

# Gastroesophageal Reflux Disease in the Neonatal Intensive Care Unit Infant Who Needs to Be Treated and What Approach Is Beneficial?

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## KEYWORDS

• GER • GERD • Preterm • Neonate • NICU

## KEY POINTS

- Gastroesophageal reflux (GER) is defined as the retrograde passage of gastric contents into the esophagus and possibly the oral cavity, and when “troublesome symptoms” persist because of these events, it is called gastroesophageal reflux disease (GERD).
- Transient lower esophageal sphincter relaxation remains the most common mechanism of GER in neonates and infants.
- Neonatal presentations are distinct from clinical findings in older infants and children with GERD.
- Symptom-based diagnosis and empirical pharmacologic therapies are not appropriate in the management of neonates with GERD.

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## INTRODUCTION

### *Definition*

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Gastroesophageal reflux (GER) is defined as the retrograde passage of gastric contents into the esophagus and possibly the oral cavity, and when “troublesome symptoms” persist because of these events, it is called gastroesophageal reflux disease (GERD).<sup>1–3</sup> Infants in the neonatal intensive care unit (NICU) present with a multitude of aerodigestive, cardiorespiratory, and somatic symptoms; it is often unclear whether these symptoms can be attributed to GER. In infants in the NICU or in nonverbal developmentally challenged patients, it is common to associate the troublesome symptoms or cues that are witnessed by an observer with GERD; however, the definition of “troublesome” can be challenging. Based on subjective definitions, the use of pharmacologic and nonpharmacologic therapies to mitigate these symptoms has become a common practice, although there is significant practice variation among providers. Many infants in the NICU are prescribed acid-suppressive therapies to treat a presumed diagnosis of GERD.<sup>4,5</sup> These and other pharmacologic approaches, including prokinetics and antacids, have all been associated with serious short-term and long-term consequences.<sup>5–9</sup> Furthermore, empirical and over-the-counter approved and unapproved therapies are commonly used, adding to the expense and contributing to unintended long-term consequences.<sup>10</sup>

### *Epidemiology and Burden*

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The exact burden of GERD in the NICU infant is not known, partly as a result of diverse definitions. To complicate matters, GER is a normal occurrence in the neonate with 2 to 3 episodes of reflux per hour,<sup>11</sup> and is related to the infants’ frequent feeding cycles. The composition of gastric contents varies with feeding methods, and therefore the physical and chemical properties of the gastric contents, vary within an infant’s feeding cycle.<sup>12</sup> Symptoms are based on the state of activity of the infant (ie, sleep-awake-activity states), with infants spending a considerable amount of time sleeping. Interventions that alter the sleep-awake-activity states may include, but are not limited to, routine examination and providing care, nasogastric tube placement and feeding methods, checking residuals, and suctioning aerodigestive tract secretions in sicker infants. Therefore, changes in sleep patterns and interventions in NICU infants may modify the symptoms and responses to reflux events.<sup>13,14</sup>

In an attempt to determine the burden of GERD, the authors studied 33 academic freestanding children’s hospital NICUs in the United States. Using the definition of GERD based on symptoms, they noted a 13-fold variation (2%–26%) in the diagnosis of GERD and found that infants with a diagnosis of GERD stayed 1 month longer in the NICU.<sup>12</sup> Preterm infants who are diagnosed with GERD have longer hospital stays and higher hospital costs than infants without this diagnostic label.<sup>12</sup> It is estimated that the diagnosis of GERD in an NICU infant increases the NICU costs by ~US\$70,000.<sup>12</sup> Furthermore, many infants continue to be treated after they are discharged from the NICU.<sup>5,15</sup>

## CONTROVERSIES SURROUNDING GASTROESOPHAGEAL REFLUX DISEASE IN THE NEONATAL INTENSIVE CARE UNIT INFANT

Ambiguity in the diagnosis of GER or GERD in the NICU may be related to lack of proper understanding and inability to differentiate normal (physiologic) from disease (pathologic) processes. In the absence of physiologic evidence, the diagnosis and management approaches are often influenced by 4 factors.

