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Neonatal gastroesophageal reflux

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1. Introduction

Gastroesophageal reflux disease (GERD) is a common diagnosis among neonates, affecting 1 in 10 infants admitted to the neonatal intensive care unit. The diagnosis is associated with increased length and cost of hospitalization [1]. GERD remains a clinical diagnosis based on non-specific, subjective symptoms that result in significant variation in practice [1,2]. Treatment for presumed GERD with acid-suppression is associated with serious complications including increased lower respiratory tract infections, necrotizing enterocolitis (NEC), late-onset sepsis, and death [3,4]. In preterm infants, GERD continues to be misunderstood, over-diagnosed, and overtreated. As a result, the American Academy of Pediatrics recognizes GERD as an area of neonatal medicine with room for improvement [5]. This article aims to explain the physiology of neonatal gastroesophageal reflux, the symptoms commonly attributed to it, and the evidence regarding its diagnosis and treatment in the neonatal intensive care unit (NICU).

2. Physiology

Gastroesophageal reflux (GER) is defined as the retrograde movement of gastric contents into the esophagus. Refluxed gastric contents are referred to as refluxate and can be liquid, solid, or gas [6]. GER is considered physiologic and has been shown to occur commonly in asymptomatic infants [7].

Neonatal GER can be described as flow between the relatively high-pressure stomach and lower-pressure esophagus. In this way, flow from the stomach into the esophagus naturally occurs, unless there is a barrier between the two compartments. The gastroesophageal junction functions as this barrier.

The gastroesophageal junction consists of the lower esophageal sphincter (LES), the crural fibers of the diaphragm, and the sling fibers of the stomach. The LES is contracted at baseline and provides the most important contribution to the integrity of the gastroesophageal junction. Evidence demonstrates that preterm and term infants have intact LES function [8]. The LES relaxes periodically, thereby allowing for the passage of contents

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between the esophagus and stomach. Triggers of LES relaxation include swallowing, gastric distention, abdominal straining, respiratory distress, and methylxanthine (caffeine) therapy [9,10]. When LES tone decreases, GER becomes more likely [9].

The LES also relaxes spontaneously at baseline, unrelated to swallowing events [9]. These relaxation events are the main mechanism of GER and are called transient lower esophageal sphincter relaxation, or TLESR. Overall, the integrity of the gastroesophageal junction is influenced by many factors including resting pressure of the LES, respiratory distress, abdominal straining, and methylxanthine therapy. Understanding factors which impact the gastroesophageal junction is essential to understanding GER.

As described earlier, GER occurs because of flow via a pressure gradient. The abdominothoracic pressure gradient is another such gradient which predisposes to reflux of gastric contents [11]. The esophagus extends from the pharynx to the stomach and travels through both the thoracic and abdominal compartments. The thoracic cavity is lower in pressure relative to the abdominal compartment. This creates a pressure gradient which favors the retrograde flow of gastric contents from the stomach into the esophagus. Any conditions that increase this gradient, also increase the likelihood of GER. The increase in the abdominothoracic pressure gradient is the primary mechanism by which respiratory distress (more negative intrathoracic pressure) and abdominal straining (more positive intraabdominal pressure) predispose to GER [9,12–14].

The relationship between methylxanthine therapy and GER is complex. There are no well-designed clinical studies to address how methylxanthine therapy affects reflux in preterm infants. Caffeine has been shown to decrease LES tone in rats [10]. However, atropine, a medication shown to decrease LES tone, has been shown to decrease GER by limiting TLESR. A recent study demonstrated that caffeine therapy increases gastric emptying time in preterm infants but did not investigate the effect of caffeine on GER [15]. Overall, there is need for well-designed clinical studies to investigate the effect methylxanthines have on clinically evident reflux.

Interestingly, refluxed gastric contents are less acidic in preterm and term infants. This is due to their unique diet that consists of relatively alkaline milk [16]. Available data suggests that up to 73 % of reflux episodes have a pH between 4 and 7 [7]. The weakly acidic composition of neonatal refluxate is a possible explanation for the lack of effectiveness of acid-suppression therapy in this population.

In summary, GER occurs because of the complex relationship between resting tone of the gastroesophageal junction and the abdominothoracic pressure gradient. Gastroesophageal junction integrity is affected by many factors including respiratory distress, abdominal straining, and possibly caffeine use [9,12–14]. When reflux does occur, it is mildly acidic.

3. Measurement of gastroesophageal reflux disease

Several technologies have been used to study GERD. These include contrast fluoroscopy, pH monitoring, and combined pH-multichannel intraluminal impedance (pH-MII).

