



Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants

Eric C. Eichenwald, MD, FAAP, COMMITTEE ON FETUS AND NEWBORN

Gastroesophageal reflux (GER), generally defined as the passage of gastric contents into the esophagus, is an almost universal phenomenon in preterm infants. It is a common diagnosis in the NICU; however, there is large variation in its treatment across NICU sites. In this clinical report, the physiology, diagnosis, and symptomatology in preterm infants as well as currently used treatment strategies in the NICU are examined. Conservative measures to control reflux, such as left lateral body position, head elevation, and feeding regimen manipulation, have not been shown to reduce clinically assessed signs of GER in the preterm infant. In addition, preterm infants with clinically diagnosed GER are often treated with pharmacologic agents; however, a lack of evidence of efficacy together with emerging evidence of significant harm (particularly with gastric acid blockade) strongly suggest that these agents should be used sparingly, if at all, in preterm infants.

INTRODUCTION

Gastroesophageal reflux (GER), generally defined as the passage of gastric contents into the esophagus,¹ is an almost universal phenomenon in preterm infants. The normal physiologic occurrence of GER in infants can be distinguished from pathologic GER disease, which includes troublesome symptoms or complications associated with GER.² GER occurs commonly in infants, in part because of relatively large volumes ingested during feeding and supine positioning, which frequently place the gastroesophageal junction in a liquid environment. Whether GER becomes clinically significant depends on both the quality (eg, degree of acidity) and quantity of reflux^{3,4} as well as potential injury to the esophageal mucosa. GER is a common diagnosis in the NICU; however, there is as much as a 13-fold variation in its diagnosis and treatment across sites.^{5,6} Preterm infants who are diagnosed with GER have longer hospital stays and higher hospital costs than infants without GER,^{5,7,8} making it an important clinical phenomenon in the NICU.

abstract

FREE

Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Dr Eichenwald is the primary author of the policy and approved the final manuscript as submitted.

This document is copyrighted and is property of the American Academy of Pediatrics and its Board of Directors. All authors have filed conflict of interest statements with the American Academy of Pediatrics. Any conflicts have been resolved through a process approved by the Board of Directors. The American Academy of Pediatrics has neither solicited nor accepted any commercial involvement in the development of the content of this publication.

Clinical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, clinical reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

DOI: <https://doi.org/10.1542/peds.2018-1061>

Address correspondence to Eric C. Eichenwald, MD, FAAP. E-mail: eichenwald@email.chop.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2018 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

To cite: Eichenwald EC and AAP COMMITTEE ON FETUS AND NEWBORN. Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants. *Pediatrics*. 2018;142(1):e20181061

GER in preterm infants is most often diagnosed and treated on the basis of clinical and behavioral signs rather than on specific testing to prove or disprove pathology,⁶ and many infants continue to be treated after they are discharged from the hospital.⁹ However, evidence that GER causes harm in preterm infants is scant.^{10,11} Indeed, routine use of antireflux medications for the treatment of symptomatic GER in preterm infants was 1 of the therapies singled out as being of questionable value in the recent American Academy of Pediatrics (AAP) Choosing Wisely campaign.¹²

In this clinical report, the following will be reviewed: (1) the physiology of GER in preterm infants, (2) methods for its diagnosis, (3) evidence that it is associated with the signs frequently attributed to GER, and (4) the safety and efficacy of nonpharmacologic and pharmacologic therapy.

PHYSIOLOGY

The primary mechanism of GER in preterm infants is transient lower esophageal sphincter relaxation (TLESR). TLESR is an abrupt reflex decrease in lower esophageal sphincter (LES) pressure to levels at or below intragastric pressure, unrelated to swallowing. Preterm infants have dozens of episodes of TLESR each day,¹³ many of which are associated with some degree of GER. As such, GER is a normal phenomenon in preterm infants, which is exacerbated by a pure liquid diet and age-specific body position.³ In addition, the presence of an indwelling gastric tube through the esophageal sphincter increases the frequency of GER, presumably secondary to impaired closure of the LES.¹⁴ Delayed gastric emptying does not appear to play a contributory role in GER in preterm infants, in that infants with symptomatic GER do not have delayed gastric emptying

compared with other infants.^{15,16} However, GER is more common immediately after a feeding, likely because of gastric distension.¹⁵ Body position also influences TLESR and GER in preterm infants. Infants placed in the right-side-down lateral position after a feeding have more TLESR episodes and liquid reflux compared with the left-side-down lateral position, despite gastric emptying being enhanced in the right lateral position.^{17,18} Prone position also decreases episodes of GER versus supine position, likely because of more optimal positioning of the LES relative to the distended stomach.¹⁷

Mechanisms to protect the esophagus and airway from GER appear to be intact in the preterm infant. These include reflex forward peristalsis of the esophagus in response to distention from refluxate in the lower esophagus with closure of the upper esophageal sphincter to prevent refluxate reaching the pharynx. Despite these mechanisms, if refluxed material does reach the upper esophagus, the upper esophageal sphincter will reflexively open to allow the material into the pharynx, which results in the frequent episodes of “spitting” or emesis observed in infants.

