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Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants

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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

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

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

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

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 infants[19] 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 saliva[21] 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 infants[14] and can be combined with a pH sensor to determine if GER is acidic, mildly acidic, or alkaline. López-Alonso et al[23] 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 al[24] 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 specificity[32] 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 BPD[36] 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 al[38] 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 al[18] 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 al[15] 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 al[50] 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 enterocolitis[53]; 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 exposure[62] 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 (H_2) receptor blockers (eg, ranitidine, famotidine) compete with histamine for the H_2 receptor in the parietal cells in the stomach, decreasing hydrochloric acid secretion and increasing intragastric pH. H_2 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 H_2 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 studies[64] 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 H_2 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 H_2 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.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
BPD: bronchopulmonary dysplasia
GER: gastroesophageal reflux
H_2: 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.

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Pediatrics originally published online June 18, 2018;

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