3.1. Contrast fluoroscopy

Contrast fluoroscopy is the radiographic examination of the upper gastrointestinal tract with a radiocontrast agent. The test is quick, and results describe only what occurs during the examination. Since GER occurs commonly in asymptomatic neonates, reflux demonstrated on contrast study is hardly pathognomonic. In fact, up to 50 % of asymptomatic children demonstrate GER during contrast study [17]. Thus, contrast fluoroscopy is an appropriate test to diagnose anatomic abnormalities which may be related to GERD, but reflux noted during the exam should not be used to diagnose GERD.

3.2. pH monitoring

Classically, GER has been studied by pH monitoring in the distal esophagus. This technology uses an esophageal catheter with a pH sensor on the distal end that is placed proximal to the gastroesophageal junction. Changes in pH are detected, which suggests the presence of acid reflux. The study usually lasts hours to days, after which a reflux index is calculated. The reflux index is defined as the percentage of recording time that the pH is less than 4. Limitations of pH monitoring include a lack of normal values in infants and inability to detect weakly acidic refluxate, which constitutes the majority of refluxate in infants [17,18]. A newer technology, called combined pH-MII testing, seeks to address these limitations.

3.3. Combined pH-multichannel intraluminal impedance (pH-MII)

Perhaps the most promising diagnostic technique to identify GERD is combined pH-multichannel intraluminal impedance, or pH-MII, measurements. This technology uses electrodes and a pH sensor attached to an esophageal catheter, which can measure both pH and impedance. Impedance is the resistance to electrical current in the esophagus. Liquid refluxate decreases impedance between electrodes, thereby allowing for the detection of weakly acidic or alkaline refluxate. Additionally, multiple electrodes on the catheter describe the distance refluxate has traveled up the esophagus. This may offer the clinician valuable information about the risk of aspiration of refluxate. Combined pH-MII monitoring shows promise as an objective method to diagnose GERD; however, more normative data are needed before the modality can be considered a gold-standard test.

4. Clinical symptoms and gastroesophageal reflux

The diagnosis of gastroesophageal reflux disease varies considerably between centers [1]. Nationally, GERD is diagnosed in one of ten infants admitted to NICUs. However, the prevalence of GERD diagnosis also varies 13-fold between hospitals [1]. Clearly, the clinical criteria used to diagnose GERD are not consistent and lead to considerable practice variation.

In studying GERD, it is important to understand the prevalence of asymptomatic reflux. Asymptomatic preterm infants have an average of 2–3 measurable reflux events per hour, the majority of which have a pH between 4 and 7 [7]. Clearly, both asymptomatic and clinically diagnosed GER are common in the neonatal intensive care unit. However, a reliable link

between the two has not been demonstrated [19]. A thorough understanding of classically associated GERD symptoms is necessary to understand the diagnosis.

Some authors have organized symptoms classically associated with GERD into categories based on their physiologic origin [20]. Categories include respiratory (coughing, stridor, wheezing, or aspiration), gastrointestinal (regurgitation, emesis, poor oral intake), cardiorespiratory (apnea, bradycardia, desaturations), or neurogenic (back-arching, irritability). Unfortunately, none of these symptoms are specific for GERD. For example, emesis may be related to GERD, when in fact it may also occur in feeding intolerance because of slow enteric motility in the developing preterm gastrointestinal tract. Conversely, the same symptom may indicate developing necrotizing enterocolitis. In neither situation would the diagnosis of GERD lead to appropriate treatment. In fact, it may lead to a delay in treatment of a more serious underlying problem.

A few studies have aimed to clarify the relationship between symptoms and GER measured with pH-MII. In one study of thirty symptomatic preterm infants, only half the measured reflux was associated with symptoms [6]. Interestingly, pH-only events (a change in pH without measured reflux) were more closely associated with symptoms. Another investigation compared pH-MII measurements and symptoms in 58 infants. The study demonstrated that only 10 % of infants had symptoms during the 10-minute period surrounding measurable reflux [19].

Overall, current evidence shows minimal correlation between clinical symptoms and measurable reflux. There may be an association with symptoms and pH changes, but not reflux, in the esophagus. Neonatal practitioners should be cautious when diagnosing GERD based on clinical symptoms because of their poor predictive value. It is prudent to treat GERD as a diagnosis of exclusion.

5. GERD's relationship with common NICU pathology

GERD has also been associated with common NICU diseases such as apnea of prematurity, bronchopulmonary dysplasia, and upper airway irritation. The association of GERD with other diagnoses has been an area of ongoing investigation.

