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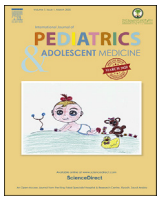

The enigma of gastroesophageal reflux disease among convalescing infants in the NICU: It is time to rethink

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ABSTRACT

Gastroesophageal reflux (GER) can be a normal physiological process, or can be bothersome, when aerodigestive consequences are associated; the latter is often interpreted as GER disease (GERD). However, the distinction between these two entities remains an enigma among infants surviving after neonatal intensive care (NICU) care. Symptoms related to GERD are heterogeneous, and are often managed with changes in diet, feeding methods, and acid suppressive therapy. However, none of these approaches have been well-tested in neonates; hence practice variation is very high world-wide. In this paper, we explain the variation in diagnosis, pathophysiology of the clinical presentation, and highlight approaches to diagnosis and management.

1. Introduction

The global prevalence of GERD in infants is not known and can be variable based on the characteristics of patients, parents, providers, prescribers and prevailing pharmaceutical policies. Hence, the use of tests and therapies can be variable, as well as the consequences in different geographic regions. The lack of uniform care and estimates for infant-GERD diagnosis is largely due to variable definitions, patient heterogeneity and lack of diagnostic criteria to monitor regression or amelioration. Most published studies are based on retrospective observational in origin and high-quality randomized control trials aimed to achieve accuracy with diagnosis and therapies are lacking in infants convalescing in the neonatal intensive care unit (NICU).

Position guidelines [1] and mechanistic studies [2,3] exist for readers to examine the reported condition in detail. In this article, we have alluded the salient aspects of GERD with reference to the convalescing infant in the NICU, although our review has relevance to other pediatric populations as well. Our goals in this article were to 1) clarify definitions and highlight the global prevalence as well as prevailing practices, 2) explain the physiology-pathophysiology of symptoms and GERD diagnosis, 3) explain approaches to diagnosis of GERD, and 4) discuss non-pharmacological approaches and pharmacological approaches, along with their consequences.

1.1. Definition and global prevalence of GERD in infants

Gastroesophageal reflux (GER) involves movement of gastric contents into esophagus and pharynx, and is a common physiologic process in infants, which often resolves with growth and maturation [4]. Regurgitation is a common presentation that occurs daily in 70% of healthy infants and often resolves with maturation by 12–14 months age and changes over childhood [5,6]. When GER events become bothersome if accompanied by other symptoms such as failure to thrive, severe arching and irritability and poor oral feeding or with signs of esophagitis or hematemesis, it is considered as GER disease (GERD) [1,7,8]. Unfortunately, the distinction between GER and GERD definitions have been used rather interchangeably with the consequence of treating many infants in whom the condition is simply physiologic and with time, resolution may happen. Therefore, there is a lack of clarity with true clinical

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Abbreviations

GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
LES	lower esophageal sphincter
UES	upper esophageal sphincter
NICU	neonatal intensive care unit

symptoms and therapeutic targets, and physiological and prognostic biomarkers; hence practice variation is very high [9,10]. Scalable accurate methods applicable to the infant with rapidly changing maturational physiology are desperately needed to overcome practice variation.

As a result of uncertainty with the diagnosis of GERD or of its accurate detection, the exact true prevalence is unclear. An estimated GERD diagnosis rates across US NICUs average 10–22% varying widely from 2 to 88% and costing approximately an additional $70,000 US per patient along with an additional month of hospitalization [9,11]. For example, globally, symptom-based prevalence of GERD ranged from an average estimation of: 10.3%–40% in USA [9,12], 22% in Australia [10] and 23.1% in Italy [6]. The exact burden and prevalence from other countries is lacking; understandably so, as the definition remains an enigma in the nonverbal patient. Importantly, it is to be noted that the global variation in GERD diagnosis may be related to parental tolerance of symptoms, accessibility of health care provider, heterogeneity of comorbidities, and changing maturational neuropathology and aerodigestive disease patterns in convalescing infants after ICU care. Regardless, there is a growing concern that GERD is over-diagnosed and over-treated in infants [13]. In fact, the use of acid-suppressive medications in presumed GERD is unacceptably high and has its own consequences in short-term and long-term [11], and a diagnostic label of GERD increases the risk for medication use [14].