DIAGNOSIS

Several methods have been used to diagnose GER in the preterm population, including contrast fluoroscopy, pH monitoring, and multichannel intraesophageal impedance (MII) monitoring. Although contrast fluoroscopy can be used to show episodes of reflux, it cannot be used to differentiate clinically significant GER from insignificant GER. Monitoring of pH in the lower esophagus has classically been used to diagnose GER in older children and adults. Reflux of acidic gastric contents results in transient periods of acidity in the

lower esophagus. Common measures obtained from pH probe monitoring include the total number of reflux episodes, the duration of the longest reflux episode, and the “reflux index” (RI), which is the percentage of the total recording time with an esophageal pH <4. In pH studies, an RI >7% is considered abnormal, an RI <3% considered normal, and RIs between 3% and 7% are considered indeterminate.² However, labeling a study “abnormal” does not prove that it is causing the symptoms in question.

Measurement of esophageal pH is not a reliable method to diagnose GER in preterm infants¹⁹ because their stomach pH is rarely <4 owing to frequent milk feedings and a higher baseline pH. In addition, abnormal esophageal pH does not correlate well with symptom severity.²⁰ Other measures that have been investigated include the presence of pepsin in saliva²¹ and the pH of oropharyngeal secretions.²² Although these measures may correlate with acidic reflux, it is unknown whether they correlate with symptom severity.

Currently, the most accurate method for detecting GER is MII monitoring, which is frequently combined with simultaneous measurement of pH.² MII can be used to track the movement of fluids, solids, and air in the esophagus by measuring changes in electrical impedance between multiple electrodes along an esophageal catheter. MII can be used to discern whether a fluid bolus is traveling antegrade (swallow) or retrograde (reflux) in the esophagus and can be used to determine the height of the retrograde bolus. It is a reliable and reproducible technique for diagnosing GER in preterm infants¹⁴ and can be combined with a pH sensor to determine if GER is acidic, mildly acidic, or alkaline. López-Alonso et al²³ measured 24-hour MII and pH in 26 healthy preterm infants with a median postmenstrual age of 32 weeks.

The median number of reflux episodes recorded in 24 hours was 71; 25.4% were acidic, 72.9% were weakly acidic, and 2.7% were alkaline. Of note, the gastric pH was higher than 4 for almost 70% of the recording time. Not surprisingly, periods of feeding were associated with a higher number of total reflux events per hour.

In practice, GER is diagnosed most often in infants on the basis of clinical and behavioral signs and/or response to a trial of pharmacologic or nonpharmacologic interventions.⁶ Signs attributed to GER include feeding intolerance, poor growth, apnea, desaturation and bradycardia, and worsening pulmonary disease as well as nonspecific behavioral signs including arching, irritability, and apparent discomfort associated with feedings. There is no evidence, however, that these signs are temporally associated with measured GER episodes.^{20,24,25} In 1 study of 40 preterm and 18 term infants evaluated with combined MII/pH testing for a clinical suspicion of GER, signs (including irritability, bradycardia and desaturations, or feeding intolerance) were rarely associated with documented reflux events.²⁰ In another study of 14 healthy preterm infants, Snel et al²⁴ recorded both esophageal pH and infant behaviors. General behavior scores did not change during esophageal acidification episodes. In addition, infants frequently demonstrated behaviors ascribed to GER (apparent discomfort, head retraction, and “mouthing”) unrelated to pH-documented GER episodes. In these results, it is suggested that preterm infant behaviors commonly ascribed to reflux are, in reality, not associated with GER and that treatment should not be based solely on clinical signs.

GER IN THE PRETERM INFANT

Several clinical conditions are thought to be associated with GER in the

preterm infant, although analyses are hampered because most cases of GER are diagnosed clinically.

Apnea, Desaturation, and Bradycardia

Preterm infants have a hyperreactive laryngeal response to chemoreceptor stimulation that precipitates apnea or bradycardia. In addition, as previously noted, almost all preterm infants have some GER. These 2 observations have led to speculation that GER can precipitate apnea, oxygen desaturation, and bradycardia episodes in preterm infants and that pharmacologic treatment of GER might decrease the incidence or severity of these events.²⁶ However, researchers examining the timing of reflux episodes in relation to apneic events have found that they are rarely temporally related^{14,27} and that GER does not prolong or worsen apnea.²⁸ In 1 study, small amounts of normal saline were infused into the pharynx of sleeping preterm infants at term-equivalent age. The investigators found that swallow frequency increased, but apnea did not occur,²⁹ and they suggested that apnea is provoked when the larynx, not the pharynx, is stimulated. The larynx is not usually stimulated by reflux of small amounts of liquid. Finally, there is no evidence that pharmacologic treatment of GER with agents that decrease gastric acidity or promote gastrointestinal motility decrease the risk of recurrent apnea or bradycardia in preterm infants.^{30,31}

