

Current Insights into the Pharmacologic and Nonpharmacologic Management of Gastroesophageal Reflux in Infants

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Educational Gaps

1. Gastroesophageal reflux testing has limited usefulness, and studies have shown poor correlation between reflux events and many symptoms traditionally attributed to reflux.
2. Acid-suppression medications are frequently used in the infant population even though these medications have clear risks and their usefulness in reducing symptoms is limited.

Abstract

Gastroesophageal reflux is common and, in most cases, is a self-limited and physiologic process in infants. However, the role of diagnostic testing and pharmacologic interventions in reflux remains controversial among providers. Various diagnostic modalities exist, but most infants do not require invasive testing and many symptoms traditionally attributed to reflux show no correlation on further testing. There are many strategies for managing reflux in infants. Nonpharmacologic approaches include positioning, thickening, changing formulas, and changing the frequency of feedings, with the benefits of these methods shown to be inconsistent. Many medications now exist to address reflux, particularly by way of acid suppression, but these pharmacologic interventions have risks, especially in young infants, and many of these therapies have shown limited success in truly reducing reflux symptoms. In conclusion, nonpharmacologic approaches should be used, because most symptoms of gastroesophageal reflux will ultimately resolve without any intervention.

EDITOR'S NOTE

This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

AUTHOR DISCLOSURE Drs Duncan and Rosen have disclosed that this work was supported by the Translational Research Program at Boston Children's Hospital, the NASPGHAN/ASTRA Diseases of the Upper Tract Grant, and by R01 DK097112-01 from the National Institutes of Health.

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

1. Describe the epidemiology, natural history, and pathophysiology of gastroesophageal reflux in infants.
2. Review the approaches to and role of diagnostic testing for gastroesophageal reflux.

3. Describe pharmacologic and nonpharmacologic strategies for treating gastroesophageal reflux and their risks and benefits.

INTRODUCTION

Despite many years of experience, the diagnosis and treatment of gastroesophageal reflux (GER) in infants remain areas of active controversy. (1)(2) Topics of particular concern include atypical reflux symptoms, usefulness of diagnostic testing, potential therapies, and whether these interventions are even beneficial. Widely varying perspectives persist, opening a divide among parents, generalists, and subspecialty physicians, and with research advances. Testing can be invasive and therapies that might not be effective can be risky and expensive. These issues only become more fraught when referring to young and preterm infants, particularly given the recent concerns about the potential negative effects of pharmacologic therapies in the neonatal population. The purpose of this review is to provide a brief overview of gastroesophageal reflux, its etiology, clinical features, and diagnosis, and to discuss current insights into its pharmacologic and nonpharmacologic management in infants.

DEFINITION AND NATURAL HISTORY

GER is defined as the physiologic passage of gastric contents into the esophagus. (3) This is a naturally occurring process that is seen in all age groups and results from the transient relaxation of the lower esophageal sphincter, allowing retrograde flow of refluxate into the esophagus. Gastroesophageal reflux disease (GERD) is differentiated from GER when the reflux of those gastric contents causes troublesome signs or symptoms including significant discomfort, poor weight gain, esophagitis, or airway symptoms. Although the definitions are clear, the actual distinction between a physiologic process that occurs in all infants and a pathologic condition that might need further evaluation and therapy becomes particularly difficult in the nonverbal infant population with often vague symptoms that can be caused by many other conditions. (2) Combining this with caretaker stress and pressure on providers to intervene and prescribe medications only complicates this situation.

All infants have some degree of reflux, with an estimated 3 to 5 of these events occurring each hour in healthy infants. (4) For most children, the peak age for reflux symptoms is 4 months, with a decline in symptoms starting around 6 months of age with the introduction of solid foods. The intensity and frequency of symptoms are variable, with 60% of infants having daily spit-ups and up to 25% spitting up

4 or more times daily. (5) After the initial peak in reflux, most infants have a decline in the frequency of their symptoms until around 1 year of age. Therefore, while GERD can be bothersome, the knowledge that the natural history is well known and the symptoms are short-lived is often reassuring.