5.1. Gastroesophageal reflux and apnea of prematurity (AOP)

In the 1970s and 1980s, researchers raised concerns about a relationship between GERD and apnea of prematurity. As an example, one study presented a case series of 14 infants and found that acid reflux precipitated apnea [21]. However, limitations of this study include the case-series study design and the heterogeneity of the patients (birth weight ranged from 760 g – 4540 g). Since apnea of prematurity and GER are both common events, it is possible any association is temporal and not causal.

A more recent study retrospectively analyzed manometry recordings in 156 preterm infants. On average, LES relaxation occurred 5.8 ± 0.8 s after, not before, the onset of apneic events [22]. This suggests that apnea may precede GER when the two are associated. However,

this hypothesis is limited by the small number of patients with apnea and the study's retrospective design.

Other studies have investigated the relationship between apnea and GER with pH-MII and more extensive cardiorespiratory monitoring. In one study, investigators blindly analyzed pH-MII and cardiorespiratory recordings of 19 preterm infants diagnosed with apnea of prematurity. There was no increase in the frequency of apnea in the presence of measurable GERD [23]. Another, larger study performed overnight monitoring of preterm infants referred because of cardiorespiratory events. In nearly 4000 GER events, less than 3 % of apneic events had measurable reflux in the preceding 30 s [24].

In summary, although previous studies suggested an association between GER and apnea, more recent, robust studies have not demonstrated an association. Instead, apnea may be a trigger of GERD and appropriately treating apnea of prematurity may decrease GERD.

5.2. Gastroesophageal reflux and bronchopulmonary dysplasia

Infants with bronchopulmonary dysplasia (BPD) are significantly more likely to be diagnosed with GERD (OR 3.37 [3.01, 3.77]) [1]. Theories linking BPD and GERD include chronic aspiration of caustic gastric contents and increased intra-abdominal pressure during respiratory distress, which in turn could lead to increased reflux. However, definitive evidence of a physiologic link between the two diseases remains elusive.

A recent prospective cohort study of symptomatic infants with and without BPD demonstrated no increase in measured reflux in either group. However, they did note an increase in pH-only reflux in the BPD group [25]. Another recent prospective cohort study noted that measured reflux was associated with an increased risk of respiratory disease in infants with a diagnosis of BPD [26]. The above studies did not focus on infants who require chronic ventilation, however.

Overall, the association between BPD and GERD remains an open question. Available evidence investigating the association is of low quality. The association between severe BPD and GERD will likely require a multicenter randomized controlled trial to conclusively answer.

5.3. Airway evaluation and gastroesophageal reflux

A frequent finding during upper airway evaluation is erythema or swelling of the larynx. GER is commonly implicated as a cause of these findings, and treatment with acid suppression therapy may be recommended as a result.

A recent prospective cohort study attempted to correlate findings during upper airway evaluation and measurable reflux. The study was performed in 77 children referred to otolaryngology for evaluation of a persistent cough. Subjects underwent direct laryngoscopy and bronchoscopy (DLB), esophagogastroduodenoscopy (EGD), and combined pH-MII testing. Video recordings of the DLBs were assessed by blinded otolaryngologists, who then assigned a reflux finding score (RFS), a scoring system designed to diagnose GERD. Results of the study demonstrated no association between a diagnostic RFS and the presence of

GERD during pH-MII study (Fig. 1) [27]. Additionally, the RFS did not correlate between blinded otolaryngologists. Overall, this study suggests that abnormalities noted during DLB should not be used to diagnose GERD.

6. GERD: a diagnosis of exclusion

Diagnosing GERD remains a challenge for neonatal clinicians because clinical symptoms are poorly correlated with measured reflux [6,19]. Inappropriately attributing symptoms to GERD may result in significant harm. Therefore, it is prudent to approach GERD as a diagnosis of exclusion.

As with any diagnosis, one should start with careful attention to the history and physical exam. History items of particular importance include the feeding history (type of milk, quantity and frequency of feedings, feeding additives), feeding techniques (including the type of nipple used, pacing, and coordination of infant swallowing), and any family history of food allergies. Additionally, physical exam findings that may be concerning for feeding intolerance should be noted, such as abdominal distention, guarding, or erythema. Such symptoms may be suggestive of a more serious underlying pathology, such as NEC.

