Enfermedad por reflujo gastroesofágico en recién nacidos: hechos y cifras.

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Resumen:

Los médicos que atienden a bebés prematuros deben reconocer la historia natural y la fisiopatología del reflujo gastroesofágico (GER) y la enfermedad de GER. Los facultativos también deben aprovechar al máximo las herramientas de diagnóstico disponibles en sus entornos clínicos y ofrecer la terapia más adecuada para estas afecciones, que constituyen una carga significativa para los pacientes y para nuestro sistema de atención médica. En este artículo se presentan algunas orientaciones basadas en hechos y ciras.

Gastroesophageal Reflux Disease in Neonates: Facts and Figures

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Education Gap

Clinicians caring for premature infants need to recognize the natural history and pathophysiology of gastroesophageal reflux (GER) and GER disease. Clinicians also need to make the most out of the diagnostic tools available in their clinical settings and offer the most appropriate therapy for these conditions, which constitute a significant burden to patients and to our health care system.

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

1. Explain the terminology, mechanisms, and controversies surrounding gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) in neonates.
2. Describe the epidemiology, pathophysiology, and risk factors of GER and GERD in neonates.
3. Explain the approach to evaluate, diagnose, and manage GERD in neonates.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
BPD	bronchopulmonary dysplasia
CMPA	cow milk protein allergy
GEJ	gastroesophageal junction
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
H2RA	histamine 2 receptor antagonist
LES	lower esophageal sphincter
NASPGHAN	North American Society of Pediatric Gastroenterology, Hepatology and Nutrition
pH-MII	multichannel intraluminal pH impedance
PPI	proton pump inhibitor
SLESR	swallow-associated lower esophageal sphincter relaxation
SSI	symptom sensitivity index
TLESR	transient lower esophageal sphincter relaxation
VLBW	very low-birthweight

INTRODUCTION

Gastroesophageal reflux (GER) is a normal physiologic process that occurs in all age groups. In healthy preterm infants, an average of 2 to 3 reflux events occur per hour, as has been reported using 24-hour pH impedance monitoring. (1) GER has historically been associated with a wide variety of behaviors commonly attributed to "GERD-like" symptoms in infants. (2) However, the association between a specific symptom and GER needs supporting data. (3) In the NICU infant, many of these symptoms may have multisystemic etiologies related to prematurity, chronic lung disease, and neuropathology, among others, rather than solely GER.

Over the years, GER has remained a controversial topic for clinicians because of the challenges that entail its accurate diagnosis, as well as the uncertainty of treatment efficacy in symptomatic neonates. Furthermore, various studies have shown that histamine 2 receptor antagonists (H2RAs), proton pump inhibitors

(PPIs), and prokinetics therapy may be associated with serious adverse outcomes in preterm infants. (4)(5)(6)(7) In addition, the American Academy of Pediatrics (AAP) through the "Choosing Wisely in Newborn Medicine" initiative highlighted routine use of antireflux medications in symptomatic GER in preterm infants as one of the top 5 therapies of debatable usefulness. (8)

The purpose of this review is to summarize the current literature regarding the definition, epidemiology, physiology, pathophysiology, diagnostic tools, and management of GER and GER disease (GERD) pertinent to the neonate, with emphasis on the preterm infant.

DEFINITIONS

The latest GER practice guidelines issued in 2018 by the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition define GER as a physiologic event related to the passage of gastric contents into the esophagus with or without regurgitation and vomiting. (9) GERD, on the other hand, is considered a pathologic condition that "occurs when GER leads to troublesome symptoms that affect daily functioning and/or complications." (9) Refractory GERD is a condition defined as GERD that does not respond to optimal treatment after 8 weeks. (9) Infants with GERD may show discomfort, irritability, feeding difficulties, and poor weight gain, among other symptoms, hence these infants are described as "scrawny screamers." In comparison, physiologic GER may present with frequent spit-ups or small emesis in an otherwise happy and thriving infant, which is why affected infants are commonly known as "happy spitters." Almost 20 years have passed since the first NASPGHAN practice guideline for GER was issued. The definition of GERD still remains nonspecific in children (Table 1). The subjectivity of a symptom-based definition leads to a great diagnostic challenge, especially in nonverbal infants and developmentally impaired patients in whom defining "troublesome" is a difficult task not only to hospitalists and subspecialists, but also to primary caregivers and parents. To date, no other consensus-based definition for GERD has been proposed for the pediatric population in general and infants in particular.

EPIDEMIOLOGY OF GERD IN PRETERM INFANTS

To this day, the exact incidence and prevalence of GERD in NICU infants remains uncertain. A large retrospective study reviewing data from preterm infants (22–36 weeks' gestation) from NICUs at 33 freestanding children's hospitals in the United States over a 7-year period showed 10.3% GERD diagnosis prevalence and 13-fold variation in GERD rate across hospitals. (10) Such wide diagnostic rate variation is likely because of the subjective definition of GERD and lack of consensus about diagnosis among health care professionals. Another study evaluating the use of H2RAs and PPIs in 122,002 NICU infants demonstrated that 24% of those patients received either an H2RA or PPI during their hospital stay, whereas only 11% of the entire study population were diagnosed with GERD. (11) GERD diagnosis in neonates has been associated with longer hospital stay and increased hospitalization cost of $70,000 more per infant. (10) In addition, it is very well-known that antireflux medication is commonly continued in infants after discharge from the NICU, representing a significant burden to patients and to the health care system. (4)(10)(11)

Further studies are necessary to have a better understanding of the true prevalence of GERD and its impact in infants. It is of utmost importance to formulate an objective definition using clinical, diagnostic, and/or therapeutic evidence-based findings.

