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Gastroesophageal Reflux Disease

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Introduction

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

Physiology

Multiple mechanisms are in place to protect from reflux: the anti-reflux barrier, esophageal clearance, and esophageal mucosal resistance. The anti-reflux barrier is composed of the lower esophageal sphincter (LES), the angle of His, the crural diaphragm, and the phrenoesophageal ligament.[3] The LES is tonically contracted circular smooth muscles, composed of the intrinsic muscles of the distal esophagus and the sling fibers of the proximal stomach.[4] 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 2cm in adults, is intraabdominal. The LES resting pressure is higher than 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.[1] Gravity and esophageal peristalsis remove volume from the esophageal lumen, while salivary and esophageal secretions neutralize acid. Esophageal

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mucosal resistance comes into play when acid contact time is prolonged; this is genetically determined.

Mechanisms of GER

Anything that interferes with these lines of defense can lead to GER. Inappropriate transient lower esophageal sphincter relaxation (TLESR) is one of the most important causes of GERD in children. [5, 6] Increased intraabdominal pressure relative to LES resting pressure permits reflux of gastric contents into the distal esophagus.[6] Increased intraabdominal pressure can be caused by medications, Valsalva maneuver, Trandelenberg position, or lifting. Position and posture influences 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.[1] While 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 age one; this would predispose their stomach to a more vertical lie and therefore increased ease of reflux.[1] 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 LES, angle of His, and the diaphragm are compromised.[3] 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.[7] This sac has increased acid exposure and impaired clearance, and can reflux during subsequent swallow relaxations of the LES. [7]

Distinguishing GER from GERD

While GER is a normal physiologic process, GERD occurs when reflux of gastric contents causes troublesome symptoms or complications.[2] 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.[2] Respiratory complications are less common, but recurrent pneumonia and interstitial lung disease secondary to reflux can occur due to aspiration of gastric contents.[8] Reflux worsening asthma symptoms has also been reported. [9, 10] Histological changes can also help distinguish the two, with esophageal biopsies in GERD typically showing findings of basal zone hyperplasia, papillary lengthening, and neutrophil infiltration. [11, 12]

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.[13] After age one, the incidence of GERD decreases with until age 12, and then reaches a maximum at age 16-17. The prevalence varies by study and age. It’s estimated that 10% of all children have GER[14] and 1.8-8.2% have GERD.[14, 15] The estimated prevalence of GERD in infants 0-23 months, children 2-11 years old, and adolescents 12-17 years old is 2.2-12.6%, 0.6-4.1%, and 0.8-7.6%, respectively.

Presenting symptoms

Infancy

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

Childhood

GERD is often diagnosed in adults based on a history of substernal, burning pain, with or without regurgitation. [2] The diagnosis of GERD can similarly be made in adolescents. [27] However, history is unreliable in children under age 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.[13] Abdominal pain and cough are also frequently reported.[28] 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 old, as compared to older children, while heartburn was less severe. Symptoms have not been found to be predictive of mucosal damage.

Children with certain underlying disorders are a high risk for developing severe and chronic GERD (Table 1). [19]

Atypical Presentations

An association between asthma and reflux measured by pH or impedance has been reported[29], though 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.[30] Alternatively, asthma may contribute to GERD. Pulmonary hyperinflation occurs as a result of chronic asthma. This causes the diaphragm to flatten, displacing the LES into the thoracic cavity which has a negative atmosphere pressure, thereby reducing the LES resting pressure and eliminating the angle of His. (503). Studies have shown that the majority of children with asthma have an abnormal pH impedance study,[31] however, use of PPI in unselected patients with wheezing or asthma is of limited benefit.[32] Patients who may benefit from GERD treatment include those with heartburn, nocturnal asthma symptoms, or steroid-dependent difficult to control asthma.[9, 10]

Recurrent pneumonia and interstitial lung disease may be the complications of GERD due to aspiration of gastric contents.[8] While 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.[33]

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

Studies revealed a cause and effect relationship between GERD and dental erosions,[39] 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.

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.[2] It must be distinguished from seizures, dystonia, or infantile spasms.[40] When related to GERD, it improves with antireflux treatment.

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.[41] The term ALTE was recently replaced by the term "brief resolved unexplained event" (BRUE), which is characterized by a sudden, brief, and resolved episode occurring in an infant under one year of age that consists of one of more of the following: cyanosis or pallor; absent, decreased or irregular breathing; marked change in tone; and altered level of responsiveness. As the change was recently made, published studies have evaluated GERD association with the ALTE definition. The results are conflicting. Though most series fail to demonstrate a temporal relationship between the two,[29, 42] multiple studies do show that there is an association.[43–45] If other causes have been ruled out and GER is suspected, the diagnosis can be better evaluated by recording synchronous symptoms on 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.[46] When utilizing 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.[47]

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

Diagnosis

The diagnosis of GERD can largely be based on history and physical 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