1.2. Physiology and pathophysiology of gastro-esophageal junction (GEJ) and basis for symptoms

Excellent articles exist on this topic that are pertinent to the NICU infant [15,16]. The length of foregut is dependent on the size of the infant, and clearly it is smaller in the premature-born than the full-term born neonate, while the feeding volumes are greater per kg per day in the former [17]. With that said, development of the foregut is a process of continuum during infancy, and most symptoms get resolved by later infancy [4,18]. The distal esophagus and lower esophageal sphincter (LES) are composed of smooth muscles comprising of inner layer of circular muscle and an outer layer of longitudinal muscle with myenteric plexus situated in between these two layers. This forms the essential contractile apparatus whose function is to protect the esophagus against any proximal spread of the gastric contents. Stomach has higher and variable intraluminal pressure than baseline intra-esophageal pressure. Baseline intra-esophageal pressure varies proportionately with intrathoracic pressures generated during breathing. Despite the pressure gradient between higher pressure in the stomach cavity and lower pressure in the esophagus, the gastric contents do not move up into esophagus. This is due to high pressure zone at gastroesophageal junction. This high-pressure zone is constituted by LES, diaphragmatic crura primarily and supported by smooth muscle fibers of greater curvature of stomach. LES is made up of highly specialized smooth muscle with unique mechano-electrical- neurotransmitter properties which have unique innervation within multiple deep muscle layers. In response to pharyngeal stimulus, esophageal distention or gastric fundal distention, the GEJ relaxes. Transit of food material across GEJ requires relaxation of high-pressure zone. Other feeding behaviors like swallowing, vomiting, eructation, reflux and esophageal distension also require relaxation of LES which involves neural network of afferents to nucleus solitaries in medulla and efferent from dorsal vagal nucleus and nucleus ambiguous through vagus nerve to mediate esophageal peristalsis. It is likely that bolus transit through GEJ is most likely to occur during simultaneous relaxation of LES and inhibition of crural diaphragm and also to some extent modulated by pressure gradient across stomach and esophagus [19–21]. Importantly, transient relaxation of LES is the main mechanism for the causation of GER [22–24].

The above physiological considerations are best described in the Fig. 1 and Fig. 2. Data from pharyngeal-esophageal motility studies reveal that transient relaxation of LES is the main reason for the GER and that the physical-chemical nature of this material or of the spatial-temporal spread of this material proximally can trigger a cascade of reflex events that can result in symptoms. In provocative manometry studies, it was revealed that infants' acid reflux severity grade has no relationship with symptom generation and that symptoms alone should not be a diagnostic criterion for GERD diagnosis and or prescription for medical or surgical treatment strategies [25].

1.3. Current symptom-based practices to diagnose and manage GERD in infants

Regurgitation can occur as a physiologic phenomenon in the neonate with 2–3 episodes of events per hour [26]. The natural history is that with infant growth and maturation, the symptoms purported to be due to regurgitation or GER resolve and by 6–12 months, these are non-consequential in most cases [4,18]. A parent/provider perception determined 12-symptom based domains have been used to diagnose GERD in infants; this was the Infant-GER-