TABLE 1. **NASPGHAN Definitions of GER and GERD in Children**

	2001	2009	2018
GER	Passage of gastric contents into the esophagus	Passage of gastric contents into the esophagus with or without regurgitation or vomiting	Passage of gastric contents into the esophagus with or without regurgitation or vomiting
GERD	Symptoms or complications of GER	Presence of troublesome symptoms and/or complications of persistent GER	When GER leads to troublesome symptoms that affect daily functioning and/or complications, such as esophagitis or stricture

Based on NASPGHAN and European Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines for evaluation and treatment in infants and children. GER=gastroesophageal reflux, GERD=gastroesophageal reflux disease; NASPGHAN= North American Society of Pediatric Gastroenterology, Hepatology and Nutrition.

PHYSIOLOGY OF GER IN INFANTS

The esophagus is a hollow fibromuscular tube that extends from the distal pharynx to the gastroesophageal junction (GEJ). (12) It originates from the endoderm of the foregut beginning in the fourth week of gestation and reaches full maturation beyond full-term birth in infancy. It is a complex structure composed of striated muscle in the proximal third, whereas the 2 distal thirds are composed of smooth muscle with specialized cells organized in 1 inner circular layer and 1 outer longitudinal layer. (12)

The lower esophageal sphincter (LES) is the most distal portion of the esophagus, and it has been described since the 1950s as a functional high-pressure barrier between the esophagus and stomach. (13)(14) The LES plays a key role in GER physiology. It not only allows the anterograde passage of food bolus from the esophagus to the stomach during swallowing, but also prevents the retrograde passage of gastric contents into the esophagus after a swallow is completed. The LES is primarily innervated by the parasympathetic system via the vagus nerve. At basal state, it remains "closed" in tonic contraction because of the excitatory cholinergic pathway. LES relaxation or "opening" occurs as a reflex response to swallowing, pharyngeal stimulation, esophageal distention (spontaneous or provoked), gastric distention, and abdominal strain via the inhibitory nitrergic pathway. (15) In addition to the LES, the diaphragmatic pinchcock formed by the striated muscle of the diaphragmatic crural fibers enhances the GEJ barrier, acting as an external LES. (16) In the past, LES contraction was believed not to be effective in premature infants. However, further studies demonstrated that the LES pressure in premature infants rises at or above intragastric pressure during tonic contraction, preventing GER. (17)

GER is a common phenomenon during the first year of age in preterm and term infants. Most regurgitation episodes occur during the first half of infancy. The highest prevalence reported is 67% at 4 months of age. Regurgitation markedly improves after age 6 months and the prevalence drops to 5% by 12 months of age. (18)(19)

Multiple factors may predispose infants to GER, especially during the first 4 months of age. Infants have a shorter esophagus and LES. This combination leads to smaller esophageal capacity, facilitating rapid backflow of gastric content into the esophagus. (20) Postprandial esophageal motor activity is primarily nonperistaltic in 73% of premature neonates, which may contribute to ineffective esophageal clearance of refluxate material. (21) Other factors are a small stomach size and capacity resulting in faster gastric distention and increased intragastric pressure, frequent feedings per day (average of 6–8 times per day), an exclusively liquid diet, high fluid intake per kilogram per day, and prolonged periods in the supine position. It was formerly thought that premature infants also had delayed gastric emptying; however, studies showed normal gastric emptying in premature infants. (22)(23) These unique features may contribute to the higher prevalence of GER in the preterm infant population and the increased occurrence during the first postprandial hour. (22)

Anatomic, physiologic, and developmental changes occur as infants get older, usually by 6 months of age. For instance, the total longitudinal dimension of the esophagus and LES increase, causing the LES to go from being in the intrathoracic compartment to an intraabdominal location. In addition, during this period, the stomach becomes larger, the introduction of solids begins along with longer feeding intervals, and infants spend more time in an upright position.

Studies investigating the postnatal maturational effect on esophageal peristalsis have shown greater proximal esophageal amplitude and greater peristaltic velocity with older postnatal age in preterm infants. (24) Furthermore, Pena et al evaluated the LES relaxation response at 2 different time points in preterm infants. Findings showed delayed and prolonged LES response to esophageal stimulation at younger postnatal age compared with those seen 4 to 6 weeks later in the same infants. (15) Those facts may provide an explanation for the decreased GER prevalence during the second half of infancy.

Physiologically, GER occurs secondary to transient LES relaxation (TLESR). This is the most relevant mechanism of GER in infants, as it is in adults. However, GER can also result from hypotonic LES, abdominal strain, swallowed-induced LES relaxation, among others. We now describe the most frequent mechanisms in infants.

GER Mechanisms (Fig 1)

Transient LES Relaxation. TLESR is the most common mechanism of GER in both term and preterm infants. (17)(22)(25)(26) It consists of a sudden brief drop in LES pressure at or below intragastric pressure (Fig 1A). This facilitates the retrograde passage of gastric contents into the esophagus. TLESR is an inhibitory vagovagal reflex via the nitrergic pathway that occurs spontaneously. It is not associated with swallowing and it is present in neonates from 26 weeks' gestation until adulthood. (12)(17) TLESR occurs as a physiologic mechanism that enables proximal gastric venting, hence its increased frequency in the early postprandial period. (22)(27) A study evaluating 36 preterm and term infants with and without GERD demonstrated that infants with GERD had a similar number of TLESR events compared with control infants. However, TLESR events had a higher association with acid GER events in the GERD group. (22) TLESRs and GER events are increased in infants lying in the right-side lateral position even though this position enhances gastric emptying. (26)