On endoscopy, visualizing endoscopic breaks in mucosa is the most reliable evidence of reflux esophagitis. [19] The classic histologic findings of GERD are basal zone hyperplasia, papillary lengthening, and neutrophilic infiltration.[12] While the histologic findings are not specific to GERD alone and have not correlated well to symptom severity of GERD in children[52], they can help support the diagnosis. The sensitivity of histology increases if multiple biopsies are taken – sampling in the mid and distal esophagus.[11, 53] If using this method, the sensitivity of histology was 96% in patients with erosive esophagitis and 76% with nonerosive reflux disease.[53] The additional utility in 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. [54]

pH and Impedance

24 hour esophageal pH monitoring measures the frequency and duration of acid esophageal reflux. This can be performed by either placing a nasal catheter, or by clipping a wireless sensor to the esophageal mucosa via endoscopy. A drop in intraesophageal pH<4 is considered acidic exposure. For criteria to diagnose acid reflux, please refer to NASPGHAN-ESPGHAN consensus paper in 2009 [19]. Main indications of 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.[55] There are limitations to standard pH monitoring. It is a poor detector of weakly acidic (pH4-7) reflux [56] and can also overestimate acid exposure by picking up “pH-only” episodes, in which there is no reflux.[57] In infants and children, weakly acidic GER is more prevalent than in adults,[57, 58] which can explain why abnormal esophageal pH monitoring does not correlate with symptom severity in infants. [59] Abnormal esophageal pH is more frequently observed in adults and children with erosive esophagitis.[60, 61]

Multichannel Intraluminal Impedance (MII) utilizes change in impedance to measure the anterograde and retrograde movement of fluid, solids, and air in the esophagus. Dual pH-multichannel intraluminal impedance (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.[62] Non-acid pH is defined as pH>4 and the reflux index is defined as the percentage of time the pH drops below 4. See Tables 2 and 3 for Reflux Parameter Definitions and Normal Values for Reflux per 24 hours in Infant and Children. Normal values for patients with non-acid reflux were selected based on the following criteria: Acid regurgitation index of ≤ 50% the upper limit of normal (≤3% in children>12month and ≤ in

infants ≤ 12 months); no positive temporal association of reflux with symptoms; off anti-reflux medications; no fundoplication. [63] pH-MII optimizes the yield of GER-symptom association in infants and children.[64] Indications of pH-MII include 1. Evaluating the efficacy of anti-reflux therapy 2. Endoscopy-negative patients with symptoms concerning for reflux despite PPI therapy in whom documentation of nonacid reflux will alter clinical management[55, 62] 3. Evaluating tube fed patients for reflux, as the majority of refluxate during tube feeding is nonacidic [62] 4. Differentiating aerophagia from GER.

Motility Testing

Findings on esophageal manometry are not sensitive or specific to make the diagnosis of GERD, but can identify alternate motor disorders that may present similar to GERD.[19, 54] Esophageal dysmotility is present in a proportion of patients with GERD,[65] with motor dysfunctions of both the lower esophageal sphincter and esophageal body being the major factors predicting medical refractoriness of reflux disease in children.[66]

Though, patients with gastroparesis are at increased risk for GERD,[67] and there are studies that show that infants and young children with delayed gastric emptying tend to be more symptomatic,[68] gastric emptying studies do not confirm the diagnosis of GERD[69] and are not recommended for its routine evaluation.

Upper GI

While GERD is commonly reported on UGI studies, the correlation between reflux reported on UGI and 24-hour pH monitoring is poor.[70, 71] Therefore, UGI should be reserved for defining anatomic abnormalities and not reflux.

Diagnostic trial of acid suppression

Since GERD is primarily diagnosed on symptoms alone in older children and adolescents, responding to empirical trial of PPI therapy helps support, though cannot confirm, a diagnosis of GERD.[72] In both children[73] and adolescent[27] patients with endoscopically proven GERD, a 4 to 8 week course of PPI significantly improves symptoms. 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.[54] 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, since symptoms suggestive of GERD are less specific.[26]

BAL and pepsin (for evidence of microaspiration with reflux or swallowing disorder)

Evaluating pulmonary aspirates for pepsin has been investigated as a biomarker for GERD. While studies support the association of the two,[74–76] problems with prior studies include pepsin assays not being specific to pepsin A, the isoform found exclusively in the stomach.[77] 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,[78] and GERD[79] have found 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.[78]

Treatment

Infant

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

PPI use has been steadily increasing in infants with the most common reasons for use being identified as GER (59%) and poor feeding (23%).[87] The mean age of use, between 4 and 8 months, correlates with timing of physiologic reflux. The majority of infants that are being placed on antireflux drugs do not meet the criteria for GERD.[88] PPIs have not been shown to benefit infant symptoms attributed to GER over placebo,[25, 26] 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 two.[89] A prospective study found that 85 of 204 patients with documented GER by pH impedance testing, had milk protein sensitivity. [21] Therefore, infants with recurrent vomiting and persistent symptoms may benefit from a 2 to 4 week trial of an extensively hydrolyzed protein formula.[22, 90]

Child/Adolescent

Lifestyle changes—Recommendations for lifestyle changes are derived from adult data. While there is some physiological 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.[91, 92] Patients should avoid foods and beverages that trigger their personal GERD symptoms. The only beneficial measures documented are weight loss in obese patients,[93] avoidance of late night eating,[94] elevation of the head of the bed, and prone or left-sided sleeping position.[95]