1. *Symptoms and cues of the patient.* In general, NICU infants have many types of presenting symptoms and cues; these can be classified into 4 groups: (a) *gastrointestinal* (regurgitation, emesis, abdominal distention), (b) *cardiorespiratory* (spells characterized with bradycardia, tachycardia, apnea, periodic breathing, tachypnea, increased respiratory effort, desaturations), (c) *somatosensory* (irritability, back arching, crying, and grimace), and (d) *aerodigestive* (swallowing and feeding difficulties, sneezing, coughing and choking, breathing disturbances) systems. Attributing such troublesome symptoms to reflux events in the absence of evidence remains controversial. Often there is more than one category of presenting symptoms and cues, which can occur with any provocation from within the airway, pulmonary, digestive, cardiac, or neurologic systems. However, the vagal response is a common attribute that can possibly link all of these 4 categories with nerve-mediated aggravating and ameliorating sensorimotor mechanisms that involve sympathetic and parasympathetic responses.
2. *Perceptions of parents and providers.* Parents and bedside care providers are often the first responders to symptoms and clinical signs, and an initial workup for GERD is often based on their reports. Parental perception of GERD may be influenced by individual experiences or readings from older literature. The presence or magnitude of symptoms as a significant predictor of GERD has been evaluated in a survey, the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R).<sup>16</sup> The I-GERQ-R is a brief 12-item validated questionnaire completed by parents and physician providers to measure GERD symptoms in infants. This questionnaire validates the diagnosis of GERD in children aged 1 to 14 months by using abnormal pH-probe studies and abnormal esophageal biopsies as gold standards. An I-GERQ-R score greater than 16 is suggestive of acid GERD. However, Salvatore and colleagues<sup>17</sup> found that the I-GERQ-R questionnaire is not reliable for predicting the severity of GERD. The questionnaire had no correlation with esophageal acid exposure as measured by pH-metry and with esophagitis as evaluated by histology of esophageal biopsies. The questionnaire also does not assess the anticipated response to therapeutic interventions.<sup>17</sup>
3. *NICU operational systems and processes.* The NICU operating systems also play an important role in the supply chain of diet and feeding methods provided to hospitalized infants. For example, the processes involving infant diet, volume intake, milk type, position during feeding, caloric density, osmolality of feedings, use of feeding pumps and gavage tube, or transitional or oral feeding methods can influence GER.<sup>12,18</sup>
4. *Physician's role in the definition of the GERD.* Responsibility ultimately rests with the physician as to whether to treat GERD empirically or wait, or to consider tests for persistent feeding difficulties or troublesome symptoms, and seek alternative diagnoses. Such a determination can be challenging when several factors, as described earlier, are at play. The absence of a highly sensitive and specific, easily available crib-side test makes it more difficult to make a diagnosis based on objective criteria.

## DEVELOPMENTAL ANATOMY AND PHYSIOLOGY OF THE GASTROESOPHAGEAL JUNCTION

The neonatal period is the only time when anatomic development and functional physiologic maturation of individual systems are rapidly evolving *ex utero*. This process further depends on the birth gestation, efficient nutrition and feeding methods, and interventions associated with coexisting morbidities. For the purpose of delineating the

pathophysiological basis of GERD as related to NICU infants, it is important to understand the development and maturation of the gastroesophageal junction (GEJ) in early infancy, because structural and functional abnormalities can influence the GERD diagnosis particularly in the NICU setting.