In healthy infants, the lower esophageal sphincter (LES) acts as a pressure barrier to separate the stomach contents from the esophagus. A relatively small stomach and esophagus combined with frequent supine positioning can easily lead to full-column reflux that extends to the mouth and results in emesis. Not surprisingly then, positioning can have a major effect on GER. It was previously believed that infants had decreased LES competence, leading to increased reflux, but more recent studies have shown that even preterm infants have LES pressures that are high enough to maintain esophagogastric competence. (6)

The primary mechanism for reflux is transient LES relaxation (TLESR), which occurs naturally throughout the day in all age groups. (6) Infants with GERD have been shown to have the same number of TLESR episodes as controls, but these episodes allow reflux with greater frequency than that seen in controls. Although delayed gastric emptying can influence the occurrence of reflux in infants, the frequency of TLESR events has been shown to have a greater effect. (7) The rate of TLESR events can, however, be decreased with left-sided positioning. (8) Reflux into the esophagus also results any time the pressure in the stomach exceeds that in the esophagus, and so its occurrence can also vary depending on an infant's position and activity in addition to events such as coughing. (6)

Discomfort from reflux events has traditionally been attributed to acid irritation of the esophagus, but most infants and children with reflux do not have esophagitis, and a large proportion of reflux events in the pediatric population are nonacidic. (9)(10) Families and clinicians are often concerned that infants with GERD produce too much acid, perhaps because of aggressive marketing on behalf of pharmaceutical companies. However, studies have shown that weight-adjusted acid production is actually significantly less in infants than in adults. (11)

Regardless of the etiology of reflux events, GER has been blamed for many symptoms in infants, frequently without good evidence to support any association. Apnea is one of the symptoms most often attributed to reflux in premature infants, but the perceived correlation is likely because of the

frequency of both events. Multiple studies have failed to show any temporal or causal correlation with acid or non-acid reflux events and apnea. (4) Similarly, no clear causal relationship has been found between GER and the development of chronic lung disease. (12) Even irritability, perhaps the most common symptom attributed to reflux, was not found to improve in double-blind placebo-controlled trials of infants treated with proton pump inhibitors (PPIs). (13)(14) Lastly, studies have shown no clear predictive value of any of the traditional reflux symptoms typically seen in older infants as a determinant of GER and medication response when applied to premature infants. This suggests that perhaps symptoms seen in younger children are not the same as those seen in older children, making the diagnosis of GERD that much more of a challenge. (15)

REFLUX EVALUATION AND THE ROLE OF DIAGNOSTIC TESTING

Most infants who present with possible reflux symptoms are given a diagnosis of GERD without any formal diagnostic testing. The nonspecific and ubiquitous nature of infants' presenting symptoms, which range from spitting to crying to hoarseness, makes it difficult to determine if GERD is actually the cause of the symptoms. As a result, and particularly in prominent proposed extraesophageal manifestations of reflux, multiple diagnostic strategies have been developed to study reflux in children.

The approach should start with a focused history and physical examination that considers additional differential diagnoses. In clinical scenarios that warrant further testing, the benefits and risks of each approach need to be considered, in addition to their ability to correlate pathologic reflux with symptoms of concern.

Relatively noninvasive radiologic tests have been used in the past but these have limitations. An upper gastrointestinal tract series is useful for detecting anatomic abnormalities but cannot be used to discriminate between physiologic and nonphysiologic GER episodes, and this test has poor sensitivity compared with pH studies. (16) Scintigraphy can be used to detect reflux and has the added benefit of evaluating gastric emptying, but the technique lacks standardization and age-specific data, making its usefulness unclear. (17) Upper gastrointestinal tract endoscopy is sometimes performed in these patients to evaluate for inflammation. This test enables visualization and biopsy of the esophagus and can reveal the presence of esophagitis and other complications of reflux disease. It also allows a distinction to be made between reflux and eosinophilic or allergic esophagitis. However, the performance of endoscopy is greatly limited by the need for

sedation and anesthesia. Therefore it tends to be infrequently performed, especially for otherwise well patients with suspected reflux. In addition, studies have shown poor correlation between reflux symptoms and presence of esophagitis diagnosed with endoscopy, suggesting that GERD cannot adequately be diagnosed based on histologic findings. (18)