Respiratory Disease and Bronchopulmonary Dysplasia

Proving a causal relationship between GER and respiratory symptoms in children has been difficult. Suggested methods of diagnostics, such as GER scintigraphy and the presence of lipid-laden macrophages in bronchoalveolar lavage, lack specificity³² or correlate poorly with esophageal impedance and fail to differentiate reflux-related

aspiration from primary aspiration from above.³³ In 1 study, children with a heterogeneous array of chronic lung problems who had documented GER had higher concentrations of pepsin and inflammatory interleukins in their bronchoalveolar lavage fluid than those without GER, suggesting microaspiration may contribute to their lung disease.³⁴

It is not clear whether GER causes “silent” microaspiration in mechanically ventilated preterm infants that worsens lung disease, particularly in infants with developing or established bronchopulmonary dysplasia (BPD). In 1 study, it was reported that pepsin was detected in 93% of tracheal aspirates obtained from intubated preterm infants during the first postnatal month,³⁵ and in addition, that ventilated preterm infants who developed BPD had higher levels of tracheal aspirate pepsin than those who did not. In addition, these investigators reported that increased concentrations of pepsin were associated with increased severity of BPD³⁶ and speculated that chronic aspiration of gastric contents may contribute to the development of BPD. However, these results should be interpreted with caution because of emerging data on the low sensitivity and specificity of pepsin in bronchoalveolar lavage assays for the detection of GER-related aspiration.³⁷

In contrast, Akinola et al³⁸ reported no relationship between the diagnosis of BPD and the clinical diagnosis of GER confirmed by esophageal pH monitoring.³⁸ In a small study comparing combined MII and pH monitoring in 12 infants with BPD and 34 without who were evaluated for clinical signs believed to be attributable to GER, infants with BPD had a similar number of documented reflux events as infants without BPD.²⁵ In both groups, fewer than 10% of the documented reflux

events were temporally associated with reflux symptoms as assessed by nursing observation. However, infants with BPD were more likely to have “pH only events” (acidic pH in the lower esophagus without an associated MII determined reflux event), which were more often associated with symptoms, but at a low frequency (9% vs 4.9% in infants without BPD). Although infants with evolving BPD are more likely to have a diagnosis of and receive therapy for GER,³⁹ with these results, it is suggested that these infants do not have an increased incidence of symptomatic GER.

Feeding Problems

Some infants and children with GER may exhibit feeding problems, including feeding resistance, failure to thrive, or food aversion.^{40,41} Although preterm infants may have frequent regurgitation, there is no evidence that this leads to poor growth or other nutritional difficulties.^{7,42} Although preterm infants with a diagnosis of GER are sometimes treated with prokinetic agents to enhance gastric emptying,⁶ there are no data to suggest that delayed gastric emptying is a physiologic mechanism for GER in this population.¹⁵ As noted previously, other feeding-related behaviors in preterm infants often attributed to GER, including feeding-associated arching or irritability and oral feeding aversion, are not temporally associated with MII or lower pH documented reflux events and, thus, are not reliable markers of clinically significant reflux.^{20,24}

TREATMENT

Although preterm infants frequently receive nonpharmacologic and pharmacologic therapy for GER, there is a paucity of data about the effect of treatment on symptoms or short- and long-term outcomes. Furthermore, the lack of randomized

placebo-controlled trials of GER therapies in preterm infants makes it difficult to assess the efficacy of long-term therapy versus the expected natural history of GER. Despite the lack of data, in recent years, the use of antireflux medications both in the NICU and after discharge has substantially increased.^{9,43}

Nonpharmacologic Management

Body Positioning

Body positioning is widely used as a conservative management approach to infants believed to have GER. Placing infants on a head-up angle is a common initial approach to management; however, head elevation is ineffective in reducing acid reflux in older infants. In addition, car seat placement was found to elicit worse acid GER in term infants.^{44–46} This position has not been studied in preterm infants to prevent symptomatic GER, but there is no reason to expect the physiologic result would be different from term infants. Placing preterm infants in the left lateral versus right lateral position after feeding and in prone versus supine position may reduce TLESRs and reflux episodes.^{15,17,18} However, although placement in the right lateral position may increase reflux episodes after feeding, van Wijk et al¹⁸ showed that this position also enhanced gastric emptying. These authors suggested placing infants in the right lateral position immediately after feeding, followed in 1 hour by placing them in the left lateral position to decrease acid reflux. However, 1 small MII and pH study of term infants at a mean postnatal age of 13 weeks revealed that, despite a reduction in reflux episodes in the left lateral position, behavioral manifestations of reflux (crying and/or irritability) did not improve.⁴⁷ Thus, whether positioning techniques can reduce signs of GER in infants with reflux remains uncertain. Given that lateral and prone positioning also