Acid Suppression

Histamine-2 Receptor Antagonists (H2RAs): Parietal cells secrete acid in response to three stimuli: histamine at the H2 histamine receptor, acetylcholine, and gastrin. H2RAs suppress gastric acid secretion by competitively inhibiting histamine at the parietal cell's H2

receptor. In adequate doses, H2RAs are effective in the treatment of peptic disease[96] and healing erosive esophagitis compared to placebo.[97, 98] However, patients requiring more than occasional use can develop to rapid tachyphylaxis.[99] Dosage requirements vary by age, but children require a relative higher dose than adults.[96]

Proton Pump Inhibitor (PPI): PPIs are the most potent acid suppressants. They work by blocking the final step in acid secretion: the gastric H^+/K^+-adenosine triphosphatase (ATPase), which causes resorption of K+ ions and secretion of H+ ions. Compared to H2RAs and placebo, PPIs provide faster and increased relief of symptoms and are more effective in healing erosive esophagitis.[97, 100, 101] After erosive esophagitis is healed, there is a low rate of relapse and GERD symptom recurrence.[102] 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.[54] Hypochlorhydria impairs vitamin B12, calcium, and iron absorption. PPI therapy has been associated with fractures in adults with osteoporosis, as well as fractures in young adults.[103] This same association has not been seen in children under 18 years old. Long-term acid suppression also has increased infectious risks. In neonates, H2RA therapy is associated with higher rates of necrotizing enterocolitis.[104] Long-term hypochlorhydria is hypothesized to alter the intraluminal environment, promoting growth of small bowel bacteria.[105] 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. Reduction of 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.[106, 107] There was a similar increased risk, though no dose-response relationship, seen with H2RA use. With both PPI and H2RA use, there is an increased risk of gastroenteritis[107] as well as community-acquired Clostridium difficile infection.[108] Gastric polyps and nodules can be noted after prolonged PPI therapy, but these changes are benign. [54]

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.[109, 110] These drugs have no efficacy in healing erosive esophagitis.[111]

Dosing of the above 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.[19] Though 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.[112] Children with neurologic impairments suffer from many conditions, such as scoliosis and epilepsy, which decrease the success rate of antireflux. In this group of children, fundoplication is associated with a high recurrence rate and significant morbidity and mortality, with a 40% surgical failure rate, 12-30% rate of recurrent reflux, 59% experiencing postoperative complications, and a 1-3% mortality rate. Surgery done in early infancy also has a higher failure rate and greater risk for surgical mortality.[113]

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 lower esophageal sphincter relaxations when fat is instilled into the small bowel.[114] Despite this phenomenon, the number of reflux events and the percentage of full-column events during transpyloric feeds are lower when compared to gastric feeds. Studies comparing transpyloric feeds and fundoplication are few, but suggest that there is a trend toward more major complications with fundoplication compared to gastrojejunal feeds in neurologically impaired children.[115] The two have comparable rates in decreasing aspiration pneumonia, though neither eliminates the risk completely.[116]

References

1. Vandenplas Y and Hassall E, Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr, 2002 35(2): p. 119–36. [PubMed: 12187285]
2. Sherman PM, et al., A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol, 2009 104(5): p. 1278–95; quiz 1296. [PubMed: 19352345]
3. Mikami DJ and Murayama KM, Physiology and pathogenesis of gastroesophageal reflux disease. Surg Clin North Am, 2015 95(3): p. 515–25. [PubMed: 25965127]
4. Mittal RK and Balaban DH, The esophagogastric junction. N Engl J Med, 1997 336(13): p. 924–32. [PubMed: 9070474]
5. Kawahara H, Dent J, and Davidson G, Mechanisms responsible for gastroesophageal reflux in children. Gastroenterology, 1997 113(2): p. 399–408. [PubMed: 9247456]
6. Werlin SL, et al., Mechanisms of gastroesophageal reflux in children. J Pediatr, 1980 97(2): p. 244–9. [PubMed: 7400890]
7. Herregods TV, Bredenoord AJ, and Smout AJ, Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil, 2015 27(9): p. 1202–13. [PubMed: 26053301]
8. Boesch RP, et al., Advances in the diagnosis and management of chronic pulmonary aspiration in children. Eur Respir J, 2006 28(4): p. 847–61. [PubMed: 17012631]
9. Khoshoo V, et al., Role of gastroesophageal reflux in older children with persistent asthma. Chest, 2003 123(4): p. 1008–13. [PubMed: 12684287]
10. Kiljander TO, et al., Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. Am J Respir Crit Care Med, 2006 173(10): p. 1091–7. [PubMed: 16357331]