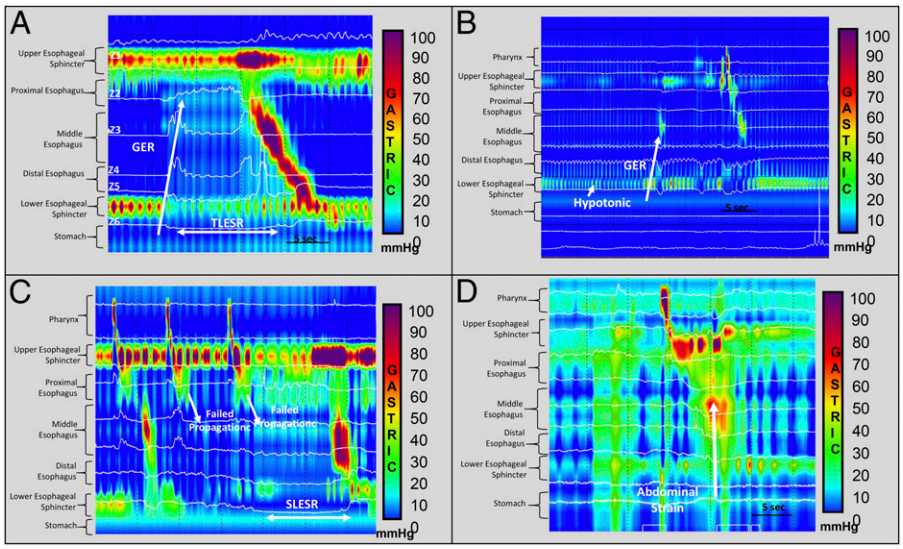

Figure 1. High-resolution impedance manometry images representing the main mechanisms of gastroesophageal reflux (GER) disease in infants. Color interpretation of the images is codified on the vertical bar on the right in each picture. Pressure ranges from 0 to 100 mm Hg represented by a "blue zone" and "purple zone," respectively. Anatomic reference of the data obtained is indicated on the left side of each picture. The white horizontal lines represent impedance. A. Transient lower esophageal sphincter (LES) relaxation (TLESR)—sudden decrease in LES pressure, not associated with pharyngeal swallow. White oblique retrograde arrow represents GER liquid episode followed by reflex complete swallow and restoration of normal LES pressure. B. Hypotonic LES—baseline low LES tone. Liquid GER event is represented by white oblique retrograde arrow. C. Swallow-associated LES relaxation (SLESR)—sudden brief LES relaxation after 2 failed propagated swallows. D. Abdominal strain—abrupt increase in abdominal pressure that leads to liquid GER episode.

Hypotonic LES. A hypotonic LES refers to consistently decreased LES tone. This prevents the creation of an effective mechanical barrier at the GEJ, thus GER is more likely to occur. (12) **(**Fig 1B) Hypotonic LES may be the result of impairment of either vagal excitatory innervation or myogenic contractile activity. A study using esophageal manometry and pH monitoring in term neonates with and without a history of birth asphyxia showed increased number and severity of acid GER events as well as lower LES tone in the asphyxia group. (28) Another study performed in children with esophagitis and a history of birth asphyxia found hypotonic LES as the main mechanism of GER. (29)

Swallow-associated LES Relaxation. Swallow-associated LES relaxation (SLESR) is LES tone relaxation that occurs as a physiologic response to swallowing. It may or may not be followed by a rebound contraction. (12) LES relaxation occurs immediately after swallowing begins and it can be present even in the setting of failed propagation (Fig 1C).

Abdominal Strain. Abdominal strain is the sudden increase in intraabdominal pressure that exceeds LES pressure, leading to an involuntary relaxation of the GEJ (Fig 1D).

PATHOPHYSIOLOGY OF GERD IN NEONATES

Healthy preterm infants exhibit a protective physiologic response during GER events. Retrograde passage of gastric contents causes esophageal body distention, eliciting 2 main physiologic reflexes: 1) esophageal secondary peristalsis that leads to refluxate bolus propulsion toward the stomach; and 2) upper esophageal sphincter contraction, which prevents refluxate from reaching the pharynx.

When the aforementioned reflexes are impaired or absent, upper esophageal sphincter relaxation reflex occurs and the refluxate reaches the pharyngeal cavity. This phenomenon could potentially trigger 2 subsequent protective reflexes: 1) the pharyngeal swallow reflex, which prompts anterograde propulsion of the refluxate bolus and airway clearance; and 2) the laryngeal chemoreflex, which is reflexive apnea and glottal closure secondary to laryngeal chemical stimulation, to prevent passage of refluxate to the lower airway. Lack or impairment of these protective reflexes may lead to the development of symptoms/complications seen in GERD.

GER RISK FACTORS IN INFANTS

Multiple risk factors contribute to the higher prevalence of GER during infancy. Prematurity is by far the main risk factor for GERD in infants. This is because of the intrinsic pathophysiologic characteristics in this population (as described earlier in the GER physiology section) and associated comorbidities. Chronic lung disease or bronchopulmonary dysplasia (BPD) is a common complication in extremely premature infants, and it has been associated with

a higher frequency of GER events. Patients with chronic lung disease experience brief increments in intraabdominal pressure secondary to labored breathing and coughing. This mechanical change leads to a higher number of TLESRs that usually last longer and have lower LES nadir pressure. (22)(30)(31)(32) Studies from our group showed greater GER events, acid clearance time, and symptom sensitivity index (SSI) in infants with BPD. (33)(34) In contrast, another study showed no significant difference in GER features between infants with and without BPD. However, higher frequency of pH-only events (refluxate of acid only up to the distal esophagus without impedance changes) and increased SSI with pH-only events were noted. (31)

Abnormal aerodigestive reflexes and esophageal dysmotility disorders, whether they present in an isolated form or secondary to other conditions such as neuropathology, could also lead to an increased frequency of GER events. A summary of the risk factors for GERD in infants is presented in Table 2.