6.1. GERD risk factors

Gastroesophageal reflux is more likely to occur in certain patient populations (Table 1), notably those with anatomic abnormalities of the gastrointestinal tract. If there is clinical suspicion for an anatomic abnormality causing GER, a contrast study of the upper gastrointestinal tract can be considered. As noted earlier, reflux demonstrated during a contrast study should not be interpreted as evidence of disease. Other comorbidities that predispose to GER include bronchopulmonary dysplasia or worsening respiratory disease (via increased abdominothoracic pressure gradient), changes in infant position, volume or duration of enteral feeding, food protein-induced enterocolitis (FPIE), caffeine use, or issues impacting neurologic control of the LES (intraventricular hemorrhage, hypoxic ischemic encephalopathy (HIE), etc.).

If the history and physical exam do not suggest another diagnosis, pH-MII with symptom correlation should be considered. Consultation with a pediatric gastroenterologist is helpful in interpreting pH-MII studies. If pH-MII is unavailable, GERD may be cautiously diagnosed. However, if symptoms do not improve with intervention, or if symptoms worsen, the diagnosis of GERD should be revisited to ensure there is not another explanation for the symptoms.

7. Treatment of GERD

Because signs and symptoms suggestive of GERD are non-specific, the treatment approach must begin with treatment of underlying disease. Again, isolated GERD should be a diagnosis of exclusion. Treatment of underlying conditions will improve most of the symptoms suggestive of GERD. As an example, if there is concern that GERD is worsening a patient’s respiratory disease, a trial of increased respiratory support may improve both respiratory distress and regurgitation or emesis.

After all underlying conditions have been explored and addressed, treatment for isolated GERD can be considered if symptoms have not resolved. The treatment of isolated GERD can be divided into three main sections: non-pharmacologic, pharmacologic, and surgical. However, most treatments of GERD have a low-quality body of evidence (mainly observational, uncontrolled studies). Therefore, most recommendations below should be considered weak based on GRADE criteria.

7.1. Non-pharmacologic treatment

Non-pharmacologic treatment is commonly the first step in treatment of GERD, particularly in preterm infants. In this section, we discuss the evidence, risks, and benefits of common non-pharmacologic treatments commonly used in the NICU setting. Interventions include feeding modification, infant positioning, changing infant formulas, and adding thickeners to feedings.

7.1.1. Feeding modification—Feeding modification is commonly used to manage GERD in preterm and term infants in the NICU. There is some evidence that smaller volume, slower feedings are associated with less reflux and esophageal acid exposure [9,28,29]. However, nutrient composition of breastmilk may be compromised with this approach [30]. Overall, decreasing feed volume and infusion rate are reasonable methods to decrease the likelihood of GER, particularly in preterm infants, but clinicians should be aware of the possibility of compromised nutrition with these adjustments.

7.1.2. Body positioning and “reflux precautions”—Changes in infant position include elevating the head of the bed, supine or prone positions, and right vs. left lateral positioning. Traditionally, these measures have been viewed as conservative or “safe” methods to mitigate GERD; see Fig. 2. However, there is evidence that some positions may worsen GERD.

Car seat placement can worsen reflux symptoms in term infants [31–33]. A possible explanation is that hip flexion leads to increased intraabdominal pressure, thereby increasing the abdominothoracic pressure gradient. No studies have investigated elevation of the head of the bed in preterm infants.

Right lateral positioning has been shown to enhance gastric emptying and was thought to improve GER. However, when investigated directly, right lateral positionings appears to increase GERD [34]. The prone and left-lateral positions reduce TLESRs and reflux episodes compared to supine and right lateral positioning [9,34,35]. However, behavioral manifestations of reflux (crying/irritability) do not improve [36].

Supine positioning is recommended for infants who are preparing for discharge home. Prone and left-lateral positioning are not recommended to decrease reflux symptoms at home because they may increase the risk of sudden unexplained infant death. The American Academy of Pediatrics recommends modeling safe sleep precautions at 32 weeks’ gestation, or when nearing discharge home [37]. They also recommend avoiding the use of commercial products designed to elevate the infant’s head.

7.1.3. Transpyloric feeding—Transpyloric feeding is the delivery of nutrients directly into the duodenum, bypassing the stomach. This method involves passing the feeding tube beyond the stomach, through the pyloric sphincter, into either the duodenum or jejunum. Enteral feeds are then administered continuously. This decreases the volume delivered to the stomach and is thought to decrease GER. However, because this feeding method is less physiologic than gastric feeding, it is typically used only in the most severe cases of GERD that do not respond to feeding modification or position changes.