11. Schneider NI, et al., Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (histoGERD Trial). Hum Pathol, 2014 45(5): p. 994–1002. [PubMed: 24746203]
12. Ismail-Beigi F, Horton PF, and Pope CE 2nd, Histological consequences of gastroesophageal reflux in man. Gastroenterology, 1970 58(2): p. 163–74. [PubMed: 5413015]
13. Ruigomez A, et al., Gastroesophageal reflux disease in children and adolescents in primary care. Scand J Gastroenterol, 2010 45(2): p. 139–46. [PubMed: 19961345]
14. Martigne L, et al., Prevalence and management of gastroesophageal reflux disease in children and adolescents: a nationwide cross-sectional observational study. Eur J Pediatr, 2012 171(12): p. 1767–73. [PubMed: 22903328]
15. Nelson SP, et al., Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med, 2000 154(2): p. 150–4. [PubMed: 10665601]
16. Hegar B, et al., Natural evolution of regurgitation in healthy infants. Acta Paediatr, 2009 98(7): p. 1189–93. [PubMed: 19397533]
17. Nelson SP, et al., Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med, 1997 151(6): p. 569–72. [PubMed: 9193240]
18. Martin AJ, et al., Natural history and familial relationships of infant spilling to 9 years of age. Pediatrics, 2002 109(6): p. 1061–7. [PubMed: 12042543]
19. Vandenplas Y, 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): p. 498–547. [PubMed: 19745761]
20. Chandran L and Chitkara M, Vomiting in children: reassurance, red flag, or referral? Pediatr Rev, 2008 29(6): p. 183–92. [PubMed: 18515335]
21. Iacono G, et al., Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol, 1996 97(3): p. 822–7. [PubMed: 8613639]
22. Vandenplas Y, et al., Gastrointestinal manifestations of cow's milk protein allergy and gastrointestinal motility. Acta Paediatr, 2012 101(11): p. 1105–9. [PubMed: 22882286]
23. Funderburk A, et al., Temporal Association Between Reflux-like Behaviors and Gastroesophageal Reflux in Preterm and Term Infants. J Pediatr Gastroenterol Nutr, 2016 62(4): p. 556–61. [PubMed: 26334254]
24. Heine RG, et al., Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health, 2006 42(3): p. 134–9. [PubMed: 16509914]
25. Moore DJ, et al., Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr, 2003 143(2): p. 219–23. [PubMed: 12970637]
26. Orenstein SR, et al., Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr, 2009 154(4): p. 514–520.e4. [PubMed: 19054529]
27. Gold BD, et al., Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr, 2007 45(5): p. 520–9. [PubMed: 18030228]
28. Gupta SK, et al., Presenting symptoms of nonerosive and erosive esophagitis in pediatric patients. Dig Dis Sci, 2006 51(5): p. 858–63. [PubMed: 16718535]
29. Tolia V and Vandenplas Y, Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. Aliment Pharmacol Ther, 2009 29(3): p. 258–72. [PubMed: 19143046]
30. Malfroot A and Dab I, Pathophysiology and mechanisms of gastroesophageal reflux in childhood asthma. Pediatr Pulmonol Suppl, 1995 11: p. 55–6. [PubMed: 7547347]
31. Scarupa MD, Mori N, and Canning BJ, Gastroesophageal reflux disease in children with asthma: treatment implications. Paediatr Drugs, 2005 7(3): p. 177–86. [PubMed: 15977963]