increase the risk of sudden infant death syndrome (SIDS),⁴⁸ the AAP and the North American Society for Pediatric Gastroenterology and Nutrition have concurred that infants with GER should be placed for sleep in the supine position, with the exception of the rare infants for whom the risk of death from GER is greater than the risk of SIDS.² The AAP Task Force on SIDS, after conferring with the authors of the North American Society for Pediatric Gastroenterology and Nutrition statement, provided additional guidance: “Examples of such upper airway disorders are those in which airway-protective mechanisms are impaired, including infants with anatomic abnormalities, such as type 3 or 4 laryngeal clefts, who have not undergone antireflux surgery.”⁴⁸ Safe sleep approaches, including supine positioning on a flat and firm surface and avoidance of commercial devices designed to maintain head elevation in the crib, should be paramount as a model for parents of infants approaching discharge (ie, infants greater than 32 weeks’ postmenstrual age) from the hospital.⁴⁹

Feeding Strategies

If GER results from increased intragastric pressure, smaller-volume feedings given more frequently might result in fewer GER episodes. Omari et al¹⁵ reported that feeding hourly, compared with feeding every 2 or 3 hours, resulted in fewer total GER episodes but more frequent acidic reflux episodes. Jadcherla et al⁵⁰ reported that longer feeding duration and slower milk flow rates were associated with fewer GER events, diagnosed by MII and pH study, although nutrient composition of expressed human milk may be compromised with this approach. No randomized trials have been used to compare the effects of continuous intragastric or transpyloric versus bolus intragastric tube feedings on GER symptom severity.⁵¹

Another feeding strategy has been to thicken feedings with agents including xanthan gum, starch, or rice cereal.⁵² Unfortunately, in recent data, researchers have linked thickening with a xanthan gum product to late-onset necrotizing enterocolitis⁵³; as such, it is recommended that xanthan gum or similar thickeners not be used in preterm or former preterm infants in the first year of life. Commercially available formula products that thicken on acidification in the stomach are not nutritionally appropriate for preterm infants. A systematic review of randomized controlled trials of thickened formulas in term infants with GER revealed that although these agents reduced episodes of regurgitation, they were ineffective in reducing acidic GER.⁵⁴ Only small trials of thickeners have been performed in the preterm population. In 1 trial of a starch-thickened preterm formula, the total number of GER episodes was unchanged compared with a standard formula feeding; however, total lower esophageal acid exposure was less with the thickened formula feeding. No assessment was made about whether the reduction in acid exposure had an effect on associated symptoms.⁵⁵

In the data, it is suggested that elemental or extensively hydrolyzed protein formulas reduce gastrointestinal transit time and reduce symptoms in term infants with symptomatic GER.⁵⁶ These observations in term infants may be an overlap of signs of cow milk protein allergy and those attributed to GER, including vomiting, failure to thrive, and irritability.⁵⁷ In contrast, in small studies of preterm infants, although feeding with extensively hydrolyzed protein formula compared with standard formula or human milk resulted in fewer reflux episodes as measured by MII and pH study,^{58,59} it did not reduce behavioral signs of GER.⁵⁹

It is unclear what role cow milk protein allergy may play in preterm infants with signs of GER; a trial of extensively hydrolyzed protein-based formula may be reasonable in age-appropriate preterm infants with signs of severe reflux.

Pharmacologic Management

Prokinetic Agents

Prokinetic (promotility) agents include metoclopramide, domperidone, and erythromycin. Prokinetic agents have been widely used in older infants to reduce the symptoms of GER. These drugs appear to improve gastric emptying, reduce regurgitation, and enhance LES tone. None of these drugs has been shown to reduce GER symptoms in preterm infants,^{60,61} and all have the potential for significant adverse effects, including a higher risk of infantile pyloric stenosis (erythromycin), cardiac arrhythmia (erythromycin), and neurologic side effects (domperidone and metoclopramide). Because of a lack of data about efficacy and a concerning safety profile, these drugs should not be used in preterm infants if the only indication is the treatment of GER.

Sodium Alginate

In older infants and children, researchers in several studies have revealed that alginate-containing formulations, which are frequently combined with sodium bicarbonate, may reduce the symptoms of GER.⁶¹ In the presence of gastric acid, alginate formulations precipitate into a low-density viscous gel that acts as a physical barrier to the gastric mucosa; when combined with sodium bicarbonate (Gaviscon), a carbon dioxide foam forms, which preferentially is refluxed into the esophagus during GER events, protecting the lower esophagus from acidification. In preterm infants in small studies, sodium alginate preparations decreased the number of acidic GER episodes and

total esophageal acid exposure⁶² and decreased the frequency of regurgitation.⁶³ However, the long-term safety of these preparations in preterm infants has not been evaluated.