Additionally, evidence to support this intervention is limited: no randomized-controlled trials have evaluated transpyloric feeding as a treatment for GERD. A retrospective study showed that transpyloric feeding decreases measurable reflux [38]. However, more reflux was observed during transpyloric feeding periods than non-feeding periods. In adults, transpyloric feeding can result in increased TLESR, reflux events, and esophageal acid exposure [39]. In neonates, risks of transpyloric feeding include diarrhea, feeding intolerance, and the rare but important complication of intestinal perforation [40–42]. Overall, a limited trial of transpyloric feeding may be attempted in severe cases of GERD, following a discussion of risks and benefits with the patient's family.

7.2. Pharmacologic treatment

7.2.1. Extensively hydrolyzed or amino-acid formulas—Some infants with clinically diagnosed GERD may have underlying food protein-induced enterocolitis (FPIE). Infants with FPIE can present with retching, vomiting, and failure to thrive. In the absence of more specific symptoms, distinguishing between the two conditions is nearly impossible [17]. For this reason, some infants with a clinical diagnosis of GERD may have improvement in symptoms after elimination of cow-milk protein. Several small trials have demonstrated that hydrolyzed formula leads to symptomatic improvement [43–45].

In term infants, a 1–2-week trial of extensively hydrolyzed formula is a reasonable treatment option. In preterm infants, eliminating cow's milk from the maternal diet is a safe and reasonable treatment for GERD. However, switching preterm infants from breastmilk to formula before 34–36 weeks PMA is not recommended even in the presence of symptoms concerning for GERD, because of the increased risk for necrotizing enterocolitis.

7.2.2. Feed thickeners—In term infants, a common strategy to treat GERD symptoms is to add a thickening agent to the feeds. Although thickeners have been shown to reduce episodes of regurgitation, they are ineffective in reducing acid GERD [46]. No randomized-controlled trials have assessed their use in preterm infants. Furthermore, use of xanthan gum as a thickening agent, has been associated with development of necrotizing enterocolitis and should not be used in preterm infants during their first year [47]. Recently, special "reflux" formulas designed for term infants thicken when exposed to gastric acid. However, these formulas are not designed to meet the unique nutritional requirements of preterm infants and cannot be recommended in this patient population. Thickening feeds may increase the osmolality of feeds beyond a maximum of 450 mOsm/kg recommended by the AAP. Other consequences of thickeners may include hypernatremia, malabsorption, constipation,

dehydration, delayed gastrointestinal transit, fatigue from nipple extraction, decreased oral intake, or prolonged transition of oral feeding [48].

7.2.3. Acid suppression therapy—Perhaps the most common pharmacologic treatment for GERD is acid suppression therapy. These therapies have been widely studied in adults and older children and as such, are the mainstay of treatment in these populations [49]. Unfortunately, there is a lack of evidence of efficacy in the neonatal population.

Histamine 2 receptor antagonists (H2RAs) competitively block the histamine 2 (H2) receptors, thereby decreasing gastric acid secretion from parietal cells. This increases the gastric pH and alleviates symptoms of GERD in other populations. Unfortunately, there is no research to demonstrate the effects of H2 receptor antagonists in the neonatal population. Additionally, H2RAs are associated with rapid tachyphylaxis, noticed as soon as the second dose [50]. Most importantly, there are reports that H2 receptor antagonists are associated with significantly increased risk of necrotizing enterocolitis and late onset sepsis [3,4]. For these reasons, it is recommended to avoid the use of these medications in the neonatal population.

Proton pump inhibitors (PPIs) also act to decrease gastric acid secretion and increase gastric pH. Additionally, some data suggests PPIs have anti-inflammatory effects; however, the mechanism is unclear and warrants further investigation [51]. Conversely, some animal models have shown that PPIs may induce relaxation of the LES [52–54]. There have been several randomized trials of PPIs in post-term infants. One of the first randomized controlled trials demonstrated that PPIs could decrease measured acid exposure in infants [55]. However, clinical symptoms were no different in the group treated with a PPI. Another randomized controlled trial compared lansoprazole to placebo in irritable, post-term infants. The study found no difference in irritability after 4 weeks of treatment [56]. Of note, there was a trend of increased lower respiratory infections in the group that received lansoprazole, although it was not statistically significant. Most recently, there were two open-label, blinded withdrawal studies comparing PPIs in term infants. Neither study demonstrated a difference in symptoms during the withdrawal phase [57,58]. Notably, during all studies symptoms improved in both placebo and treatment groups over time, suggesting an improvement in symptoms regardless of medical therapy.

It should be noted that available studies were performed in post-term infants with clinical symptoms classically associated with GERD. Although some infants with congenital anomalies, such as infants with esophageal atresia, may benefit post-operatively from treatment with proton pump inhibitors, [59] recent evidence suggests the opposite, demonstrating that PPIs do not prevent the formation of anastomotic strictures [60].