32. Stordal K, et al., Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. Arch Dis Child, 2005 90(9): p. 956–60. [PubMed: 16113133]
33. Cucchiara S, et al., Simultaneous prolonged recordings of proximal and distal intraesophageal pH in children with gastroesophageal reflux disease and respiratory symptoms. Am J Gastroenterol, 1995 90(10): p. 1791–6. [PubMed: 7572896]
34. Koufman JA, The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope, 1991 101(4 Pt 2 Suppl 53): p. 1–78.
35. Wo JM, et al., Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study. Am J Gastroenterol, 1997 92(12): p. 2160–5. [PubMed: 9399745]
36. Branski RC, Bhattacharyya N, and Shapiro J, The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope, 2002 112(6): p. 1019–24. [PubMed: 12160267]
37. Hicks DM, et al., The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. J Voice, 2002 16(4): p. 564–79. [PubMed: 12512644]
38. McMurray JS, et al., Role of laryngoscopy, dual pH probe monitoring, and laryngeal mucosal biopsy in the diagnosis of pharyngoesophageal reflux. Ann Otol Rhinol Laryngol, 2001 110(4): p. 299–304. [PubMed: 11307903]
39. Pace F, et al., Systematic review: gastro-oesophageal reflux disease and dental lesions. Aliment Pharmacol Ther, 2008 27(12): p. 1179–86. [PubMed: 18373634]
40. Kabakus N and Kurt A, Sandifer Syndrome: a continuing problem of misdiagnosis. Pediatr Int, 2006 48(6): p. 622–5. [PubMed: 17168985]
41. National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring, Sept 29 to Oct 1, 1986. Pediatrics, 1987 79(2): p. 292–9. [PubMed: 3808807]
42. Cendon RG, et al., [Intraluminal impedance technique in the diagnosis of apparent life-threatening events (ALTE)]. Cir Pediatr, 2008 21(1): p. 11–4. [PubMed: 18444383]
43. Newman LJ, et al., Patterns of gastroesophageal reflux (GER) in patients with apparent life-threatening events. J Pediatr Gastroenterol Nutr, 1989 8(2): p. 157–60. [PubMed: 2709246]
44. Semeniuk J, et al., Is acid gastroesophageal reflux in children with ALTE etiopathogenetic factor of life threatening symptoms? Adv Med Sci, 2007 52: p. 213–21. [PubMed: 18217421]
45. Gorrotxategi P, et al., Characteristics of continuous esophageal pH-metering in infants with gastroesophageal reflux and apparent life-threatening events. Eur J Pediatr Surg, 1995 5(3): p. 136–8. [PubMed: 7547796]
46. Hasenstab KA and Jadcherla SR, Respiratory events in infants presenting with apparent life threatening events: is there an explanation from esophageal motility? J Pediatr, 2014 165(2): p. 250–255.e1. [PubMed: 24681180]
47. Arad-Cohen N, Cohen A, and Tirosh E, The relationship between gastroesophageal reflux and apnea in infants. J Pediatr, 2000 137(3): p. 321–6. [PubMed: 10969254]
48. Jaimchariyatam N, et al., Association between respiratory events and nocturnal gastroesophageal reflux events in patients with coexisting obstructive sleep apnea and gastroesophageal reflux disease. Sleep Med, 2016 22: p. 33–8. [PubMed: 27544833]
49. Qureshi A, et al., The Role of Sleep in the Modulation of Gastroesophageal Reflux and Symptoms in NICU Neonates. Pediatr Neurol, 2015 53(3): p. 226–32. [PubMed: 26149107]
50. Machado R, et al., Gastroesophageal reflux causing sleep interruptions in infants. J Pediatr Gastroenterol Nutr, 2013 56(4): p. 431–5. [PubMed: 23201711]
51. Machado RS, et al., Gastroesophageal Reflux Affects Sleep Quality in Snoring Obese Children. Pediatr Gastroenterol Hepatol Nutr, 2016 19(1): p. 12–9. [PubMed: 27066445]
52. Quitadamo P, et al., Gastroesophageal reflux in young children and adolescents: Is there a relation between symptom severity and esophageal histological grade? J Pediatr Gastroenterol Nutr, 2015 60(3): p. 318–21. [PubMed: 25373865]

53. Zentilin P, et al., Reassessment of the diagnostic value of histology in patients with GERD, using multiple biopsy sites and an appropriate control group. Am J Gastroenterol, 2005 100(10): p. 2299–306. [PubMed: 16181384]
54. Kahrilas PJ, et al., American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology, 2008 135(4): p. 1383–1391, 1391.e1–5. [PubMed: 18789939]
55. Hirano I and Richter JE, ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol, 2007 102(3): p. 668–85. [PubMed: 17335450]
56. Rosen R, Lord C, and Nurko S, The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. Clin Gastroenterol Hepatol, 2006 4(2): p. 167–72. [PubMed: 16469676]
57. Woodley FW and Mousa H, Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements. Dig Dis Sci, 2006 51(11): p. 1910–6. [PubMed: 17053958]
58. Wenzl TG, et al., Association of apnea and nonacid gastroesophageal reflux in infants: Investigations with the intraluminal impedance technique. Pediatr Pulmonol, 2001 31(2): p. 144–9. [PubMed: 11180691]
59. Salvatore S, et al., Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? J Pediatr Gastroenterol Nutr, 2005 40(2): p. 210–5. [PubMed: 15699699]
60. Cucchiara S, et al., Value of the 24 hour intraoesophageal pH monitoring in children. Gut, 1990 31(2): p. 129–33. [PubMed: 2311969]
61. Vandenplas Y, et al., Area under pH 4: advantages of a new parameter in the interpretation of esophageal pH monitoring data in infants. J Pediatr Gastroenterol Nutr, 1989 9(1): p. 34–9. [PubMed: 2778567]
62. Mousa HM, et al., Esophageal impedance monitoring for gastroesophageal reflux. J Pediatr Gastroenterol Nutr, 2011 52(2): p. 129–39. [PubMed: 21240010]
63. Mousa H, et al., Combined multichannel intraluminal impedance-pH (MII-pH): multicenter report of normal values from 117 children. Curr Gastroenterol Rep, 2014 16(8): p. 400. [PubMed: 25064319]
64. Loots CM, et al., Addition of pH-impedance monitoring to standard pH monitoring increases the yield of symptom association analysis in infants and children with gastroesophageal reflux. J Pediatr, 2009 154(2): p. 248–52. [PubMed: 18823910]
65. Patcharatrakul T and Gonlachanvit S, Gastroesophageal reflux symptoms in typical and atypical GERD: roles of gastroesophageal acid refluxes and esophageal motility. J Gastroenterol Hepatol, 2014 29(2): p. 284–90. [PubMed: 23926926]
66. Cucchiara S, et al., Predictive value of esophageal manometry and gastroesophageal pH monitoring for responsiveness of reflux disease to medical therapy in children. Am J Gastroenterol, 1996 91(4): p. 680–5. [PubMed: 8677928]
67. Fass R, McCallum RW, and Parkman HP, Treatment Challenges in the Management of Gastroparesis-Related GERD. Gastroenterol Hepatol (N Y), 2009 5(10 Suppl 18): p. 4–16. [PubMed: 20574506]
68. Argon M, et al., Relationship between gastric emptying and gastroesophageal reflux in infants and children. Clin Nucl Med, 2006 31(5): p. 262–5. [PubMed: 16622332]
69. Knatten CK, et al., Gastric emptying in children with gastroesophageal reflux and in healthy children. J Pediatr Surg, 2013 48(9): p. 1856–61. [PubMed: 24074657]
70. Serna-Gallegos D, et al., Gastroesophageal reflux reported on esophagram does not correlate with pH monitoring and high-resolution esophageal manometry. Am Surg, 2014 80(10): p. 1026–9. [PubMed: 25264653]
71. Aksglaede K, et al., Gastro-esophageal reflux demonstrated by radiography in infants less than 1 year of age. Comparison with pH monitoring. Acta Radiol, 2003 44(2): p. 136–8. [PubMed: 12694095]