CLINICAL MANIFESTATIONS OF GER IN INFANTS

A wide variety of nonspecific and heterogeneous signs and symptoms have been associated with GERD in preterm infants. They can be grouped into 4 categories: aerodigestive, behavioral, cardiorespiratory, and gastrointestinal (Fig 2). In the NICU setting, the most common clinical conundrums for GERD considerations are pathologic apneas of uncertain origins, acute life-threatening events, feeding difficulties, chronic lung disease, arching, and irritability. (35)(36) A study of 77 NICUs in the United Kingdom showed that 42% of clinicians diagnosed GERD based solely on clinical presentation. (37)

TABLE 2. **GERD Risk Factors in Infants**

PREMATURITY (GERD BIRTH PATH)	ANATOMIC ABNORMALITIES
Anatomic features	• Craniofacial anomalies
• Gastroesophageal junction in the intrathoracic cavity	• Airways anomalies
• Esophageal and LES decreased size	• Esophageal atresia
• Reduced stomach capacity	• Tracheoesophageal fistula
• Decreased muscle tone	• Congenital diaphragmatic hernia
Comorbidities	• Hiatal hernia
• Bronchopulmonary dysplasia	• Abdominal wall defect
• Intraventricular hemorrhage	• Malrotation
• Reflex abnormalities: Absent/decreased or exaggerated laryngeal and pharyngo-UES-LES and esophageal reflexes	• Pyloric Stenosis
• Tube feedings for prolonged time	• Duodenal atresia
• Hypoxic-ischemic injury	• Annular pancreas
Pathophysiologic Features	• Intestinal atresia or strictures
• Peristalsis – ineffective	• Brain structural abnormalities
• Airway response – exaggerated	**Other Factors**
• Transient LES Relaxation	• Feeding pattern (frequency and volume)
• Hypotonic LES	• Positioning: Supine, right lateral decubitus
	• Pharmacological therapy: caffeine
	• Metabolic disorders
	• Infection Inflammation

GERD=gastroesophageal reflux disease, LES=lower esophageal sphincter; UES=upper esophageal sphincter.

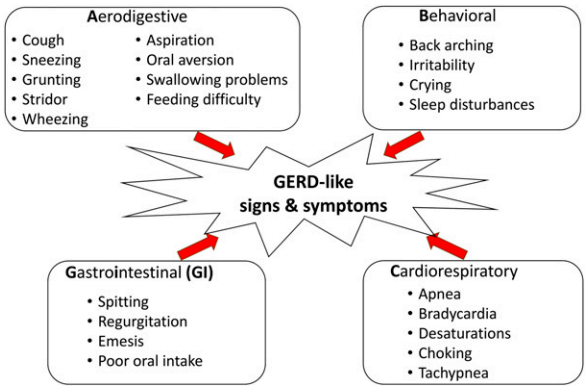

Figure 2. Gastroesophageal reflux disease (GERD)–like signs and symptoms: the A, B, C, and GI "clinical manifestations" of GERD.

GER and Apnea

For many years, apnea has been thought to be a consequence of GER in preterm infants, likely because of a higher prevalence of both conditions in the postprandial period. (38)(39) Premature infants have immature respiratory regulation and display decreased hypercapnic response, hypoxia-associated respiratory depression, and increased inhibitory respiratory reflexes (ie, laryngeal chemoreflex). (40) This makes it reasonable to believe that the presence of refluxate could subsequently lead to apnea. Clinicians have reported apnea in 70% of NICU infants as part of their diagnostic clinical criteria for GERD. (37) However, various studies failed to show temporal or causal association between GER (acid and nonacid) and apnea in premature infants. Esophageal pH-monitoring performed in 20 preterm infants during wakefulness and sleep showed no relationship between GER and apnea (defined as breathing cessation >10 seconds). (41) Another study of 71 preterm infants evaluated a total of 12,957 cardiorespiratory events (apnea, bradycardia, and desaturations) and 4,164 GER episodes using esophageal pH impedance. (42) It showed that less than 3% of all cardiorespiratory events were preceded by GER episodes. Also, GER did not increase the duration or severity of the cardiorespiratory events. (42) Interestingly, it has been reported that in premature infants, LES tone decreases concurrently with apnea events, which could lead to an increased likelihood of GER after the onset of an apneic episode. (43)

GER and Chronic Lung Disease

A causal relationship between GER and chronic lung disease remains controversial. It is presumed that lung injury occurs secondary to repeated episodes of gastric refluxate aspirating into the lungs. Several studies have tested this hypothesis. One study evaluated 27 infants with and without BPD using a pH probe in the proximal esophagus; results revealed fewer acid GER events in infants with BPD. (44) Another study evaluated 21 children with suspected recurrent pulmonary aspiration who underwent esophageal pH impedance monitoring, fiber-optic bronchoscopy, and bronchoalveolar lavage. (45) Results showed that nonacid reflux events to the proximal esophagus correlate with a diagnostic marker for pulmonary microaspiration. (45) A study performed in 59 preterm infants receiving mechanical ventilation analyzed the presence of pepsin in serial tracheal aspirates. Pepsin was found in 91% of the samples, with higher levels in infants with BPD compared to those without BPD. Furthermore, pepsin levels were significantly higher with increased BPD severity. (46) Some other studies reported that children with a history of GERD and chronic lung disease exhibited clinical improvement of symptoms after medical and/or surgical management of GERD, suggesting GERD as a potential cause of lung disease. (47)(48) In contrast, in a retrospective study evaluating a total of 629 preterm infants, 137 infants underwent an evaluation for GERD because of suspected clinical presentation and showed no difference in the incidence of GERD in infants with and without BPD. (49)

GER and Failure to Thrive

GER is commonly diagnosed in infants with failure to thrive. So far, no causal link has been proven between these 2 conditions. A study comparing NICU infants with and without clinically significant GER showed no differences between groups in average weight gain, caloric intake, or increments in head circumference and length. (49) Nonetheless, a longer time to attain full oral feedings and longer hospital stay were found in infants with clinically significant GERD. (50)

DIAGNOSTIC APPROACH FOR GERD EVALUATION IN INFANTS

History and Physical Examination

A thorough history and physical examination are key to distinguishing suspected GERD from physiologic GER. Potential GERD complications can be identified, including poor weight gain, feeding difficulties and most importantly, alarm features associated with other serious or underlying conditions such as pyloric stenosis, malrotation, and ear-nose-throat disorders, which need further investigation and management. (9) Moreover, a detailed feeding and dietary history is an extremely valuable tool for clinicians during an evaluation for GERD (Table 3). This approach provides