Overall, available evidence does not support the routine use of PPIs or H2RAs to treat classically associated GERD symptoms in post-term infants, although some sub-populations may benefit from treatment. Outside of proven acid-reflux, treatment with a PPI should be time limited and all caregivers should be aware of possible side-effects. Acid-suppression therapy should not be used in preterm infants given the risk of severe side effects [3,4].

7.2.4. Prokinetic agents—Prokinetic agents are another, less commonly used, class of medications to treat GERD. These medications function to increase gastric emptying and increase LES tone. Metoclopramide, domperidone, and erythromycin are examples of prokinetic agents. None of these have been shown to reduce GERD symptoms in preterm infants [61,62]. Similar to other medical therapies for GERD, most are not well studied in neonates and are associated with significant and concerning side effects. Side effects of metoclopramide and domperidone are primarily neurologic including irritability, drowsiness, apnea, and possible irreversible tardive dyskinesia. Erythromycin is associated with infantile pyloric stenosis and cardiac arrythmias. Given the lack of evidence for efficacy and the potential for significant side effects, the use of prokinetic agents to treat neonatal GERD is not recommended [17].

7.2.5. Bethanechol—Bethanechol is a direct cholinergic agonist that stimulates the parasympathetic nervous system. This drug is usually prescribed for non-obstructive urinary retention because it increases bladder muscle tone causing contractions which initiate urination. However, it can also stimulate gastric motility, increase gastric tone, and may restore peristalsis. For this reason, bethanechol was historically used to treat infants and children with GERD. However, its action is not limited to the GI tract and bladder. The heart and lungs are also affected, leading to significant side effects such as increased secretions (salivary, gastric, pancreatic, and intestinal), bronchoconstriction, increased vomiting, and anorexia [63]. In addition to its side-effects, its efficacy remains unclear. A double-blind, crossover study utilizing bethanechol reported improvement in reflux symptoms when taking bethanechol vs. placebo [64]. Another trial comparing bethanechol vs. antacids in older infants did not show any difference in their efficacy for treating reflux [65]. Other researchers reported that bethanechol increased reflux episodes in two thirds of the participants in a prospective, blind, controlled study [66]. Because the risk of adverse events outweigh any potential benefit, bethanechol is no longer recommended to treat GERD by the American Academy of Pediatrics [67] and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN/ESPGHAN) [68,69].

7.3. Surgical treatment

High quality evidence is lacking in the surgical management of GERD in neonates. Although anti-reflux surgery has a poor success rate in the treatment of extraesophageal symptoms (including aspiration pneumonia), fundoplication is sometimes performed for this reason [69–73]. Nissen fundoplication is the most common surgical intervention for refractory GERD. In this procedure, the fundus of the stomach is wrapped 360 degrees posteriorly around the lower esophagus [74]. In the population of children with extraesophageal symptoms, multiple studies have failed to show consistent benefit in the reduction of mechanical ventilation, pneumonias, and asthma [70–72,75]. Pediatric data report no significant reduction in the use of acid suppression medication after fundoplication, with more than 75 % of patients taking acid suppressant medications 1 year after surgery [75].

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Abbreviations:

GERD	gastroesophageal reflux disease
GER	gastroesophageal reflux
LES	lower esophageal sphincter
TLESR	transient lower esophageal sphincter relaxation
FPIE	food protein-induced enterocolitis
PPI	proton pump inhibitor
H2RA	histamine 2 receptor antagonist

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Key guidelines

- It is important to note that most data on GERD treatment is considered low quality and recommendations based on these data are weak, unless otherwise noted, see Fig. 3.
- GER occurs in all infants and symptoms classically associated with GERD are non-specific.
- It is imperative that neonatal clinicians manage GERD as a diagnosis of exclusion by first ruling out other serious diseases with a similar clinical presentation. Treatment of underlying disease often improves symptoms that are associated with GERD.
- Ideally, treatment for GERD would only occur following objective evidence of disease, as demonstrated by pH-MII. Unfortunately, this test is not widely available in most NICUs.
- Once underlying conditions are ruled out, feeding modification, positioning (while monitored in the NICU), and a trial of elimination of cow-milk protein are reasonable treatments in preterm infants, although formula should not be substituted for breastmilk when it is available.
- If there are severe symptoms that do not improve based on the above treatments, transpyloric feeding can be trialed with caution. Acid-suppression therapy is contraindicated in preterm infants.
- In term infants, thickening of feeds and elimination of cow-milk may be reasonable as suggested by NASPGHAN/ESPGHAN.
- If trialed, pharmacologic therapy should be time-limited, with a discrete endpoint of therapy proposed at treatment outset. Available evidence supports the assertion that GER naturally resolves over time. In many cases, the side-effects of treatment for GERD may be worse than the disease.