### ***Embryology and Clinical Implications***

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The neuroanatomic relationship between the airway and foregut can be explained by their embryologic origins from adjacent segments of the primitive foregut.<sup>19–22</sup> The tracheobronchial diverticulum, the pharynx, the esophagus, the stomach, and the diaphragm are all derived from the primitive foregut or its mesenchyme and share similar control systems. By 4 weeks' gestation, the tracheobronchial diverticulum appears at the ventral wall of the foregut, with the left vagus located anterior and the right vagus located posterior. The stomach is a fusiform tube with a growth rate of the dorsal side that is greater than the ventral side, thus creating greater and lesser curvatures. At 7 weeks' gestation, the stomach also rotates 90° clockwise, with the greater curvature displaced to the left. By the sixth or seventh week of gestation, a structure superior to the true vocal cords evolves to protect the vocal cords and lower airway. This superior structure consists of the epiglottis, aryepiglottic folds, false vocal cords, and the laryngeal ventricles. The epiglottis starts as a hypobranchial eminence behind the future tongue. By week 7, the epiglottis is separated from the tongue and 2 lateral folds are connected to the base of the epiglottis, and the distal end of the lateral folds develops into the arytenoids cartilages. The larynx begins as a groove in the primitive foregut, which folds on itself to become the laryngotracheal bud, the subsequent divisions of which form the bronchopulmonary segments. From this phase, 20 generations of conducting airways form. The first 8 generations constitute bronchi and acquire cartilaginous walls; the next 9 to 20 generations constitute the non-respiratory bronchioles, which are not cartilaginous and contain smooth muscle. Subsequent divisions form the bronchopulmonary segments. At 10 weeks' gestation, the esophagus and the stomach are properly positioned; the circular and longitudinal muscle layers and the ganglion cells are in place. The true vocal cords begin as glottal folds.

Thus, from 4 weeks to 24 weeks of intrauterine growth, rapid changes in development, maturation, and functioning of the organs related to the pharyngoesophageal and cardiorespiratory apparatus occur. In the premature infant developing ex utero, further development and maturation of these inadequately developed organ systems can influence the overlapping reflexes involving the 4 categories of symptoms described earlier. Therefore, the structural maldevelopment of the aerodigestive tract and GEJ can result in situations predisposing to GER. Such predisposing conditions for a causal increase in GER events or maladaptive presenting symptoms may include, but are not limited to, craniofacial anomalies, airway anomalies, esophageal atresia and tracheoesophageal fistula, congenital diaphragmatic hernia, hiatal hernia, abdominal wall defects, malrotation, pyloric stenosis, atresia and stricture, and duplication of the small intestine.

### ***Neuromuscular Physiology of Gastroesophageal Junction and Clinical Implications***

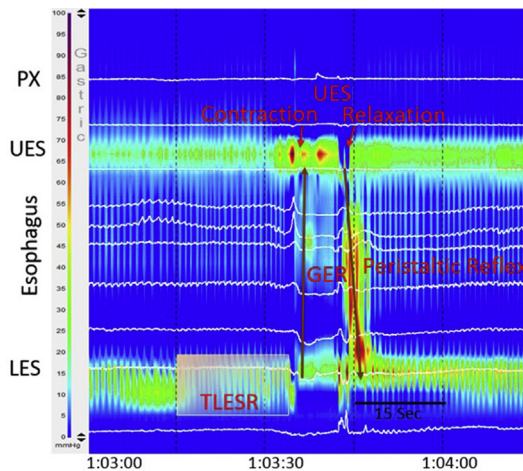
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The pharynx, upper esophageal sphincter (UES), and proximal esophagus are composed of striated muscle. The UES is a high-pressure zone generated by the cricopharyngeus, proximal cervical esophagus, and inferior pharyngeal constrictor, and is located between the pharynx and the esophagus.<sup>23</sup> The UES is innervated by the vagus nerve via the branches of the pharyngoesophageal, superior laryngeal, and recurrent laryngeal nerve, the glossopharyngeal nerve, and the sympathetic nerve