72. Numans ME, et al., Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med, 2004 140(7): p. 518–27. [PubMed: 15068979]
73. Tolia V, et al., Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5–11 years) with symptomatic gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr, 2006 42(4): p. 384–91. [PubMed: 16641576]
74. Reder NP, et al., The diagnostic value of gastroesophageal reflux disease (GERD) symptoms and detection of pepsin and bile acids in bronchoalveolar lavage fluid and exhaled breath condensate for identifying lung transplantation patients with GERD-induced aspiration. Surg Endosc, 2014 28(6): p. 1794–800. [PubMed: 24414458]
75. Starosta V, et al., Bronchoalveolar pepsin, bile acids, oxidation, and inflammation in children with gastroesophageal reflux disease. Chest, 2007 132(5): p. 1557–64. [PubMed: 17925430]
76. Njere I, Stanton M, and Davenport M, Identification of pepsin in bronchoalveolar fluid (BAL) as a new test for the detection of pulmonary aspiration associated with gastroesophageal reflux. J Pediatr Surg, 2006 41(10): p. 1787; author reply 1787–8. [PubMed: 17011295]
77. Kia L, Pandolfino JE, and Kahrilas PJ, Biomarkers of Reflux Disease. Clin Gastroenterol Hepatol, 2016 14(6): p. 790–7. [PubMed: 26404867]
78. Rosen R, et al., The presence of pepsin in the lung and its relationship to pathologic gastro-esophageal reflux. Neurogastroenterol Motil, 2012 24(2): p. 129–33, e84–5. [PubMed: 22141343]
79. Dy F, et al., Salivary Pepsin Lacks Sensitivity as a Diagnostic Tool to Evaluate Extraesophageal Reflux Disease. J Pediatr, 2016.
80. Orenstein SR and McGowan JD, Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux. J Pediatr, 2008 152(3): p. 310–4. [PubMed: 18280832]
81. Loots C, et al., Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. J Pediatr Gastroenterol Nutr, 2014 59(2): p. 237–43. [PubMed: 24732026]
82. Corvaglia L, et al., The effect of body positioning on gastroesophageal reflux in premature infants: evaluation by combined impedance and pH monitoring. J Pediatr, 2007 151(6): p. 591–6, 596.e1. [PubMed: 18035136]
83. Craig WR, et al., Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years. Cochrane Database Syst Rev, 2004(4): p. Cd003502. [PubMed: 15495056]
84. Moukarzel AA, Abdelnour H, and Akatcherian C, Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER. J Clin Gastroenterol, 2007 41(9): p. 823–9. [PubMed: 17881928]
85. Bailey DJ, et al., Lack of efficacy of thickened feeding as treatment for gastroesophageal reflux. J Pediatr, 1987 110(2): p. 187–9. [PubMed: 3806288]
86. Khoshoo V, et al., Smaller volume, thickened formulas in the management of gastroesophageal reflux in thriving infants. J Pediatr Gastroenterol Nutr, 2000 31(5): p. 554–6. [PubMed: 11144442]
87. Barron JJ, et al., Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr, 2007 45(4): p. 421–7. [PubMed: 18030207]
88. Khoshoo V, et al., Are we overprescribing antireflux medications for infants with regurgitation? Pediatrics, 2007 120(5): p. 946–9. [PubMed: 17974730]
89. Nielsen RG, et al., Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. J Pediatr Gastroenterol Nutr, 2004 39(4): p. 383–91. [PubMed: 15448429]
90. Vandenplas Y and De Greef E, Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy. Acta Paediatr, 2014 103(6): p. e243–50. [PubMed: 24575806]
91. Eherer A, Management of gastroesophageal reflux disease: lifestyle modification and alternative approaches. Dig Dis, 2014 32(1–2): p. 149–51. [PubMed: 24603400]
92. Meining A and Classen M, The role of diet and lifestyle measures in the pathogenesis and treatment of gastroesophageal reflux disease. Am J Gastroenterol, 2000 95(10): p. 2692–7. [PubMed: 11051337]