Research directions

- Normative data for pH-MII are needed before this modality can be considered a gold standard for the diagnosis of GERD.
- Well-designed studies in preterm infants are needed to investigate the effect of methylxanthines (caffeine) on GERD.
- The relationship between GERD and bronchopulmonary dysplasia needs to be further explored.
- Elevating the head of the bed in preterm infants and its effects on GERD symptoms needs to be investigated.
- Well-designed studies on transpyloric feeding to treat GERD must be conducted.
- The use of thickeners to treat GERD needs to be investigated in the preterm population.
- A randomized controlled trial must be conducted to compare fundoplication vs. no fundoplication in infants with retractable GERD to investigate the effects on extraesophageal symptoms.

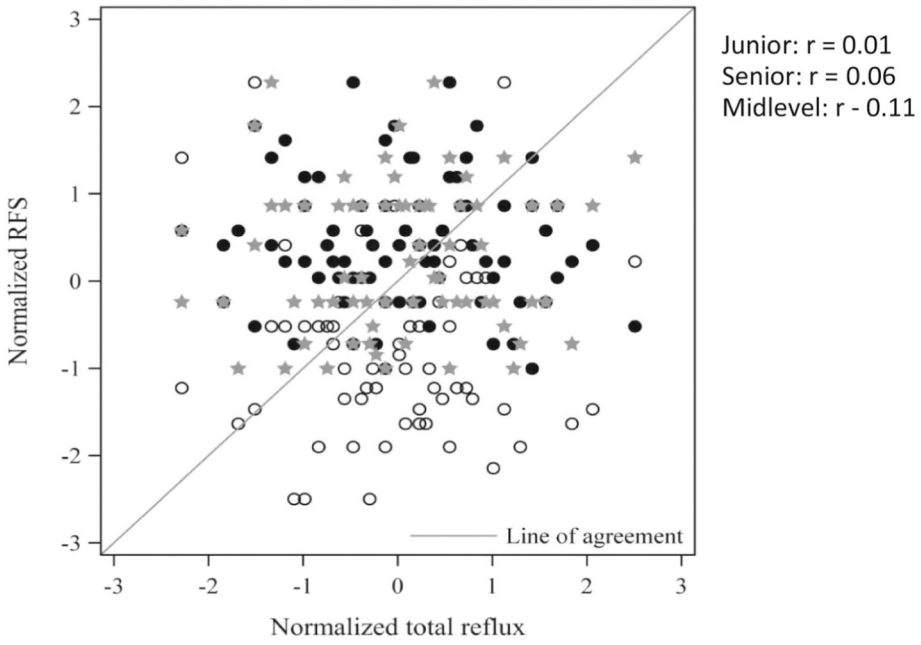

Fig. 1.

Scatter plot of normalized RFS and normalized total reflux.

Adapted from Rosen R, Mitchell PD, Amirault J, Amin M, Watters K, Rahbar R. The Edematous and Erythematous Airway Does Not Denote Pathologic Gastroesophageal Reflux. J Pediatr. 2017;183:127–31. Fig. 2, Lack of correlation between RFS and total number of reflux events; p. 130.

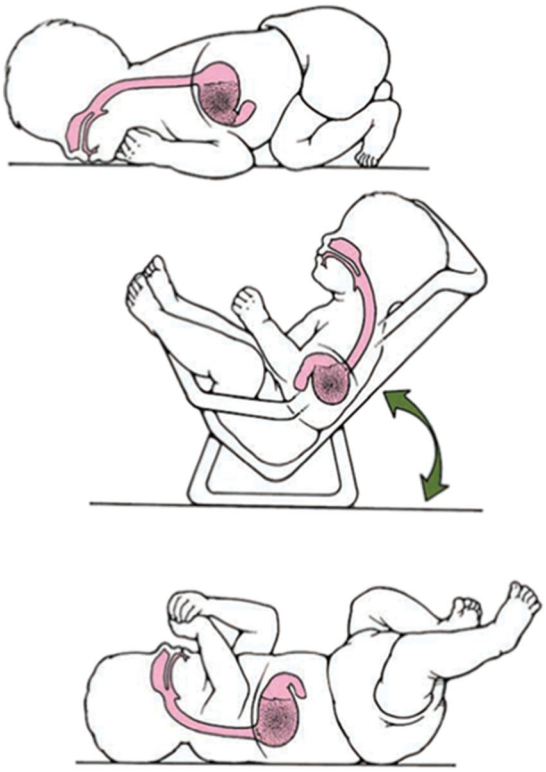

Fig. 2.