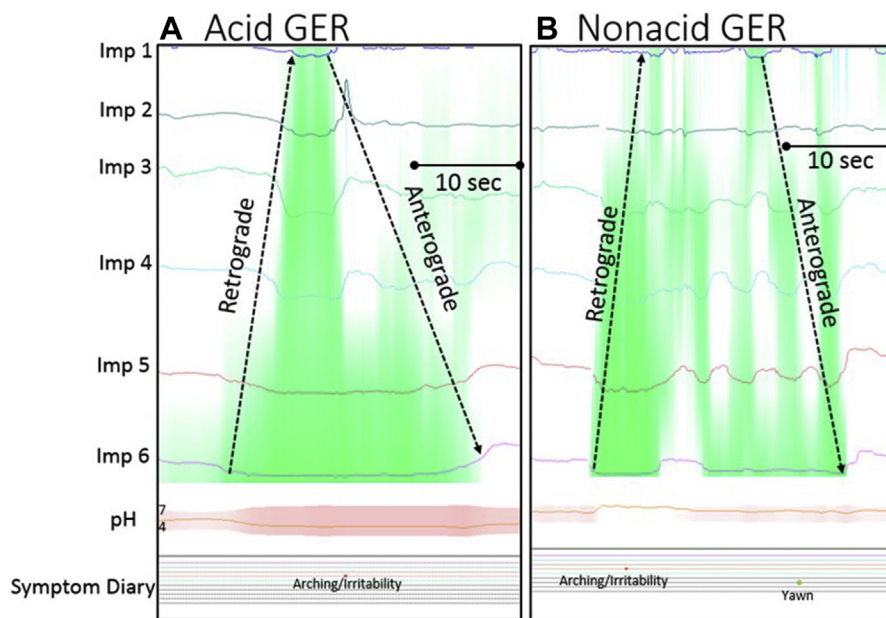
fibers via the cranial nerve ganglia. The distal esophagus and the lower esophageal sphincter (LES) are composed of smooth muscle with an inner layer consisting of circular muscle cells and an outer layer consisting of longitudinal muscle cells with a myenteric plexus in between. The LES is an autonomous contractile apparatus that is tonically active and relaxes periodically to facilitate bolus transit. The integrity of the GEJ is augmented by the LES, diaphragmatic crural fibers, intra-abdominal esophagus, and sling fibers of the stomach.<sup>2</sup>

The high-pressure zone at the GEJ relaxes via inhibitory neural pathways to allow the passage of contents into the stomach during swallowing or into the proximal esophagus and higher structures, as in GER. As shown in the high-resolution impedance manometry recording (Fig. 1), the high-pressure zone at the LES abruptly drops, and this reflex is known as transient LES relaxation (TLESR), the most common mechanism of GER.<sup>24–26</sup> The LES relaxes during basal swallowing, pharyngeal stimulation, esophageal distention, abdominal strain, and GER.<sup>27</sup> In general, the clearance of the refluxate occurs via peristaltic reflexes, and retrograde movement is abruptly halted through the contraction of the UES (see Fig. 1); this barrier function matures with post-natal development. The retrograde movement and clearance of refluxate is captured on the pH-impedance recording (Fig. 2).

In summary, the high-pressure zone at the GEJ depends on the tone generated by the intrinsic LES and also on the magnitude of crural diaphragmatic contraction.



**Fig. 1.** GER event in a neonate recorded by high-resolution manometry capturing the actual occurrence of a GER event in a neonate. The blue zone reflects 0 mm Hg, whereas the purple zone reflects 100 mm Hg (*designated on the left*). The white horizontal lines represent impedance lines that detect bolus presence, directionality, and characteristic of the bolus (air, liquid, and mixed). As the liquid refluxate moves retrograde (decrease in impedance), it drags air with it (shown as increase in impedance). Note that the most proximal extent of reflux stops at the upper esophageal sphincter (UES). At that point there is an increase in UES contractility (protective UES contractile reflex), immediately followed by relaxation of UES associated with swallowing and the peristaltic reflex. Note also that the UES barrier maintains integrity after swallowing (UES relaxation). PX stands for pharynx. The peristaltic reflex is the mechanism for clearance of the bolus. TLESR is the transient relaxation of lower esophageal sphincter wherein the LES resting pressure drops abruptly (relaxes), during which time the ascent of the reflux material occurs. TLESR is the most common mechanism for a GER event. The burdensome symptoms that result as a consequence of GER events contribute toward the diagnosis of GERD.