Esophageal pH monitoring has traditionally been used to detect episodes of acid reflux and can accurately determine the temporal association between acidic GER and symptoms. In medication-unresponsive patients, it can also be used to assess the adequacy of acid-suppressive medications. Unfortunately, the traditional probes do not differentiate the direction of flow (swallowed vs refluxed liquid), cannot measure the height of the refluxate (distal vs full-column reflux), and are completely blind to nonacid reflux. In addition, studies have shown poor correlation between acid reflux burden and symptoms in infants undergoing this evaluation, supporting adult data that have shown poor reproducibility of pH probe results. (19)

In recent years, multichannel intraluminal impedance with pH (pH-MII) has become the dominant test for evaluating reflux burden. (2) Similar to pH probe studies, it also involves the placement of a catheter through the nose into the esophagus for 24-hour monitoring. Its great strength is that in addition to pH changes, it can also measure esophageal flow and bolus presence as well as height of the refluxate, so that both acidic and nonacidic reflux can be detected and correlated with symptoms. Its sensitivity is superior to that of the pH probe, particularly in infants taking acid suppression medication, who have a higher nonacid reflux burden. (20) However, there are a number of limitations to pH-MII testing, including length of time to interpret the large amount of data, limited normal values for children, and difficulty in proving causality.

Given the increased recognition of possible testing strategies, it is reasonable to consider whether infants with GER need to be tested at all and what useful information will be obtained from a given test. Rather than assess total reflux burden, the main role of pH-MII testing (and pH-metry) is to correlate reflux event with symptoms in an effort to assess temporal association as a proxy for causality; this helps determine which patients might benefit from therapies. Perceptions about the role of diagnostic testing in pediatric reflux vary widely, even among pediatric specialists, and so the performance of testing is quite variable depending on the practice setting. (21) However, testing should be considered in any patient in whom symptoms are atypical, do not respond to standard therapies, or are severe enough to consider surgical interventions.

TREATMENT STRATEGIES

Treatment for reflux has the goal of relieving symptoms and preventing any potential long-term or dangerous secondary effects of reflux. Treatment strategies can be divided into nonpharmacologic, pharmacologic, and surgical approaches (Table). For any given approach, providers must weigh the risks and benefits, in addition to proven efficacy, to choose the optimal intervention for each patient. A multidisciplinary and thoughtful strategy is essential to maximize therapeutic benefit and minimize harm for any approach, particularly for sick infants in the NICU.

Nonpharmacologic Therapies

Nonpharmacologic strategies are the least invasive approaches for the treatment of reflux in infants. Particularly in the NICU, positioning is perhaps the most widespread intervention for reflux. Studies using both pH and pH-MII have shown that prone and left lateral positioning reduce reflux to the greatest degree compared with the supine and right lateral positions. These positioning differences affect both TLESR episodes and gastric emptying. Although right-sided positioning speeds gastric emptying and thus decreases stomach contents, it also has a deleterious effect by increasing TLESR episodes, which is an effect significant enough to cause an increase in reflux events. In contrast, left-sided positioning slows gastric emptying but results in fewer TLESR episodes, which has a much more significant beneficial effect. (22)(23) Despite widespread use, elevation of the head of the bed has not been studied in infants, and data from adults have shown marginal benefits. (24) Outside a monitored setting, however, supine positioning is still the safest recommended position because of the risk of sudden infant death syndrome; sleep positioners are not recommended because of associated deaths. (25)