93. Ness-Jensen E, et al., Lifestyle Intervention in Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol, 2016 14(2): p. 175-82.e1-3.
94. Piesman M, et al., Nocturnal reflux episodes following the administration of a standardized meal. Does timing matter? Am J Gastroenterol, 2007 102(10): p. 2128–34. [PubMed: 17573791]
95. Kaltenbach T, Crockett S, and Gerson LB, Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med, 2006 166(9): p. 965–71. [PubMed: 16682569]
96. Kelly DA, Do H2 receptor antagonists have a therapeutic role in childhood? J Pediatr Gastroenterol Nutr, 1994 19(3): p. 270–6. [PubMed: 7815256]
97. Khan M, et al., Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev, 2007(2): p. Cd003244. [PubMed: 17443524]
98. Sabesin SM, et al., Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. Results of a multicenter, placebo-controlled, dose-ranging study. USA Merck Gastroesophageal Reflux Disease Study Group. Arch Intern Med, 1991 151(12): p. 2394–400. [PubMed: 1746996]
99. McRorie JW, Kirby JA, and Miner PB, Histamine2-receptor antagonists: Rapid development of tachyphylaxis with repeat dosing. World J Gastrointest Pharmacol Ther, 2014 5(2): p. 57–62. [PubMed: 24868486]
100. Chiba N, et al., Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology, 1997 112(6): p. 1798–810. [PubMed: 9178669]
101. van Pinxteren B, et al., Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev, 2010(11): p. Cd002095. [PubMed: 21069670]
102. Boccia G, et al., Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable? Am J Gastroenterol, 2007 102(6): p. 1291–7. [PubMed: 17319927]
103. Freedberg DE, et al., Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporos Int, 2015 26(10): p. 2501–7. [PubMed: 25986385]
104. Guillet R, et al., Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics, 2006 117(2): p. e137–42. [PubMed: 16390920]
105. Hegar B, et al., A double-blind placebo-controlled randomized trial on probiotics in small bowel bacterial overgrowth in children treated with omeprazole. J Pediatr (Rio J), 2013 89(4): p. 381–7. [PubMed: 23796359]
106. Laheij RJ, et al., Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. Jama, 2004 292(16): p. 1955–60. [PubMed: 15507580]
107. Canani RB, et al., Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics, 2006 117(5): p. e817–20. [PubMed: 16651285]
108. Dial S, et al., Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. Jama, 2005 294(23): p. 2989–95. [PubMed: 16414946]
109. Cucchiara S, et al., Antacids and cimetidine treatment for gastro-oesophageal reflux and peptic oesophagitis. Arch Dis Child, 1984 59(9): p. 842–7. [PubMed: 6385868]
110. Iacono G, et al., [Magnesium hydroxide and aluminum hydroxide in the treatment of gastroesophageal reflux]. Minerva Pediatr, 1991 43(12): p. 797–800. [PubMed: 1798406]
111. Behar J, et al., Medical and surgical management of reflux esophagitis. A 38-month report of a prospective clinical trial. N Engl J Med, 1975 293(6): p. 263–8. [PubMed: 237234]
112. Hauer JM, Does nissen fundoplication decrease reflux-related problems including respiratory illness in children with neurological impairment? JAMA Pediatr, 2014 168(2): p. 188.
113. Kubiak R, et al., Effectiveness of fundoplication in early infancy. J Pediatr Surg, 1999 34(2): p. 295–9. [PubMed: 10052808]
114. Rosen R, Hart K, and Warlaumont M, Incidence of gastroesophageal reflux during transpyloric feeds. J Pediatr Gastroenterol Nutr, 2011 52(5): p. 532–5. [PubMed: 21464758]

115. Livingston MH, et al., Fundoplication and gastrostomy versus percutaneous gastrojejunostomy for gastroesophageal reflux in children with neurologic impairment: A systematic review and meta-analysis. J Pediatr Surg, 2015 50(5): p. 707–14. [PubMed: 25783384]

116. Srivastava R, et al., Impact of fundoplication versus gastrojejunal feeding tubes on mortality and in preventing aspiration pneumonia in young children with neurologic impairment who have gastroesophageal reflux disease. Pediatrics, 2009 123(1): p. 338–45. [PubMed: 19117901]

Synopsis

Gastroesophageal reflux (GER) is a normal physiologic process. It is important to distinguish GER from gastroesophageal reflux disease (GERD), as the former does not require treatment. While the diagnosis of GERD can largely be based on history and physical alone, endoscopy and pH impedance studies can help make the diagnosis when there is an atypical presentation. In children and adolescents, lifestyle changes and acid suppression are first line treatments for GERD. In infants, acid suppression is not effective for GER but a trial of hydrolyzed formula can be considered, as milk protein sensitivity can be difficult to differentiate from GER symptoms.

Key Points

- Gastroesophageal reflux is a normal physiologic process that does not require treatment.
- In infants, the following can reduce reflux episodes: reducing feeding volumes, offering smaller, more frequent meals, thickening feeds, and positioning; these infants should not be placed on acid suppression.
- Gastroesophageal reflux disease (GERD) occurs when reflux of gastric contents causes troublesome symptoms or complications
- 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.
- First line treatment for GERD in children and adolescents include lifestyle modification and acid suppression.