**Fig. 2.** Example of pH-impedance recordings. There are 6 impedance (Imp) channels, and 1 and 6 refer to the proximal channel and the distal channel, respectively. During this measurement, the pH sensor records the degree of acid exposure over a period of time. (A) During an acid-related GER event, the acid exposure at the distal channel is shown by a drop in pH at the acid sensor, and a decrease in impedance is also associated with retrograde migration of acid reflux material. This is followed by clearance of the refluxate, which is mediated via anterograde peristalsis, as evidenced by the return of the impedance to baseline. Of note, this infant presented with arching and irritability during the GER event. (B) During a nonacid GER event, the pH is not in the acidic range and liquid material is moving retrograde, and is followed by anterograde clearance and peristalsis.

Transit of material through the GEJ is most likely to occur during simultaneous relaxation of the LES and inhibition of the crural diaphragm, and also depends on the pressure gradients across the stomach and esophageal lumen.

### PHYSIOLOGY OF GASTROESOPHAGEAL REFLUX IN NEONATAL INTENSIVE CARE UNIT INFANTS

TLESR (see Fig. 1) remains the most common mechanism of GER in neonates and infants.<sup>25,28,29</sup> Regurgitation is very common in this age group; 40% to 60% of normal 0- to 4-month-old infants regurgitate some amount of their feedings. Basic mechanical considerations provide some explanation for the high frequency of regurgitation in infants.<sup>1,30-34</sup> Newborns sleep or spend most of their time in the supine position, a position that is protective against sudden infant death syndrome (SIDS). Supine and right lateral positions increase the risk for GER, whereas prone and left lateral positions are associated with less GER but an increased rate of SIDS.<sup>1,35-37</sup> Preterm infants are noted to have GER immediately following their feeding, which is most likely due to gastric distension rather than delayed gastric emptying. Studies have shown a normal gastric emptying pattern in both infants with symptomatic GER and those without symptoms.<sup>25,38</sup> Preterm infants who receive tube feedings may have increased



episodes of GER because of incomplete closure of the LES secondary to the presence of a feeding tube.<sup>39</sup> However, on the contrary, in symptomatic dysphagic neonates evaluated for suspected GERD using pH-impedance methods, the authors showed that tube-fed infants had fewer GER events than the exclusively oral-fed group.<sup>12</sup> The length of the infant's esophagus and LES are short and increase with maturation.<sup>40</sup> A term infant's esophagus may be only 8 to 10 cm; the intra-abdominal esophagus develops during the first 6 months of life after full-term birth. Thus, refluxed material has a greater chance of extending to a more proximal extent in preterm infants who are at 6 months corrected age.

Manometric studies in both premature and term neonates have confirmed normal primary esophageal peristalsis. However, premature infants at 30 to 34 weeks' gestational age have lower esophageal peristaltic velocity and amplitude than term infants,<sup>41,42</sup> and preterm infants as young as 33 weeks' postmenstrual age have a reduced esophageal high-pressure zone, which increases with age.<sup>43–45</sup> In response to midesophageal liquid stimulus provocations, premature infants have a longer delay to LES relaxation, but once relaxation occurs it is of longer duration than that found in term infants.<sup>27</sup> Premature infants have an elevated frequency of nonperistaltic esophageal contractions in the absence of a swallow, and this lack of coordination may lead to inadequate clearance of refluxed material.<sup>43,45</sup> As in adults, it seems that transient relaxations of the high-pressure zone are the primary mechanism of GER in neonates.<sup>43,45,46</sup>

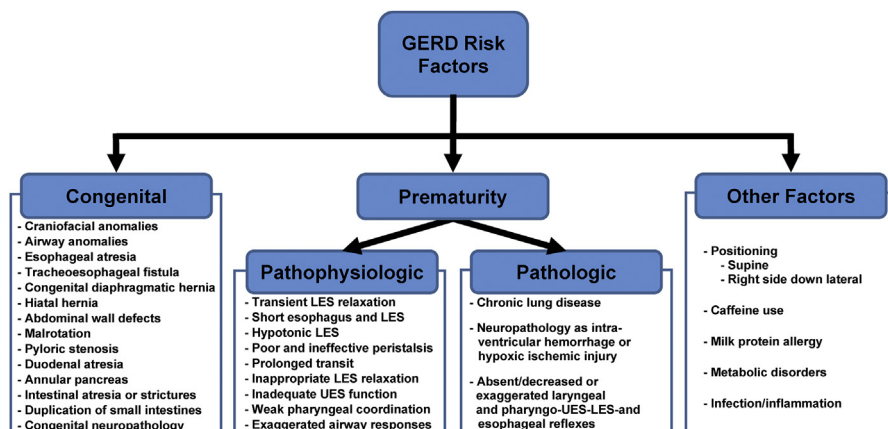
In summary, the most frequent mechanism for GER is TLESR, a common mechanism in neonates and adults. Factors unique to neonates include anatomic factors, position, feeding methods, immaturity, esophageal clearance mechanisms, and presence of inflammation or anomalies.