Histamine-2 Receptor Blockers

Histamine-2 (H₂) receptor blockers (eg, ranitidine, famotidine) compete with histamine for the H₂ receptor in the parietal cells in the stomach, decreasing hydrochloric acid secretion and increasing intragastric pH. H₂ receptor blockers are frequently prescribed for infants in whom GER is clinically diagnosed^{6,9} on the theory that these symptoms are secondary to acidic reflux into the lower esophagus. However, no researchers have assessed the efficacy of H₂ blockers on the symptom profile of preterm infants with presumed reflux. In addition, use of these drugs in preterm infants has been linked to an increased incidence of necrotizing enterocolitis in several studies⁶⁴ and a higher incidence of late-onset infections and death,⁶⁵ possibly resulting from alteration of the intestinal microbiome.⁶⁶

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) block the gastric proton pump, decreasing both basal and stimulated parietal cell acid secretion. PPIs in older children have been associated with a higher risk of gastric bacterial overgrowth, gastroenteritis, and community-acquired pneumonia.^{67–69} PPIs are used less often than H₂ blockers in preterm infants but are used for similar indications.⁹ Given their effect on gastric acid secretion, it is likely that PPIs would have similar potential adverse effects as H₂ blockers, although this has not been investigated. Although there is evidence that administration of PPIs will consistently maintain the stomach pH >4 in preterm infants, they are largely ineffective in relieving clinical signs of GER. In

randomized double-blind placebo-controlled trials, both omeprazole and lansoprazole were ineffective in reducing GER signs in infants. In addition, lansoprazole was associated with a higher rate of adverse events.⁷⁰

SUMMARY AND RECOMMENDATIONS

1. GER is almost universal in preterm infants. It is a physiologic process secondary to frequent TLESR, relatively large-volume liquid diet, and age-specific body positioning. As such, it is a normal developmental phenomenon that will resolve with maturation.
2. Pathologic GER occurs when reflux of acidic gastric contents causes injury to the lower esophageal mucosa. Although preterm infants do have some acidic GER episodes, most GER episodes in this population are only weakly acidic because of their lower gastric acidity and frequent milk feedings, making such esophageal injury unlikely to occur.
3. Signs commonly ascribed to GER in preterm infants include feeding intolerance or aversion, poor weight gain, frequent regurgitation, apnea, and desaturation and bradycardia and behavioral signs, including irritability and perceived postprandial discomfort. In the data, the temporal association of these perceived signs of GER with either acidic or nonacidic reflux episodes as measured by MII and pH is not supported, and the signs will usually improve with time without treatment.
4. Data regarding the possible association between worsening lung disease attributable to GER and microaspiration in mechanically ventilated preterm infants are sparse. Further studies to elucidate such an association and to assess the effect of GER treatment on the severity of lung disease are needed.
5. There is marked variability in the diagnosis and treatment of GER in preterm infants among NICUs, perhaps because the diagnosis is usually made by clinical assessment of signs and symptoms and/or a trial of nonpharmacologic or pharmacologic treatment rather than definitive tests.
6. Conservative measures to control reflux, such as left lateral body position, head elevation, and feeding regimen manipulation, have not been shown to reduce clinically assessed signs of GER in the preterm infant; for infants greater than 32 weeks' postmenstrual age, safe sleep approaches, including supine positioning on a flat and firm surface and avoidance of commercial devices designed to maintain head elevation in the crib, should be paramount as a model for parents of infants approaching discharge from the hospital.
7. Preterm infants with clinically diagnosed GER are often treated with pharmacologic agents; however, a lack of evidence of efficacy together with emerging evidence of significant harm (particularly with gastric acid blockade) strongly suggest that

these agents should be used sparingly, if at all, in preterm infants.

LEAD AUTHOR

Eric C. Eichenwald, MD, FAAP

COMMITTEE ON FETUS AND NEWBORN, 2017–2018

James J. Cummings, MD, FAAP, Chairperson
Susan Wright Aucott, MD, FAAP
Eric C. Eichenwald, MD, FAAP
Jay P. Goldsmith, MD, FAAP
Ivan L. Hand, MD, FAAP
Sandra E. Juul, MD, PhD, FAAP
Brenda Bradley Poindexter, MD, MS, FAAP
Karen M. Puopolo, MD, PhD, FAAP
Dan L. Stewart, MD, FAAP

LIAISONS

RADM Wanda D. Barfield, MD, MPH, FAAP – *Centers for Disease Control and Prevention*
Thierry Lacaze, MD – *Canadian Paediatric Society*
Maria A. Mascola, MD – *American College of Obstetricians and Gynecologists*
Meredith Mowitz, MD, MS, FAAP – *Section on Neonatal-Perinatal Medicine*
Tonse N. K. Raju, MD, DCH, FAAP – *National Institutes of Health*