Thickening of formula is another frequently used nonpharmacologic approach. The thickening serves 2 purposes: it improves swallow function in infants with neonatal swallowing dysfunction and aspiration, and it reduces the

amount of visible reflux. Trials of formula thickening have not shown benefit when reflux is measured using pH-metry. However, pH-MII studies have shown a reduction in visible vomiting with thickening, but no significant decrease in the number of reflux episodes or height of the reflux. (26)(27) Significant marketing efforts are made for branded prethickened formulas, such as Enfamil AR, and data suggest that these formulas can also be effective in reducing regurgitation. However, in a direct comparison, these prethickened products show the same efficacy as home-thickening. (28)(29) According to a meta-analysis by Horvath et al, thickening is only moderately effective in treating GER. (30)

Modulating the method of delivering feedings may change reflux burden. Jadcherla et al found that changing the rate and duration of feeding alters reflux burden whereas changing caloric density and volume has no significantly effect. (31) Similarly, smaller and more frequent feedings have been attempted, which show some subjective improvements, such as a change in acid versus nonacid type of reflux, but the total number of reflux episodes is not altered. (31)

Changing the type of formula may also benefit infants with GER. Several studies have evaluated the effect of hypoallergenic formula on reflux events and gastric emptying. Tolia et al compared casein-predominant, soy, or whey-hydrolysate formulas, and found decreased gastric emptying in casein compared with whey-hydrolysate formulas but no significant difference in reflux events among the formula types when measured with pH-metry. (32) More recently, however, Corvaglia et al used pH-MII to show that extensively hydrolyzed protein formula can reduce the number of GER episodes and the reflux index in symptomatic preterm infants compared with standard protein formula. (33) Logarajaha et al showed a decrease in the total number of GER episodes in preterm infants fed extensively hydrolyzed protein formula via orogastric or nasogastric tubes. They found no difference in reflux index or number of long-lasting episodes using pH-MII and also found no difference in symptoms recorded over the study period. (34)

TABLE. Therapies for Gastroesophageal Reflux Disease in Infants

GENERAL APPROACH	SPECIFIC MANAGEMENT	DEGREE OF EVIDENCE FOR SYMPTOM CONTROL
Nonpharmacologic	Positioning changes (left lateral) Thickening of feeds Changing formula (elemental) Changing location of feeding (postpyloric)	Strong Moderate Moderate Moderate
Pharmacologic	H ₂ antagonists Proton pump inhibitors Motility medications (macrolides, cisapride)	Weak Weak None
Surgical	Fundoplication Postpyloric feeding tubes	Weak Moderate

As discussed before, data show that a trial of hypoallergenic formula may be effective in infants with GER but this effect is likely to result from the symptom overlap between GER and milk protein intolerance. (35) Whether these formulas decrease reflux independently of an allergy is often difficult to prove because allergy symptoms are identical to reflux in infants; teasing out if an infant has reflux or a food allergy is difficult and there are no tests to prove either cause, so patients are often treated with one therapy or another. Current guidelines of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend that reflux symptoms be treated with a hypoallergenic diet for at least 2 weeks, even before considering pharmacologic therapy for GERD. (3)

The last and perhaps most extreme nonpharmacologic interventions for reflux are the surgical approaches, including fundoplication and transpyloric feeding tube placement. Case reviews from the early 1990s, when funduplications were more common, showed high rates of improvement, with 70% to 87% of patients having resolved symptoms; however, these studies had no control groups and the actual improvement measures were not objective. (36) More recent retrospective studies have shown more mixed results, with no significant decrease in reflux-related hospitalizations after fundoplication. (37) In preterm patients in the NICU, surgical interventions are often high risk but nasojejunal feeding tubes can be used as an alternative approach. Transpyloric feeding can be used to successfully reduce the incidence of reflux by decreasing the volume in the stomach. Several trials have shown that this approach can effectively decrease the rates of apnea and bradycardia events in some premature infants. (38)

Lastly, it can be useful to consider additional factors that might be modulated to decrease reflux episodes. These include suctioning, chest physiotherapy, and the decreased administration and dosing of xanthine and beta-mimetic agents. However, these therapies are often required in a given clinical situation and cannot be significantly decreased.