## **PATHOPHYSIOLOGY OF GASTROESOPHAGEAL REFLUX DISEASE**

The esophageal and laryngeal reflexes that protect the esophagus and airway from damage caused by GER appear to be present in healthy preterm infants. Esophageal distension from the reflux of gastric contents activates anterograde peristalsis reflex of the esophagus along with closure of the UES. This prevents the refluxate from reaching the pharynx. However, if the UES relaxes to allow the refluxate to reach the pharynx, the laryngeal chemosensitive receptors trigger the initiation of the laryngeal chemoreflex to prevent aspiration of gastric contents by glottis closure, which is always accompanied by a period of apnea (glottal closure reflex), although the duration of pause in breathing varies. In addition, primary peristalsis is triggered when the refluxate is present in the pharynx. Theoretically, GERD and retrograde aspiration could result from the failure of these mechanisms. Abnormalities of all of these reflexes are unlikely in physiologically healthy infants, which is why most healthy infants are asymptomatic despite having frequent episodes of GER.<sup>47–49</sup>

## **RISK FACTORS FOR GASTROESOPHAGEAL REFLUX DISEASE**

Several risk factors for GERD have been identified in infants, and the most common causes are listed in **Fig. 3**. Apart from the congenital causes and physiologic consequences of prematurity, it is important to analyze the causes of GER events that arise from complications of prematurity. Bronchopulmonary dysplasia is a major complication of prematurity that affects 30% of extremely low birth weight infants.<sup>50</sup> These infants have an increased risk of GER events secondary to increased respiratory effort and transient increase in intra-abdominal pressure resulting from coughing, airflow obstruction, and crying. This causes the LES tone to decrease and in turn contributes



**Fig. 3.** Risk factors for GERD in the NICU infant. Owing to embryologic and neuroanatomic considerations on the aerodigestive functions, the neonate in the NICU is in a much more vulnerable state than at any other periods of life. The risk factors are classified into 4 domains as stated in the text.

to TLESR.<sup>1,46,51</sup> In addition, these infants are usually treated with respiratory stimulants such as caffeine, which may exacerbate GER events because of an increase in secretion of gastric acid and lowering of LES pressure.<sup>52,53</sup> Neuropathology such as intraventricular hemorrhage, noted in 30% to 40% of preterm infants,<sup>54,55</sup> and hypoxic-ischemic encephalopathy<sup>56</sup> are some of the common risk factors likely to alter the causal or ameliorating mechanisms for reflux events and resulting troublesome symptoms. The incidence of GERD is about 15% to 75% in children with

#### Box 1

##### Screening history for GERD in NICU infants

- Age at symptom onset
- Length of feeding periods
- Volume of each feeding
- Type of milk
- Methods of mixing the formula
- Additives to the feedings
- Attention to food allergens
- Time interval between feeding
- Pattern of regurgitation/spitting/vomiting
- Family medical history
- Environmental triggers—position
- Infant's growth trajectory
- Prior pharmacologic and dietary interventions
- Presence of warning signs such as failure to thrive, back arching and irritability, airway signs, poor oral intake, coughing, and choking spells



neurologic impairment, and the prevalence of GERD in the presence of neuropathology is estimated to be 50%.<sup>57</sup> Neuropathology contributes to GERD through dysregulation of aerodigestive reflexes. Several other causes may contribute to GERD, including metabolic disorders, body positioning, milk protein allergy, and infections, to name a few. These conditions must be investigated in preterm infants who present with signs concerning GERD.