TABLE 3. **Detailed Feeding and Dietary History**

Feeding source: Quantity and quality
• Type of milk: breast milk vs formula
• Quality of milk supply when breastfeeding
• Additives to the feedings
• Volume per feeding
• Daily total fluid intake
Feeding technique: Methods of mixing the formula
• Feeding position (direct breastfeeding and/or bottle feeding)
• Type of bottle and nipple used
• Length of feeding period
• Interval between feedings
Feeding-related symptoms
• Pattern of regurgitation, spitting, vomiting
• Temporal relationship between concerning symptoms and feedings (before, during, or after)
Family history
• History of food allergies

unique information about feeding characteristics and associated symptoms. (9)

Ancillary Tests

Various tests have been used throughout the years to evaluate for GERD in infants, but a diagnostic gold standard is yet to be determined. Current ancillary tests provide diverse information from either anatomic abnormality, esophageal motility disorders, presence of GER and its characteristics, or ruling out other non-GERD pathologies, but not all together. Thus, clinicians should wisely select test(s) based on a patient's history and physical examination findings and targeted to what is being sought in each individual case. As of now, a patient's response to therapy and/or outcome cannot be anticipated by a single test.

Radiographic Fluoroscopy Studies

Upper Gastrointestinal Series. This test is helpful in assessing infants for conditions that could simulate or predispose them to GERD and infants in whom regurgitation or frequent emesis is the main symptom. (9) It evaluates for structural abnormalities such as esophageal strictures or narrowing, hiatal hernia, malrotation, congenital upper gastrointestinal anomalies, pyloric stenosis, duodenal web, scars/strictures, etc. Ideally, barium contrast should be given to infants by mouth rather than through a feeding tube to allow for a full esophageal assessment. Although this test can capture GER episodes momentarily, it does not provide information regarding frequency, severity, or chemical characteristics (acid vs nonacid) of events. Thus, an upper gastrointestinal series is considered a nonspecific test for the diagnosis of GERD.

Video Fluoroscopic Swallow Study. Even though this study does not evaluate for GERD, it is considered useful in infants with suspected aspiration whose symptoms could be similar to those reported in GERD. It provides clinicians with structural and functional (suck, swallowing) information. (41)

Esophagogastroduodenoscopy with Biopsy

Esophagogastroduodenoscopy with biopsy permits direct visual examination of the esophageal mucosa and histopathologic evaluation. (51)(52) Some endoscopic findings in patients with GERD are esophagitis, erosions, exudates, ulcers, strictures, hiatus hernia, and areas of suspected metaplasia. An esophageal mucosal biopsy plays a critical role in excluding non-GERD conditions such as eosinophilic esophagitis, infectious esophagitis, or other causes of esophageal inflammation. This technique requires experienced operators and procedural sedation, and its sensitivity could be affected by acid suppression therapy in patients.

Scintigraphy

Gastric scintigraphy is conventionally used in the evaluation of gastric emptying. Guidelines for its use in GER evaluation in children exist, however, lack of standardization limits the clinical application of this test. (53)

Esophageal pH Monitoring

Continuous esophageal pH monitoring, also known as esophageal pH-metry or pH probe monitoring, was developed in the 1990s. It was the leading diagnostic technique for GERD for many years. This test consists of transnasal passage of a microelectrode containing a pH sensor on its distal end into the esophagus and it may remain in place for up to 24 hours. Importantly, the accuracy of this test lies in the correct location of the pH sensor (acid), which should be just above the upper border of the LES. The Strobel formula is used for a more accurate catheter placement by correlating the patient's height and esophageal length. (54) Adequate placement position should be confirmed radiographically. Even so, under- or overestimation of acid GER secondary to pH sensor misplacement is not uncommon, mostly in the smallest infants.

Esophageal pH monitoring detects acid GER in the distal esophagus. It provides information about the number of acid reflux episodes during the study period, reflux index (defined as the percentage of time with a pH <4 divided by the total time of the study), mean duration of the episodes, and duration of the longest acid GER episode. For the pediatric population, the normal upper limit of the reflux index is up to 12% in the first year of age and up to 6% thereafter. It is important to know that the reflux index calculation does not include feeding periods. Thus, the longer the feeding time in a patient, the fewer data that are available for analysis. This issue becomes more relevant in infants with prolonged feeding times through enteral tubes. Another limitation of pH monitoring is related to frequent feedings in infants and its buffering effect on gastric acidity, which could decrease the likelihood of recognizing acid GER episodes.

Multichannel Intraluminal pH Impedance Monitoring

Multichannel intraluminal pH impedance monitoring (pH-MII) is a novel diagnostic tool that combines esophageal pH monitoring with intraluminal esophageal impedance. It uses a catheter with multiple intraluminal impedance sensors symmetrically distributed at different esophageal levels, and 1 pH sensor (located on its distal end). Impedance measures the opposition in the electrical circuit to the electrical flow of the esophageal content (liquid, gas, or both) when it passes through 2 electrodes. The pH-MII test provides valuable information that can be used to classify GER based on 4 categories (55)(56):

- Chemical: Acid or nonacid GER
- Temporal: Duration of the GER episode
- Physical: Liquid, gas, or mixed refluxate
- Spatial: Height of the refluxate (distal, mid-, or proximal esophagus) and bolus direction (anterograde or retrograde)

These features increase pH-MII sensitivity for GER identification compared with pH monitoring only (Fig 3), particularly in patients in whom nonacid reflux is more common. (9) Another advantage of this technique is the ability to correlate symptoms with GER episodes. Three symptom correlation indices are used: 1) symptom index, which is the percentage of symptoms that are associated with GER events; 2) SSI, which is the percentage of GER events that are associated with symptoms; and 3) symptom-associated probability, which is the probability that there is an association between reflux and symptoms. Symptom correlation is considered to be positive if symptoms occur within 120 seconds of reflux onset. Nevertheless, it has been shown that parents and/or caregivers fail to report more than 50% of symptoms during the study. This directly affects the reliability of the symptom index, SSI, and symptom-associated probability values. (9)

It is known that impedance methods have been used to assess nonerosive reflux disease in adults, specifically correlating with baseline impedance values. (57) Esophageal mucosal inflammation is linked with low distal baseline impedance values (<900Ω) and higher values (>2,000Ω) are indicative of mucosal integrity. (57) A study performed by our group using pH-MII in 198 preterm NICU infants compared pH impedance and symptom characteristics based on baseline impedance values. (57) Results showed that distal baseline impedance less than 900Ω was associated with prolonged acid exposure, delayed clearance time, and a greater aerodigestive symptom prevalence in infants, likely because of esophageal mucosal inflammation. (57) pH-MII has provided meaningful information for a better understanding of GERD in infants. Nevertheless, the technique is time-consuming and expensive, and requires a highly specialized team for data analysis and interpretation. Therefore, this procedure is not available in many centers. Another consideration is the sparse reference ranges in preterm infants because of lack of control patients (similar to pH monitoring).