Pharmacologic Therapies

Even before trying nonpharmacologic approaches, many clinicians still use antireflux medications in infants with GER. These drugs are some of the most commonly prescribed medications in pediatrics and a dramatic increase in their use in recent years has added to the significant health care costs already associated with the high incidence and health burden of pediatric reflux. (39)(40) Recent studies also suggest that pharmacologic therapies are still frequently used in premature infants and up to 25% of infants are discharged from the NICU with antireflux medications. (41)

The primary pharmacologic approach for infants with GERD is acid suppression in the form of either histamine-2

(H₂) antagonists or PPIs. H₂ antagonists are older medications that function by selectively blocking the H₂ receptor on parietal cells and, therefore, preventing the signaling cascade that leads to the release of acid into the stomach. Data supporting the efficacy of these medications in children, and especially in infants, are sparse. Modest evidence shows that H₂ antagonists are effective in symptom reduction in older children. Placebo-controlled studies in infants have shown that H₂ antagonists were only more effective in histologic healing with documented erosive esophagitis, but without clearly reducing reflux symptoms. (42) In the only placebo-controlled double-blind trial of H₂ receptor antagonists in infants, Orenstein et al were unable to show significant symptom reduction for infants of age 1.3 to 10.5 months treated for 4 weeks with famotidine. (43) They also noted multiple, nonserious drug-related adverse experiences in treated infants, including agitation and presumed headache.

PPIs are more potent than H₂ antagonists and work by directly binding to and blocking the hydrogen-potassium ATPase found on gastric parietal cells, thereby decreasing acid secretion into the stomach. The degree and reversibility of this effect depends on the structure of each individual pharmacologic agent. (44) Although adult data suggest that PPIs are more effective at reducing heartburn compared with H₂ antagonists, randomized trials in children do not show a clear benefit of one pharmacologic approach over the other. (45)(46)

Very few studies have showed the efficacy of both types of medications in neonates, but many have shown no clear benefit. Multiple double-blind, randomized, placebo-controlled trials of both H₂ antagonists and multiple PPIs have failed to show any advantage in reducing any of the classic reflux symptoms of crying, spitting up, refusing food, arching, coughing, or wheezing. (13)(43)(47) Moore et al showed no significant improvement in reflux symptoms during a 4-week crossover trial with omeprazole in irritable infants of age 3 to 12 months despite evidence of decreased acid GER on pH-probe studies and esophageal acid exposure at endoscopy in the PPI-treated group. (13) The group concluded that despite effective acid suppression, omeprazole failed to suppress symptoms of irritability and therefore suggested that treatment of irritable infants with GER should not include PPIs unless they also have esophagitis. The authors also observed that irritability in study subjects improved over time regardless of treatment, which supports historical data and could be a confounding factor in any study purporting to show therapeutic GER intervention leading to improvement in infant irritability. (13)

In a trial of premature infants, Omari et al similarly failed to show any symptom improvement with omeprazole compared with placebo despite sufficient gastroesophageal acid

suppression based on pH-probe studies. (48) In this study, 10 infants with a postmenstrual gestational age between 34 and 40 weeks received omeprazole for 7 days, followed by placebo for 7 days, in randomized order. They were then studied with 24-hour pH monitoring at 7- and 14-day time points. The group showed that omeprazole significantly reduced gastric and esophageal acidity in addition to the number and duration of acid GER episodes, but the number of symptomatic events, including vomiting, apnea, bradycardia, or behavioral changes, was not significantly changed by omeprazole. The authors concluded that although omeprazole was clearly effective in reducing acid GER, there was no evidence that it decreased any of the symptoms attributed to reflux in the infants treated. (48)