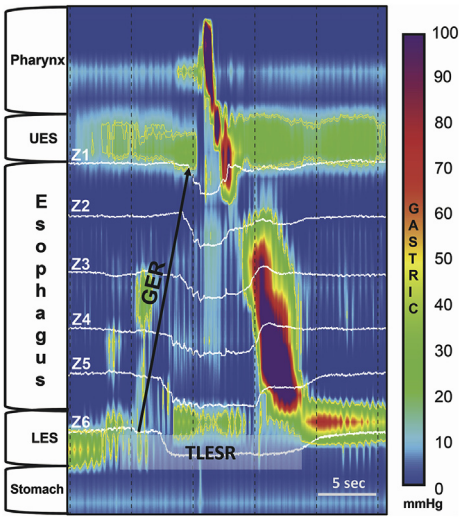

Fig. 1. *Important Causal and Protective Mechanisms for gastroesophageal reflux.* Depicted is high resolution impedance manometry with white lines representing impedance (a measurement method to detect bolus direction of propagation) and colored plots representing esophago-pressure topography (a measurement method to detect swallowing activity with low pressures in blue and high pressures in purple). The most common mechanism of GER events in infants includes transient LES relaxation (TLESR) characterized by spontaneous prolonged relaxation (>10 s) with retrograde bolus. The retrograde bolus may trigger peristaltic reflexes which facilitates clearance, and/or symptoms. TLESR is the primary mechanism of GER in infants. Note later onset peristaltic sequences that facilitate clearance.

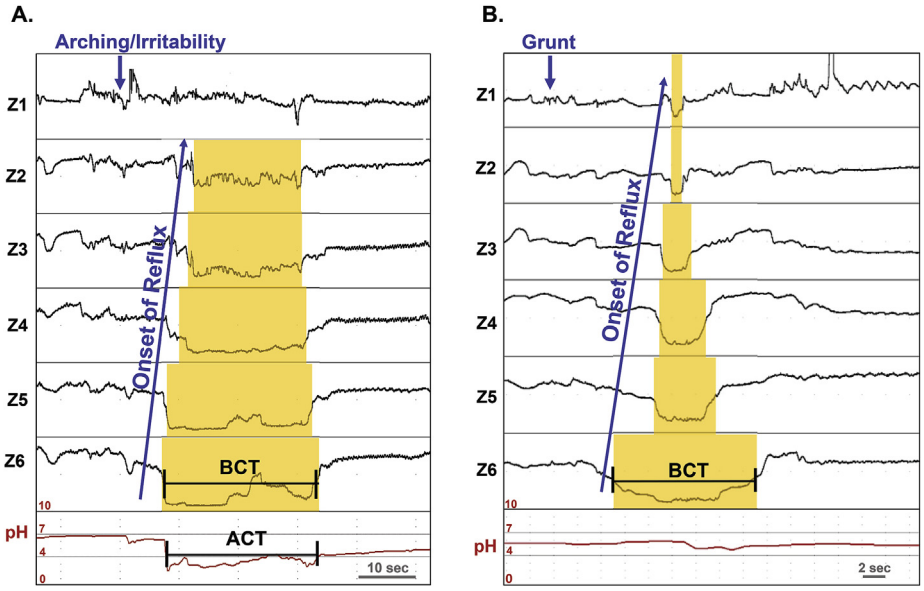

Fig. 2. Characterization of GER events during pH-impedance. 24-hr pH-impedance characterizes physical-chemical (liquid/gas/mixed, acid/non-acid) and spatial-temporal (height, clearance times).
GER characteristics and symptom correlation. Potential examples are: A) liquid acid characterized by retrograde drop in impedance and pH drop below 4. Note this is not full-column GER (does not reach Z1). Bolus clearance time (BCT) determines bolus contact and clearance efficiency. B) Gas non-acid characterized by rapid rise in impedance reaching the most proximal impedance channel (Z1) and pH > 4. Crying is associated with this GER event. C) Mixed acid characterized by liquid and gas components with pH < 4. Acid clearance time (ACT) measures esophageal acid contact time. As numerous iterations are possible, it is important to discern the true cause of symptoms for effective diagnosis and therapies.

Questionnaire-Revised score which was validated for use in infants [8,18], however the validity of which in convalescing NICU infants is yet to be proven. In fact, the Rome criteria considered to evaluate the prevalence of regurgitation in healthy infant at checkups visit to differentiate clinically meaningful change from clinically non-significant change by choosing the IGERQR score [6]. The scores in NICU infants run the risk of provider bias as the same providers are not always present to score. Importantly, owing to the heterogeneity of disease in the NICU infant, the combination of developing maturational-neurological-aerodigestive-and gastrointestinal symptoms can all be erroneously attributed to GERD symptoms or signs, and thus symptom-based scores alone are less reliable.