Esophageal Manometry/Motility Studies

Esophageal manometry evaluates esophageal motility characteristics using pressure sensors located along a manometry catheter, which converts the intraluminal pressure signal into graphic data displayed on a screen in real time. It measures the quantity and quality of contractile events in the esophagus and its 2 sphincters during basal and/or feeding states. High-resolution manometry is the gold standard for the diagnosis of esophageal motility disorders. This technique does not measure GER characteristics, nonetheless it is helpful in determining the pathophysiologic GERD mechanism(s), that is, TLESRs, hypotonic LES, and SLESRs (Fig 1). In adults, it is frequently used to guide the precise positioning of pH or pH impedance sensors. (20)

PPI Test

The PPI test consists of a short empirical PPI trial (usually 2 weeks) in patients with suspected GERD to evaluate their clinical response. It is often used in infants with a high clinical suspicion of GERD in facilities without access to other diagnostic tests or in infants with a clinical condition that does not allow for more invasive testing. This is a common practice in adults, but it has not been validated for infants. A PPI trial should be avoided, if possible, in the high-risk vulnerable preterm population, given the potential association with serious complications.

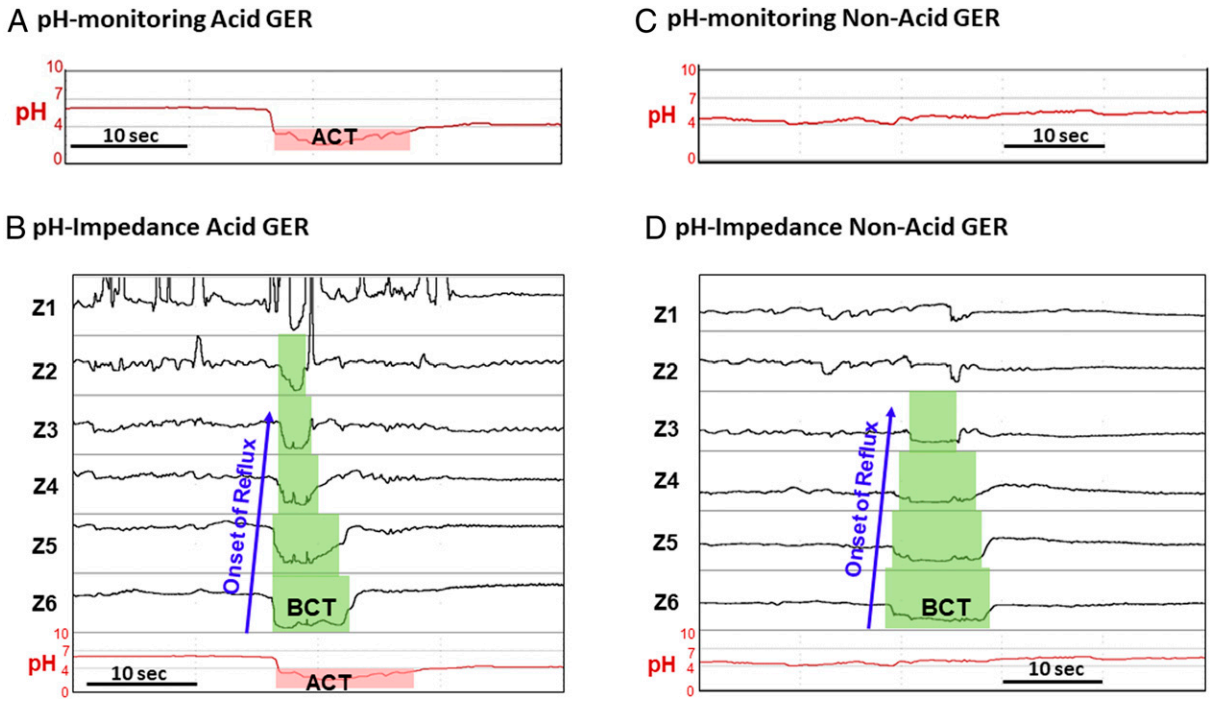

Figure 3. pH monitoring versus pH impedance graphical representation in acid and nonacid gastroesophageal reflux (GER) events. A. pH monitoring represents an acid GER event (pH <4). Duration of the episode (acid clearance time) is highlighted. B. pH impedance representation of the same acid GER event. This provides detailed information in 4 categories: chemical (acid), physical (liquid refluxate), temporal (duration of acid clearance time and bolus clearance time), and spatial (height of refluxate up to Z2). C. pH monitoring representation of a nonacid GER event (pH >4). Nonacid GER episodes are not detected with pH monitoring only. D. pH impedance representation of nonacid GER event. Additional information: liquid refluxate, bolus clearance time, and height of refluxate (Z3). ACT=acid clearance time, BCT=bolus clearance time.

MANAGEMENT OF GERD IN INFANTS

Pharmacologic and nonpharmacologic therapies are widely used in the inpatient and outpatient settings for GERD management in preterm infants. However, scientific data do not support routine use of these interventions. No standard therapy exists to date for GERD management, and therapy should be focused on addressing individual patient needs when benefits outweigh risks.