Effects of position on gastric contents.

Adapted from Ramenofsky ML, Leape LL. Continuous upper esophageal pH monitoring in infants and children with gastroesophageal reflux, pneumonia, and apneic spells. J Pediatr Surg. 1981;16(3):374–8. Fig. 3 Representation of the position of the gastroesophageal junction with a patient in various positions; p. 377.

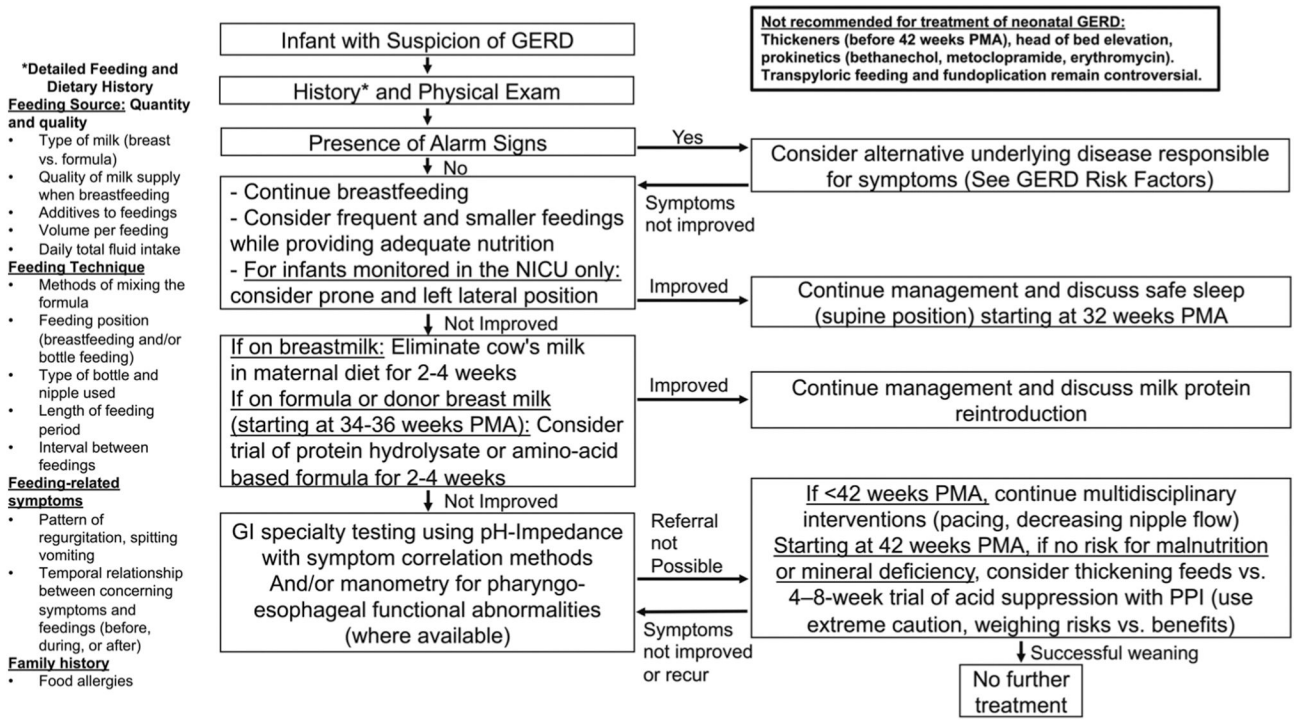

Fig. 3.

Sample algorithm for the evaluation and management of GERD in the NICU.

*Detailed Feeding and Dietary History was adapted from Sanchez JB, Jadcherla SR. Gastroesophageal Reflux Disease in Neonates: Facts and Figures. NeoReviews. 2021;22(2):e104-e17. Table 3 Detailed Feeding and Dietary History; p. e110.

Table 1

GERD risk factors.

Craniofacial anomalies	GI anomalies		Neurologic anomalies
Airway anomalies	Abdominal wall defects	Pyloric stenosis	Intraventricular hemorrhage
Tracheoesophageal fistula	Malrotation	Duodenal or other intestinal atresia	Periventricular leukomalacia
Esophageal atresia	Congenital diaphragmatic hernia	Intestinal strictures	Hypoxic-Ischemic encephalopathy
	Hiatal hernia	Annular pancreas	