STAFF

Jim Couto, MA

ABBREVIATIONS

AAP: American Academy of Pediatrics
BPD: bronchopulmonary dysplasia
GER: gastroesophageal reflux
H₂: histamine-2
LES: lower esophageal sphincter
MII: multichannel intraesophageal impedance
PPI: proton pump inhibitor
RI: reflux index
SIDS: sudden infant death syndrome
TLESR: transient lower esophageal sphincter relaxation

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

REFERENCES

- Lightdale JR, Gremse DA; Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics*. 2013;131(5). Available at: www.pediatrics.org/cgi/content/full/131/5/e1684
- Vandenplas Y, Rudolph CD, Di Lorenzo C, et al; North American Society for Pediatric Gastroenterology Hepatology and Nutrition; European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2009;49(4):498–547
- Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. *Pediatrics*. 2004;113(2). Available at: www.pediatrics.org/cgi/content/full/113/2/e128
- Poets CF, Brockmann PE. Myth: gastroesophageal reflux is a pathological entity in the preterm infant. *Semin Fetal Neonatal Med*. 2011;16(5):259–263
- Jadcherla SR, Slaughter JL, Stenger MR, Klebanoff M, Kelleher K, Gardner W. Practice variance, prevalence, and economic burden of premature infants diagnosed with GERD. *Hosp Pediatr*. 2013;3(4):335–341
- Dhillon AS, Ewer AK. Diagnosis and management of gastro-oesophageal reflux in preterm infants in neonatal intensive care units. *Acta Paediatr*. 2004;93(1):88–93
- Khalaf MN, Porat R, Brodsky NL, Bhandari V. Clinical correlations in infants in the neonatal intensive care unit with varying severity of gastroesophageal reflux. *J Pediatr Gastroenterol Nutr*. 2001;32(1):45–49
- Ferlauto JJ, Walker MW, Martin MS. Clinically significant gastroesophageal reflux in the at-risk premature neonate: relation to cognitive scores, days in the NICU, and total hospital charges. *J Perinatol*. 1998;18(6, pt 1): 455–459
- Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR. Neonatal histamine-2 receptor antagonist and proton pump inhibitor treatment at United States children's hospitals. *J Pediatr*. 2016;174:63–70.e3
- Golski CA, Rome ES, Martin RJ, et al. Pediatric specialists' beliefs about gastroesophageal reflux disease in premature infants. *Pediatrics*. 2010;125(1):96–104
- Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database Syst Rev*. 2014;(11):CD008550
- Ho T, Dukhovny D, Zupancic JA, Goldmann DA, Horbar JD, Pursley DM. Choosing wisely in newborn medicine: five opportunities to increase value. *Pediatrics*. 2015;136(2). Available at: www.pediatrics.org/cgi/content/full/136/2/e482
- Omari TI, Barnett C, Snel A, et al. Mechanisms of gastroesophageal reflux in healthy premature infants. *J Pediatr*. 1998;133(5):650–654
- Peter CS, Sprodowski N, Bohnhorst B, Silny J, Poets CF. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. *Pediatrics*. 2002;109(1):8–11
- Omari TI, Barnett CP, Benninga MA, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. *Gut*. 2002;51(4): 475–479
- Ewer AK, Durbin GM, Morgan ME, Booth IW. Gastric emptying and gastro-oesophageal reflux in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1996;75(2):F117–F121
- Corvaglia L, Rotatori R, Ferlini M, Aceti A, Ancora G, Faldella G. The effect of body positioning on gastroesophageal reflux in premature infants: evaluation by combined impedance and pH monitoring. *J Pediatr*. 2007;151(6): 591–596. 596.e1
- van Wijk MP, Benninga MA, Dent J, et al. Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. *J Pediatr*. 2007;151(6):585–590. 590.e1–e2
- Mitchell DJ, McClure BG, Tubman TR. Simultaneous monitoring of gastric and oesophageal pH reveals limitations of conventional oesophageal pH monitoring in milk fed infants. *Arch Dis Child*. 2001;84(3):273–276
- Funderburk A, Nawab U, Abraham S, et al. Temporal association between reflux-like behaviors and gastroesophageal reflux in preterm and term infants. *J Pediatr Gastroenterol Nutr*. 2016;62(4):556–561
- Farhath S, He Z, Saslow J, et al. Detection of pepsin in mouth swab: correlation with clinical gastroesophageal reflux in preterm infants. *J Matern Fetal Neonatal Med*. 2013;26(8):819–824
- James ME, Ewer AK. Acid oropharyngeal secretions can predict gastro-oesophageal reflux in preterm infants. *Eur J Pediatr*. 1999;158(5):371–374
- López-Alonso M, Moya MJ, Cabo JA, et al. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. *Pediatrics*. 2006;118(2). Available at: www.pediatrics.org/cgi/content/full/118/2/e299
- Snel A, Barnett CP, Cresp TL, et al. Behavior and gastroesophageal reflux in the premature neonate. *J Pediatr Gastroenterol Nutr*. 2000;30(1):18–21
- Nobile S, Noviello C, Cobellis G, Carnielli VP. Are infants with bronchopulmonary dysplasia prone to gastroesophageal reflux? A prospective observational study with esophageal pH-impedance monitoring. *J Pediatr*. 2015;167(2): 279–285.e1
- Eichenwald EC; Committee on Fetus and Newborn, American Academy of Pediatrics. Apnea of Prematurity. *Pediatrics*. 2016;137(1):e20153757
- Poets CF. Gastroesophageal reflux and apnea of prematurity—coincidence, not causation. Commentary on L. Corvaglia et Al.: a thickened formula does not reduce apneas related to