In addition to the unclear efficacy of acid-blocking agents, use of these medications has very clearly been associated with significant risks, including increased risk of both gastrointestinal and pulmonary infections in the pediatric population. (49) Additional reported negative effects include increased small bowel bacterial overgrowth and altered digestion in all age groups. Neonates receiving these medications also have notable infectious risks, including increased incidence of necrotizing enterocolitis, sepsis, and urinary tract infections. Terrin et al reported a 6.6-fold increased risk of necrotizing enterocolitis in ranitidine-treated very-low-birthweight infants, with a significantly higher mortality rate in the newborns receiving acid-blocking medications. (50) Other groups have shown similar risks in these infant populations. Canani et al showed an increased risk of acute gastroenteritis and pneumonia in otherwise healthy infants and children treated with acid suppression. (49) A more recent study in adults revealed that PPIs directly alter the microbiome, with increases in genes that cause microbial invasion, perhaps providing a mechanism for the increased prevalence of infections in patients treated with gastric acid suppression. (51)

As a result of the documented risk of both H₂ antagonists and PPIs, national guidelines have strongly cautioned against the overuse of these medications, and suggest, at most, a thoughtful and brief, time-limited (2 week) trial of acid suppression only in severe cases. (3) Even the US Food and Drug Administration has provided guidance on this issue and reported that PPIs should not be administered to otherwise healthy infants without clear evidence of acid-induced disease. (52) Therefore, the tide has clearly turned against the routine use of acid-suppressing medications in the neonatal period until more evidence of benefit can justify the safety issues. (53)

Alternative pharmacologic approaches for GERD do exist. These previously included the use of promotility agents

Many traditional medications such as cisapride, a serotonin 5-HT₄ receptor agonist, and metoclopramide, a dopamine receptor antagonist, which were once thought to be quite effective, have either been removed from the market or now have black box warnings because of adverse effects including cardiac and neurologic problems, and are therefore very rarely used in infants. (54)(55) Some centers have attempted to use erythromycin, a motilin agonist that improves antral contractility. The only study to be conducted in neonates shows no significant reduction in reflux measured with pH-metry compared with placebo, though there may be some possible benefit to reducing the time to full enteral feedings. (56) This latter benefit needs to be weighed against the risk of pyloric stenosis with macrolide administration. (55) Buffering agents, alginate and sucralfate, can be useful for on-demand relief in older patients, but are generally contraindicated in infants because of the potential for electrolyte and acid-base disturbances.

CONCLUSIONS

GER remains common, and in most cases, is a self-limited and physiologic process in infants. Most infants do not require any diagnostic testing and will improve over time with conservative, nonpharmacologic measures including positioning and thickening of feedings. Although acid-suppressive medications are effective in some patients, their risks likely outweigh any perceived benefits in most cases. Therefore, their use in infants should be limited to short trials and acid suppression should be discontinued if there is no clear symptomatic benefit.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations and diagnostic features of gastroesophageal reflux in neonates.
- Know the management of gastroesophageal reflux in neonates.

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Parent Resources from the AAP at HealthyChildren.org

- <https://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/GERD-Reflux.aspx>
- Spanish: <https://www.healthychildren.org/spanish/health-issues/conditions/abdominal/paginas/gerd-reflux.aspx>