### **APPROACH TO THE PROBLEM THOUGHT TO BE DUE TO GASTROESOPHAGEAL REFLUX DISEASE IN INFANTS IN THE NEONATAL INTENSIVE CARE UNIT**

In 2018, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Pediatric Gastroenterology Hepatology and Nutrition<sup>1</sup> published guidelines on the approach to children presenting with GER or GERD. However, further research is needed because these guidelines are not entirely clear about applicability to infants in the NICU. Infants in the NICU presenting with

#### **Box 2**

#### **Signs and symptoms that may be associated with GERD in NICU infants**

##### *Symptoms*

##### Gastrointestinal

- Regurgitation
- Spitting
- Emesis
- Abdominal distension

##### Aerodigestive

- Swallowing problems
- Feeding problems
- Sneezing
- Coughing
- Choking
- Wheezing
- Stridor

##### Cardiorespiratory Spells

- Bradycardia
- Tachycardia
- Apneas
- Periodic breathing
- Tachypnea
- Increased respiratory effort
- Desaturations

##### Somatosensory

- Irritability
- Back arching
- Crying
- Grimace

##### *Signs*

##### Aerodigestive

- Esophagitis
- Recurrent pneumonia with aspiration
- Recurrent otitis media

##### General

- Anemia
- Failure to thrive

troublesome signs and symptoms suspected to be due to GERD should be evaluated thoroughly for any findings suggestive of disorders other than GERD. A wide range of clinical symptoms are attributed to GERD in NICU infants; however, the reliability of these symptoms as a manifestation of GERD is not clear. The evaluation of a neonate with a suspicion for GERD begins with a thorough focused history (**Box 1**) and physical examination while paying attention to the pharyngoesophageal, cardiorespiratory, and neurologic systems, nutrition, feeding methods, and growth characteristics. In particular, the evaluation should pay attention to signs and symptoms of aerodigestive problems, nonspecific behavioral signs including arching and irritability, and feeding problems that may be associated with GERD (**Box 2**). Additionally it is imperative to exclude any symptoms and signs that masquerade as GERD. Relevant risk factors (see **Fig. 3**) must be addressed. Initial management should include paying attention to optimal nutrition and feeding methods, and continued breastfeeding. However, if there are no improvements a trial of protein hydrolysate or amino acid–based formula or, in breastfed infants, elimination of cow’s milk in the maternal diet should be considered for 2 to 4 weeks. If there are no improvements despite these interventions, gastrointestinal specialty testing using pH impedance with symptom correlation methods, and/or manometry for pharyngoesophageal functional abnormalities, may be considered when available to ascertain the causal and ameliorating mechanisms. In such situations, or if a referral for specialty testing is not possible, 4 to 8 weeks’ trial of acid suppression using proton-pump inhibitors may be considered with extreme caution, while weighing the benefits versus risks, and this can only be considered when infants are at and beyond full term age.<sup>10</sup> There are no safe prokinetic agents for use in premature infants. The role of antacids remains uncertain in the premature infant population.

## SUMMARY

Diagnosis and management considerations for GER and GERD in the NICU infant can be challenging. Neonatal presentations are not as typical as those seen in older infants and children with GERD. Symptom-based diagnosis and empirical pharmacologic therapies are not appropriate. Developmental pathologies and maturational deficits in the causal and ameliorating mechanisms of GER may be associated with GERD risks. When relevant, structural anomalies and risk factors of GERD must be addressed. Emphasis must first be placed on optimal nutrition, feeding methods, growth, conservative management, and reassurance. Because symptoms are nonspecific, other causes and diagnoses that masquerade as GERD must be considered. Minimizing the use and duration of acid-suppressive therapies is appropriate while weighing benefits and risks. Further research is critically needed in this high-risk population of NICU infants, with relevance to screening, diagnostic algorithms, objective criteria, and nonpharmacologic and pharmacologic approaches, to manage objectively determined acid and nonacid GERD and their consequences.

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