Box 1:

Differential for emesis is 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/Choledochalithiasis

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:

Vandeplas Y 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): p. 498-547.

Chandran, L et al, *Vomiting in children: reassurance, red flag, or referral?* Pediatr Rev, 2008. 29(6): p. 183-92.

Box 2:

Warning signals that require investigation in infants with vomiting

Bilious emesis
GI 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
Micro/macrocephaly
Seizures
Abdominal tenderness or distention
Suspected genetic syndrome

Adapted from:

Vandeplas Y 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): p. 498-547.

Table 1:

Medical Conditions at High Risk for GERD

Condition	Contributing factors
Neurologic impairment	Decreased esophageal clearance - supine position - abnormal swallow - abnormal muscle tone Increased reflux episodes - heightened gag reflex - delayed gastric emptying - constipation - skeletal abnormalities - medication side effects
Obesity	
Esophageal Atresia	Esophagus is congenitally dysmotile Post surgery, a hiatal hernia is often present
Chronic Respiratory Disorders - Bronchopulmonary dysplasia - Cystic Fibrosis - Idiopathic interstitial fibrosis	Unknown
Lung Transplant	Pneumonectomy contributes to esophageal and gastric motor dysfunction

Adapted from:

Vandeplas Y 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): p. 498-547.

Chandran, L et al, *Vomiting in children: reassurance, red flag, or referral?* Pediatr Rev, 2008. 29(6): p. 183-92.

Table 2:

Reflux Parameters on pH-MII

Definitions	
Liquid Reflux	Drop in impedance of ≤50% of baseline value with subsequent recovery, in 2+ of the distal-most channels
Acid GER	pH decreases and remains below 4 for ≥5 seconds; if pH was already below 4, it decreases by at least 1 pH unit for ≥5 seconds; with or without drop in impedance of ≤50% of baseline value
Non-Acid GER	pH increases, remains unchanged, or decreases by at least 1 pH unit while remaining ≥4, with retrograde drop in impedance of ≤50% of baseline value in 2+ of the distal-most channels
Gas Reflux	Simultaneous and rapid increases in impedance in 2+ channels (>3000 Ohms) of the distal-most channels
Extent of Reflux Migration	
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)
Paramaters of Symptom Association	
Reflux Index (RI)	% of time pH falls below 4
Symptom index (SI)	% of symptoms episodes that are related to reflux ([#of reflux-related symptom episodes ÷ total number of symptom episodes) × 100] - positive when >50%
Symptom sensitivity index (SSI) -	% of symptom associated reflux episodes ([#of reflux-related symptom episodes ÷ total number of reflux episodes) × 100] - positive when >10%
Symptoms associated probability (SAP)	Statistical probability that symptoms and GER events are associated - positive when >95%

Adapted from:

Woodley FW et al, *Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements.* Dig Dis Sci, 2006. **51**(11): p. 1910-6.

Singendonk MM et al. *Reflux monitoring in children*. Neurogastroenterol Motil, 2016. **28**(10): p.1452-9.

Table 3:

Normal values for Reflux on pH/MII per 24 hours in infants and children

	Infants		Children	
	Median (IQR)	95th %	Median (IQR)	95th %
Index of Acid Regurgitation (%)	0.6 (0.3-0.9)	1.4	0.4 (0.2-0.8)	1.3
Number of Acid Regurgitation episodes in 24 hours	20 (11-26)	48	14 (11-15)	55
Index of Non-Acid Regurgitation (%)	0.7 (0.5-1.2)	2.5	0.1 (0-0.3)	1
Number of Non-Acid Regurgitation episodes in 24 hours	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
Number of GER episodes in 24 hours	54 (33-69)	93	21 (11-41)	71

Adapted from:

Mousa H et al. *Combined Multichannel Intraluminal Impedance-pH (MII-pH): Multicenter Report of Normal Values from 117 Children*. Curr Gastroenterol Rep, 2014. **16** (8): p. 400.

Vandenplas, Y., 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): p. 498-547.

Table 4:

Pharmacologic Agents for the Treatment of GERD

Medication	Dose	Age
Proton Pump Inhibitors		
Omeprazole	0.7-3.3 mg/kg/d, max 20mg daily	2+ years
Lansoprazole	0.7-3 mg/kg/d	1+ years
Esomeprazole	<20kg: 10mg daily ≥20kg: 10mg-20mg daily	1+ years
Pantoprazole	≥15kg to <40kg: 20mg daily ≥40kg: 40mg daily	Pediatric indication for erosive esophagitis in ≥5yo
Histamine2 Receptor Antagonists		
Famotidine	1 mg/kg/d div in 2-3 doses, max 20mg bid	1mo+
Ranitidine	5-10mg/kg/d div in 2-3 doses, max 300mg/d	1mo+
Cimetidine	400mg 4×/day	No pediatric indication
Antacids		
Calcium Carbonate	2-5yo: 375-400mg prn; max 1500mg daily 6-11yo: 750-800mg prn; max 3000 mg daily 12yo+: 500-3,000mg prn; max 7,500mg daily	2+ years
Sucralfate		No pediatric indication for independent treatment of GERD

Doses obtained from LexiComp