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1. A 5-day-old term infant is seen in the clinic for an episode of choking at home that was associated with emesis. Which of the following statements regarding gastroesophageal reflux in newborn infants is correct?
 - A. Gastroesophageal reflux in this age group is always a pathologic phenomenon.
 - B. Gastroesophageal reflux disease is differentiated from gastroesophageal reflux when there are signs or symptoms such as significant discomfort, poor weight gain, esophagitis, or airway symptoms.
 - C. By definition, a healthy term infant may have no more than 1 or 2 events of reflux per day.
 - D. Most infants have a peak in reflux symptoms at 1 week of age, with a steady decline to no reflux by 1 month of age.
 - E. Reflux in this age group is most often caused by transient relaxation of the upper esophageal sphincter.
2. A 28-week gestational age infant in the NICU is now 4 weeks old. She is in room air, in the incubator, and on full enteral gavage feedings. A few episodes of spit-up are noted each day. Which of the following statements regarding reflux in preterm infants is correct?
 - A. In most cases, preterm infants have proportionally higher acid production in the stomach and esophagus compared with older children or adults.
 - B. The primary mechanism for reflux is transient lower esophageal sphincter relaxation, with infants having gastroesophageal reflux disease having similar numbers of these transient relaxation events as other infants, but with these episodes allowing reflux with greater frequency.
 - C. All preterm infants do not have lower esophageal sphincter pressures that are high enough to maintain esophagogastric competence, thereby negating any effect of positioning on reflux symptoms.
 - D. Approximately 75% to 80% of asymptomatic preterm infants have evidence of esophagitis, with 15% to 25% having ulcerations.
 - E. Multiple studies have shown a strong correlation between apnea episodes and both nonacid and acidic reflux events.
3. A 2-week-old infant has had frequent spit-ups and poor weight gain and is being evaluated for possible gastroesophageal reflux disease. Which of the following is correct regarding testing for this condition?
 - A. An upper gastrointestinal tract series is useful for detecting anatomic abnormalities but cannot be used to discriminate between physiologic and nonphysiologic gastroesophageal reflux, and has poor sensitivity compared with pH studies.
 - B. Scintigraphy is able to detect reflux in preterm infants but cannot evaluate gastric emptying.
 - C. Esophageal endoscopy has been shown to be highly sensitive and specific for reflux disease, with a high correlation between reflux symptoms and presence of esophagitis on endoscopy.
 - D. Traditional pH probes can differentiate direction of flow of liquid, but cannot accurately determine the temporal association between acidic reflux and clinical symptoms.
 - E. Multichannel intraluminal impedance with pH can detect multiple aspects of reflux disease, but is limited by its inability to detect nonacid reflux.
4. You are considering the treatment of gastroesophageal reflux disease for a growing preterm infant who is in the NICU. Which of the following treatment strategies is described correctly?
 - A. Right-sided positioning of the infant can decrease transient lower esophageal sphincter relaxation events and has been shown to decrease the frequency of reflux events in preterm infants.

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- B. Left-sided positioning speeds gastric emptying and can reduce symptoms of constipation, though the number of reflux events is actually increased.
 - C. Thickened formulas can lead to increased aspiration risk for infants who are feeding orally and may also increase acid production in the stomach.
 - D. Transpyloric feeding may reduce the incidence of reflux by decreasing the volume in the stomach and potentially decrease rates of apnea and bradycardia events in some premature infants.
 - E. Fundoplication has 90% to 100% efficacy in treating reflux symptoms, and has been demonstrated to decrease length of stay and rehospitalizations for reflux disease for preterm and term infants.
5. A father in the NICU notes that he has been using antireflux medication himself with a good response and asks whether his infant may also benefit from antireflux medication. Which of the following statements regarding pharmacologic therapy for gastroesophageal reflux in infants is correct?
- A. Histamine-2 blockers have been shown in several trials to reduce symptoms in both preterm and term infants, including apnea events, failure to thrive, and subjective discomfort.
 - B. The use of antireflux medications has been associated with an increased risk of necrotizing enterocolitis in very-low-birthweight infants.
 - C. Randomized trials in neonates and children have shown a clear benefit of proton pump inhibitors compared with histamine-2 antagonists in terms of both increased efficacy and decreased side effect profile.
 - D. Omeprazole is the only pharmacologic agent that has been shown to be effective in reducing apnea, emesis events, and growth failure in preterm infants, but without a decrease in esophagitis.
 - E. Famotidine and ranitidine are approved by the US Food and Drug Administration for otherwise healthy infants for the treatment of subjective symptoms such as discomfort, feeding intolerance, and colic.

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NeoReviews 2016;17:e203

DOI: 10.1542/neo.17-4-e203

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