Nonpharmacologic Therapy

Body Positioning. Body positioning is a widely used conventional approach in the treatment of infants with suspected GERD in the hospital setting. (45) Interestingly, some traditional methods (eg, head elevation) have been proven unsuccessful in decreasing acid GER episodes in infants. Car seat positioning increases acid reflux frequency. (58) A study in asymptomatic preterm infants using pH-MII evaluated the effects of body positioning on GER events (acid and nonacid). (59) Prone and left lateral position resulted in lower acid and nonacid reflux indexes. In addition, studies using esophageal manometry techniques showed increased number of TLESRs and GER episodes in infants lying in the right-side lateral position. (26) In the monitored hospital setting, body positioning could be a useful intervention in infants with GERD. However, because of concerns of sudden infant death syndrome, the AAP and NASPGHAN recommend that infants with GER should be placed in a supine position during sleep. (10)

Feeding Interventions

Avoid Overfeeding. Postprandial increased intragastric pressure could result in GER in infants; hence, frequent and smaller feedings may be beneficial in decreasing GER events in this population. (60) Our group studied the effect of various feeding strategies on GER in a total of 35 infants with feeding difficulties. (60) We found that longer feeding duration and slower flow rate decreased the total number of GER episodes whereas feeding type (breast milk or formula) and caloric content had no effect on GER features. A frequent practice in NICU infants with either feeding intolerance or GERD concerns is to change enteral tube feedings from a bolus to continuous approach, which seems to help with GER symptoms. One study showed that more frequent feedings in infants with GERD positively correlated with a decreased reflux index. (26) Thus, modifying feeding volumes and frequency according to age and weight while maintaining an appropriate total daily volume intake to provide adequate nutrition is suggested in infants with GERD.

Elimination of Cow Milk Protein. Cow milk protein allergy (CMPA) affects 2% to 6% of children, particularly infants. (9) CMPA and GERD are difficult conditions to distinguish during infancy, because both may present with frequent regurgitation/emesis, failure to thrive, and irritability. (9) However, CMPA is usually associated with a strong family history of atopy or allergy. Also, infants with CMPA exhibit clinical improvement in symptoms within 1 to 2 weeks after elimination of cow milk allergen. In breastfed infants, this is accomplished by a dairy-free maternal diet whereas formula-fed infants should be fed hydrolyzed protein formula. Compared with regular formulas, hypoallergenic formulas have been shown to improve gastric emptying. (9) One study demonstrated that infants extensively fed hydrolyzed protein formula had decreased GER events and reflux index in pH monitoring compared with infants fed regular preterm formula, whereas no difference in GER characteristics was noted on impedance. (61) In addition, another study evaluating the impact of extensively hydrolyzed protein formula in preterm infants with GERD showed fewer total number of GER events without any difference in behavioral symptoms. (17) It is challenging to determine if the hypoallergenic formula effect in GER is independent of underlying atopic disease in infants given their similar clinical presentation. NASPGHAN recommends a trial with hypoallergenic formula for a minimum of 2 weeks in infants without response to other nonpharmacologic GERD interventions. (9)

Thickened Feeding. Formula thickeners are commonly used for GERD treatment in infants. They have been shown to decrease visible regurgitation. (62) However, thickened formula does not improve acid GER and its impact in nonregurgitation symptoms is unclear. (62) Thickeners are also used in infants with sucking and/or swallowing disorders and in those with concerns for aspiration. In such situations, thickened feedings decrease the flow rate, giving infants more time for suck-swallow-breathing coordination. Nonetheless, occasionally its use may increase the infant's effort during feedings, affecting formula extraction with a subsequent decrease in oral intake. Thickeners have also been associated with other complications such as necrotizing enterocolitis, hypernatremia, malabsorption, constipation, and delayed gastric transit. The AAP Committee on Nutrition recommends that feedings should not exceed 450 mOsm/kg in healthy infants. Nonetheless, it is known that the addition of thickeners to preterm formulas can exceed the established safety threshold. (63) Given the increased risk for necrotizing enterocolitis, the AAP discourages thickener use in preterm infants until they reach at least 44 weeks' postmenstrual age. (64) Our group studied the effects of additives for reflux or dysphagia therapy on the osmolality of preterm formula. (63) We found an increase in osmolality by 30 mOsm/kg for every 0.5 teaspoon per ounce of thickener (oatmeal or rice). Final osmolality exceeded the AAP recommendations in many cases. Hyperosmolar feedings lead to an increased total caloric intake, feeding intolerance, and delayed gastric transit. The latter can lead to malabsorption, bacterial overgrowth, and diarrhea, which increases the risk for intestinal mucosal inflammation. (63)

Pharmacologic Therapy

Prokinetics. Prokinetics, also known as promotility agents, include cisapride, domperidone, metoclopramide, and erythromycin. These agents improve gastrointestinal motility and enhance anterograde bolus transit; thus, their use in GER management has been reported. Domperidone and metoclopramide are dopamine receptor antagonists that ease gastric emptying. They are both associated with neurologic adverse effects such extrapyramidal symptoms, and metoclopramide is known to have a narrow therapeutic window. Cisapride is a serotonin receptor agonist, which has been removed from the market in many countries around the world because of its side effect of long QT syndrome and associated cardiac arrhythmias. Erythromycin is a macrolide antibiotic and is a gastrointestinal motilin agonist. It exerts its effect mainly at the gastroduodenal level, leading to enhanced gastric emptying. Erythromycin is strongly associated with infantile hypertrophic pyloric stenosis, especially if used early in the neonatal period (first 2 weeks after birth). (65) Use of prokinetics has not demonstrated improvement in GERD symptoms in preterm infants. (9) Hence, their use is not routinely recommended for GERD management in infants.