- gastroesophageal reflux in preterm infants (*Neonatology* 2013;103:98-102). *Neonatology*. 2013;103(2):103–104
28. Di Fiore JM, Arko M, Whitehouse M, Kimball A, Martin RJ. Apnea is not prolonged by acid gastroesophageal reflux in preterm infants. *Pediatrics*. 2005;116(5):1059–1063
 29. Page M, Jeffery HE. Airway protection in sleeping infants in response to pharyngeal fluid stimulation in the supine position. *Pediatr Res*. 1998;44(5):691–698
 30. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr*. 2009;155(4):516–521
 31. Kimball AL, Carlton DP. Gastroesophageal reflux medications in the treatment of apnea in premature infants. *J Pediatr*. 2001;138(3):355–360
 32. Kazachkov MY, Muhlebach MS, Livasy CA, Noah TL. Lipid-laden macrophage index and inflammation in bronchoalveolar lavage fluids in children. *Eur Respir J*. 2001;18(5):790–795
 33. Bar-Sever Z. Scintigraphic evaluation of gastroesophageal reflux and pulmonary aspiration in children. *Semin Nucl Med*. 2017;47(3):275–285
 34. Starosta V, Kitz R, Hartl D, Marcos V, Reinhardt D, Griese M. Bronchoalveolar pepsin, bile acids, oxidation, and inflammation in children with gastroesophageal reflux disease. *Chest*. 2007;132(5):1557–1564
 35. Farhath S, Aghai ZH, Nakhla T, et al. Pepsin, a reliable marker of gastric aspiration, is frequently detected in tracheal aspirates from premature ventilated neonates: relationship with feeding and methylxanthine therapy. *J Pediatr Gastroenterol Nutr*. 2006;43(3):336–341
 36. Farhath S, He Z, Nakhla T, et al. Pepsin, a marker of gastric contents, is increased in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. *Pediatrics*. 2008;121(2). Available at: www.pediatrics.org/cgi/content/full/121/2/e253
 37. Abdallah AF, El-Desoky T, Fathi K, Elkashef WF, Zaki A. Clinical utility of bronchoalveolar lavage pepsin in diagnosis of gastroesophageal reflux among wheezy infants. *Can Respir J*. 2016;2016:9480843
 38. Akinola E, Rosenkrantz TS, Pappagallo M, McKay K, Hussain N. Gastroesophageal reflux in infants < 32 weeks gestational age at birth: lack of relationship to chronic lung disease. *Am J Perinatol*. 2004;21(2):57–62
 39. Fuloria M, Hiatt D, Dillard RG, O'Shea TM. Gastroesophageal reflux in very low birth weight infants: association with chronic lung disease and outcomes through 1 year of age. *J Perinatol*. 2000;20(4):235–239
 40. Dellert SF, Hyams JS, Treem WR, Geertsma MA. Feeding resistance and gastroesophageal reflux in infancy. *J Pediatr Gastroenterol Nutr*. 1993;17(1):66–71
 41. Mathisen B, Worrall L, Masel J, Wall C, Shepherd RW. Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study. *J Paediatr Child Health*. 1999;35(2):163–169
 42. Frakaloss G, Burke G, Sanders MR. Impact of gastroesophageal reflux on growth and hospital stay in premature infants. *J Pediatr Gastroenterol Nutr*. 1998;26(2):146–150
 43. Malcolm WF, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotten CM; National Institute of Child Health and Human Development Neonatal Research Network. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics*. 2008;121(1):22–27
 44. Orenstein SR, Whittington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. *N Engl J Med*. 1983;309(13):760–763
 45. Orenstein SR. Effects on behavior state of prone versus seated positioning for infants with gastroesophageal reflux. *Pediatrics*. 1990;85(5):765–767
 46. Bağucka B, De Schepper J, Peelman M, Van de Maele K, Vandenplas Y. Acid gastro-oesophageal reflux in the 10 degrees-reversed-Trendelenburg-position in supine sleeping infants. *Acta Paediatr Taiwan*. 1999;40(5):298–301
 47. Loots C, Kritas S, van Wijk M, et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. *J Pediatr Gastroenterol Nutr*. 2014;59(2):237–243
 48. Moon RY; Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: evidence base for 2016 updated recommendations for a safe infant sleeping environment. *Pediatrics*. 2016;138(5):e20162940
 49. American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. *Pediatrics*. 2008;122(5):1119–1126
 50. Jadcherla SR, Chan CY, Moore R, Malkar M, Timan CJ, Valentine CJ. Impact of feeding strategies on the frequency and clearance of acid and nonacid gastroesophageal reflux events in dysphagic neonates. *JPEN J Parenter Enteral Nutr*. 2012;36(4):449–455
 51. Richards R, Foster JP, Psaila K. Continuous versus bolus intragastric tube feeding for preterm and low birth weight infants with gastro-oesophageal reflux disease. *Cochrane Database Syst Rev*. 2014;(7):CD009719
 52. Madhoun LL, Siler-Wurst KK, Sitaram S, Jadcherla SR. Feed-thickening practices in NICUs in the current era: variability in prescription and implementation patterns. *J Neonatal Nurs*. 2015;21(6):255–262
 53. Beal J, Silverman B, Bellant J, Young TE, Klontz K. Late onset necrotizing enterocolitis in infants following use of a xanthan gum-containing thickening agent. *J Pediatr*. 2012;161(2):354–356
 54. Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. *Pediatrics*. 2008;122(6). Available at: www.pediatrics.org/cgi/content/full/122/6/e1268
 55. Corvaglia L, Aceti A, Mariani E, et al. Lack of efficacy of a starch-thickened preterm formula on gastro-oesophageal reflux in preterm infants: a pilot study. *J Matern Fetal Neonatal Med*. 2012;25(12):2735–2738