1.4. Evidence-guided approach to diagnosis and management of GERD in infants [3,25,27–29]

Majority of healthy preterm and full-term infants regurgitate, and continue to feed, gain weight and do not have worsening respiratory illness. Parental and allied-health care provider reassurance, growth and dietary evaluation and counselling, and follow up is all that is required. Therapeutic interventions should be considered if complications ensue in the presence of GER. The purpose of diagnostic testing is to determine whether GER is contributing to symptoms and disease state and to help with predicting treatment success. Diagnostic approach and therapeutic intervention should be limited to high-risk infants. Various testing modalities have been used to evaluate GERD and unfortunately, no single test provides a definite diagnosis.

Risk factors for GERD in the NICU setting: Infants at-risk may include those born with congenital craniofacial and upper gastrointestinal anomalies, infants with growth failure, perinatal neurological illness, airway-, pulmonary- and digestive pathologies. Such infants require careful evaluation. GERD may be the contributing factor and needs to be ruled out in those high-risk infants who have recurrent vomiting or regurgitation, excessive crying and irritability, difficulty feeding, worsening pulmonary disease and failure to thrive. Persistence of troublesome symptoms in presence of chronic GER constitutes GERD. These symptoms may include excessive regurgitation, recurrent aspiration leading to airway hyperreactivity, and other pulmonary complications, neurobehavioral manifestations such as excessive arching, irritability and Sandifer syndrome. Excessive regurgitation can lead to persistent stimulation of upper aerodigestive tract leading to cough, sneezing and cardio-respiratory changes like bradycardia and desaturations. Another important clue to GER may be symptom of dysphagia. Lack of swallowing can cause nasal regurgitation, hoarse cry, choking and stridor if there is anterograde aspiration during swallowing of a bolus.

Survey for anomalies in infants-at risk for GERD: It is important to rule out foregut malformations before instituting functional studies. Upper Gastrointestinal fluoroscopy contrast study is recommended whenever anatomical malformation of foregut is suspected. Additional fluoroscopic studies like video fluoroscopic swallow study and esophageal fluoroscopy are also used to evaluate sucking and swallowing function along with anatomical defects. It is to be noted that radiological studies are not diagnostic for GERD, but rather provide clues to structural abnormalities if any. Specific to those include upper esophageal sphincter and lower esophageal sphincter abnormalities (achalasia), hiatal hernia, diaphragmatic defects, trachea-esophageal fistula, pyloric stenosis, gastroparesis, gastroschisis and omphalocele, malrotation, duodenal and intestinal webs, intestinal duplications, and esophageal and intestinal strictures.

Pathophysiological mechanism behind GERD and the role of pH-Impedance studies: are based on physical (solid, liquid, gas or mixed) and chemical (acid, weakly acid, nonacid, alkaline) compositions of refluxate, milk constituent variability and proximal esophageal extent. Concurrent pH monitoring with multichannel intraluminal impedance studies is currently the gold standard to

diagnose acid GERD. An esophageal study provides frequency of reflux in 24-h period, reflux index or the percentage of the total duration of testing that the esophageal pH remains less than 4, mean duration of each reflux episode, duration of longest episode. Additional impedance technology evaluates bolus transit in esophagus and proximal extent of bolus. Combined pH and impedance testing allow us to detect acid, weakly acid or alkaline reflux and association of symptoms with no time delay. It is important to recognize that normal values for preterm infants have not been established. NASPGHAN guidelines recommend treating an acid reflux index of 7% [30]. Other researchers recommend treating an acid reflux index of 10% [31]. Evaluation of GERD with sleep related events are investigated with concurrent pH- impedance and polysomnogram studies.

1.5. Treatment strategies for GERD in the NICU setting

The therapy depends on the specific cause and correction of contributing factor by understanding the underlying pathophysiology. The above mentioned-diagnostic approaches will give us clues to pursuing expectant surveillance, medical, or surgical approaches. Sometimes simple observation of natural history of GER is all that is necessary as GER or GERD like condition can get better with conservative approaches. A holistic approach is proposed to ensure better growth and maturation so that GERD causal and ameliorating factors will improve over time.