Histamine 2 Receptor Antagonists. H2RA medications affect histamine-induced gastric acid production by selective blockage of H2 receptors of gastric parietal cells. Nevertheless, long-term use of ranitidine is associated with tachyphylaxis, which diminishes its reported beneficial effects. H2RA therapy is linked to serious adverse events in preterm infants. One study showed a higher incidence of necrotizing enterocolitis in very low-birthweight (VLBW) infants exposed to H2RAs (ranitidine, famotidine, cimetidine) therapy. (5) Moreover, a prospective study evaluating VLBW infants with and without exposure to ranitidine treatment demonstrated an increased risk for necrotizing enterocolitis, sepsis, pneumonia, and death in the exposed group. (6) Recently, the US Food and Drug Administration called for all ranitidine products to be pulled off the market because of an ongoing investigation evaluating the presence of a probable human carcinogen (N-nitrosodimethylamine). (66)

Proton Pump Inhibitors. PPIs are strong and long-lasting blockers of the gastric proton pump in the parietal cells. A double-blind placebo-controlled trial in irritable infants (3–12 months of age) showed a lower reflux index in the omeprazole-treated group but no difference in irritability. (67) A smaller study in preterm infants demonstrated that omeprazole therapy in infants led to improvement in esophageal acid exposure and number of GER events but no changes in clinical manifestations were noted. (68) Continuous acid gastric production is a protective gastrointestinal mechanism against infections. It is significantly altered by the profound blockage of PPIs. This could explain its association with adverse outcomes such as bacterial overgrowth, necrotizing enterocolitis, and upper and lower respiratory infections in infants and children. (69) Likely for this reason, the Food and Drug Administration advises against PPI use in the treatment of GERD-like symptoms in healthy infants with no evidence of acid-induced disease. (51)(70)

Surgical Therapy

Surgical management (partial or complete fundoplication) is an extreme step for infants with GERD. It must be considered after careful evaluation in infants with refractory GERD to medical management (non-pharmacologic and pharmacologic) and with appropriate parental consent and understanding.

RECENT ADVANCES TO ADDRESS CONTROVERSIES IN GERD PATHOPHYSIOLOGY AND MANAGEMENT

Randomized Clinical Trial on GERD Diagnosis and Management in Neonates: Clinical Outcomes

In NICU infants, GERD is frequently managed in a stepwise manner of conservative, pharmacologic, and surgical approaches. Conservative GERD therapies include feeding modifications such as restricted feeding volumes and slower feeding times, in addition to positional changes, while common pharmacologic therapies include acid suppression. Little is known about which approaches are truly effective in managing GERD or whether combinations of these approaches may be beneficial. In a recent randomized clinical trial evaluating a bundled GERD management approach (conservative and pharmacologic) versus a pharmacologic approach alone, (71) the bundled approach had no impact on improving clinical outcomes (increase in oral feeding and/or decrease in symptom burden as measured with the Infant Gastroesophageal Reflux Questionnaire).

Pharyngoesophageal and Cardiorespiratory Event Mechanisms Caused by Esophageal Provocation

Cardiorespiratory events during feedings are a frequent concern in NICU infants, often prolonging hospital discharge. Feeding is a complex process involving multiple reflexes for safe feeding. It often improves with maturation and can be tested using adaptive techniques. (72) Swallowing reflexes are functional in preterm infants with a history of bradycardia; however, when bradycardia events do actually occur, airway swallowing rhythms become dysfunctional and worsen with increasing bradycardia severity. (73) Specifically, during bradycardia events, respiratory rhythm disturbances are prolonged, pharyngeal activity is increased, esophageal inhibition and motor activity are increased, and LES relaxation is prolonged. Therefore, cardiorespiratory events should target swallowing dysfunction rather than GER-related mechanisms, because they are rarely caused by GER events. (74)

GERD Phenotypes Classified Based on pH Impedance Metrics and Symptoms

In NICU infants with aerodigestive symptoms and feeding difficulties, diagnostic approaches and mechanisms are unclear. There is no established gold standard for understanding the basis of symptoms of GERD; however, GERD diagnosis, acid-suppressive therapies, gastrostomy, and/or fundoplication remain widely prevalent.

Symptoms associated with GERD may result from esophageal sensitivity to acid, bolus volumes, both acid and bolus volumes, or another cause. Our group examined esophageal sensitivity phenotypes to better understand how therapeutic strategies can be developed to target the mechanistic basis of symptoms. (55) Phenotypes of GERD were determined based on the strength of reflux evidence on pH impedance monitoring. We found that nearly 279 infants at 42 weeks' postmenstrual age referred for possible GERD experienced symptoms of arching/irritability and coughing episodes. Isolated acid sensitivity only occurred in 10% of the study group, which may explain the poor response to acid-suppressive therapy, because symptoms were predominantly linked with bolus refluxate (GER events). Bolus GER events were defined as retrograde movement of bolus as evidenced by 50% drop in impedance. Nearly 67% had sensitivity to acid and/or bolus components (liquid or mixed) of GER. The magnitude of esophageal acid exposure and the bolus ascent or the composition of the bolus may provide a pathophysiologic explanation of the symptoms. The number of coughs, sneezes, and emesis episodes were higher in those with sensitivity to bolus component. When evaluating infants for GERD, those with a higher magnitude of symptoms for cough, sneezing, and/or emesis need further investigation. Diagnostic and therapeutic strategies for GERD in infants should be individualized and tested objectively. (55)

CONCLUSIONS

GER is a physiologic condition that affects many infants around the world. It clinically improves over time especially after 6 months of age. Prematurity constitutes the main risk factor for GER and GERD development in infants because of its associated anatomic and pathophysiologic features. Clinical presentation of GER is nonspecific, making the diagnosis of GERD a challenging task. Various diagnostic tools have been implemented over the years; however, no single test can provide definitive diagnosis in preterm infants. The pH impedance testing offers promise in examining the type of events, pathophysiologic classification, symptom attribution, detection of inflammation, severity of the condition, and/or response to therapies. Feeding volume restrictions and positional changes during feedings offer no advantage in managing objectively determined esophageal acid exposure. Aerodigestive symptoms are likely to be the result of activation of reflexes upon esophageal or pharyngeal provocation. Therapy should be focused on nonpharmacologic interventions, and pharmacologic therapy should be reserved for those infants with objectively proven GERD in whom benefits outweigh risks. Further randomized controlled trials that will include a placebo are needed among those with objectively determined GERD.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

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

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