for the evaluation and management of specific patient populations with suspected GERD. Finally, groups at high risk for gastroesophageal reflux disease were considered. The article begins with an initial three-page synopsis of all of these areas. This provides an effective summary review, and all surgeons are encouraged to read at least the synopsis.

These guidelines provide an effective starting point for a consideration of how to approach gastroesophageal reflux disease in infants and children. Unfortunately, like many such guidelines, recommendations are limited by the lack of high-quality evidence. The clinician is therefore left with many situations in which no sound guidance can be provided. This is particularly the case with regards to surgical treatment of reflux. Much of the discussion in the guidelines regarding surgical treatment of GERD is extrapolated from adult data.

### Medical treatment (briefly)

Thickened feedings have long been a recommended treatment for GERD. However, the efficacy of this approach is limited; some have suggested that this has been driven in part by the baby food industry. A review of 14 randomized controlled trials (RCTs) found that thickeners significantly increased the percentage of infants with no regurgitation and *slightly* reduced the daily frequency of regurgitation and vomiting, and increased weight gain per day.<sup>21</sup> There was no effect on many of the severity of reflux parameters. The authors concluded that thickeners were only moderately effective.

Positional therapy is another longstanding treatment for GERD. A recent review from the United Kingdom evaluated seven RCTs, with data on nine positions. They concluded that positional therapy should not be used in sleeping infants (due to the risk of SIDS, the supine position is strongly recommended even though GER is diminished when prone).<sup>22</sup> “Tummy time” in the awake and supervised infant is permissible, but positional therapy overall was not recommended. Another recent RCT suggested a mild benefit (decreased emesis) with left lateral positioning.<sup>23</sup>

Pharmacologic treatment for GERD primarily consists of prokinetic or motility agents and acid-reduction therapy. Probably the most widely used H2-blocker is ranitidine, although little benefit from one agent over another has been identified.<sup>22</sup> A 2014 Cochrane review found “moderate evidence” to support the use of PPIs (proton pump inhibitors), particularly in infants. PPIs and histamine antagonists demonstrated moderate improvement in

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