56. Garzi A, Messina M, Frati F, et al. An extensively hydrolysed cow's milk formula improves clinical symptoms of gastroesophageal reflux and reduces the gastric emptying time in infants. *Allergol Immunopathol (Madr)*. 2002;30(1):36–41
57. Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? *Pediatrics*. 2002;110(5):972–984
58. Corvaglia L, Mariani E, Aceti A, Galletti S, Faldella G. Extensively hydrolyzed protein formula reduces acid gastroesophageal reflux in symptomatic preterm infants. *Early Hum Dev*. 2013;89(7):453–455
59. Logarajaha V, Onga C, Jayağobib PA, et al. PP-15 the effect of extensively hydrolyzed protein formula in preterm infants with symptomatic gastro-oesophageal reflux. *J Pediatr Gastroenterol Nutr*. 2015;61(4):526
60. Hibbs AM, Lorch SA. Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. *Pediatrics*. 2006;118(2):746–752
61. Corvaglia L, Monari C, Martini S, Aceti A, Faldella G. Pharmacological therapy of gastroesophageal reflux in preterm infants. *Gastroenterol Res Pract*. 2013;2013:714564
62. Corvaglia L, Aceti A, Mariani E, De Giorgi M, Capretti MG, Faldella G. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. *Aliment Pharmacol Ther*. 2011;33(4):466–470
63. Atasay B, Erdevi O, Arsan S, Türmen T. Effect of sodium alginate on acid gastroesophageal reflux disease in preterm infants: a pilot study. *J Clin Pharmacol*. 2010;50(11):1267–1272
64. Guillet R, Stoll BJ, Cotten CM, et al; National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2006;117(2). Available at: www.pediatrics.org/cgi/content/full/117/2/e137
65. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012;129(1). Available at: www.pediatrics.org/cgi/content/full/129/1/e40
66. Gupta RW, Tran L, Norori J, et al. Histamine-2 receptor blockers alter the fecal microbiota in premature infants. *J Pediatr Gastroenterol Nutr*. 2013;56(4):397–400
67. Wang K, Lin HJ, Perng CL, et al. The effect of H2-receptor antagonist and proton pump inhibitor on microbial proliferation in the stomach. *Hepatogastroenterology*. 2004;51(59):1540–1543
68. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292(16):1955–1960
69. Canani RB, Cirillo P, Roggero P, et al; Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics*. 2006; 117(5). Available at: www.pediatrics.org/cgi/content/full/117/5/e817
70. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. 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):514–520.e4

Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants

Eric C. Eichenwald and COMMITTEE ON FETUS AND NEWBORN

Pediatrics originally published online June 18, 2018;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/early/2018/06/14/peds.2018-1061>

References

This article cites 70 articles, 23 of which you can access for free at:
<http://pediatrics.aappublications.org/content/early/2018/06/14/peds.2018-1061#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Current Policy

http://www.aappublications.org/cgi/collection/current_policy

Committee on Fetus & Newborn

http://www.aappublications.org/cgi/collection/committee_on_fetus_newborn

Fetus/Newborn Infant

http://www.aappublications.org/cgi/collection/fetus_newborn_infant_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:

<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants

Eric C. Eichenwald and COMMITTEE ON FETUS AND NEWBORN

Pediatrics originally published online June 18, 2018;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/early/2018/06/14/peds.2018-1061>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2018 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