Non-pharmacologic therapies: It is important to recognize and minimize GERD provoking risk factors such as frequent suctioning, frequent feeding tube manipulation, and frequent chest physical therapy. Attention to airway symptoms and lung disease will help. Efforts to minimize coughing and wheezing episodes in those with chronic lung disease will be advisable. Safe-sleeping positions and supine position is protective in infants as airway protective mechanisms are well maintained in such situations [27,29,32]. Although prone position decreases GER events, it is not recommended owing to the high risk for life-threatening events and sudden deaths owing to airway closure [1,33].

Feeding strategies: Prevailing feeding strategies are very wide and are not evidence-based and are based on retrospective observations [34,37]. Cow's milk allergy is shown to cause indistinguishable GERD like symptoms in the full-term infant. Therefore, considering a hydrolyzed formula for 1–2 weeks may treat reflux type of manifestations. Human milk has better gastric emptying time and should always be encouraged. There is evidence that human milk has fewer GER episodes and breast-fed infants have less esophageal acid exposure than formula fed infants [35,36,38]. Increasing calories concentration and thickening the feed with added starch (rice cereal, sodium alginate, corn starch) can reduce regurgitation and GER events however such approaches have not been studies longitudinally and systematically in preterm and term infants for long-term effects. Method of feeding may alter GERD frequency in selected patients where other nonpharmacological approaches are ineffective. Continuous drip feeds via intragastric or transpyloric method may be a short-term bridge for selected tube dependent infants to prevent growth failure. All these approaches have not been rigorously tested and systematically studied in convalescing NICU infants.

Pharmacologic therapy: There is no good pharmacological agent recommended for GERD in the NICU setting. Despite lack of benefit, there is a high prevalence of GERD medication administration in both inpatient and outpatient setting, and systematic data is lacking to support efficacy of these medications. These include acid-suppressive agents including Histamine 2 receptor antagonists (H2RA) and proton pump inhibitors (PPI) that are used commonly. Both these agents have a high risk for short-term and long-term side effects [39–41]. Besides causing profound acid suppression, other side effects include small bowel bacteria overgrowth, infections, bowel inflammation and necrotizing enterocolitis, malabsorption of nutrients, decreased absorption of calcium and altered digestion, diarrhea and vomiting, in addition to osteopenia and bone fractures. Acid suppressive agents should not be used unless there is a strong objective-evidence based indication. Prokinetics such as Erythromycin may improve gastroduodenal motility in preterm infant older than 33 weeks PMA improving gastric emptying but has no effect on GER events. However, it has been associated with higher incidence of hypertrophic pyloric stenosis.

Surgical Therapy: Indications for anti-reflux surgery include those with anomalies, failure of both medical and behavioral therapies and if GERD related supra-esophageal and extra-esophageal complications should arise. However, accuracy with diagnosis, anatomical and functional integrity studies of gastro-esophageal junction need to be undertaken prior to surgical procedures, whenever possible. Any surgical procedure carries a risk of anesthesia, surgery and post-surgical complications. Adverse complications of fundoplication include bloating, GER recurrence due to wrap breakdown and small bowel obstruction, in addition to anterograde aspiration that may occur during swallowing.

2. Summary

Management approaches of infant GERD are summarized in Table 1. GER and GERD in convalescing infants are sometimes indistinguishable clinically, and clinical diagnostic criteria are lacking for precision and reproducibility. Evaluation of dietetic history, anomalies, instrumentation and diagnosis based on symptom-correlation may be necessary in the NICU infant setting. Expectant management with better quality nutrition and feeding management strategies while monitoring for growth and development are helpful. Supine position is the best position for optimal airway safety. Pharmacological therapy to suppress gastric acidity must be limited and weighed with caution. Surgical therapies are rarely needed unless strong clinical indication exists. Further systematic research is needed to develop generalizable guidelines for the care of convalescing NICU infant who is of a different phenotype and has heterogeneity with symptom presentation along with co-existing morbidities.

Table 1
Key highlights.

- The complexity in the convalescing infant in the NICU need careful consideration prior to GERD diagnosis.
- Pathophysiological basis for symptoms commonly ascribed to reflux can be multifactorial and not always associated with GER or GERD.
- The severity of acidity, frequency of non-acid events, proximal extent of the refluxate and infant's sensitivity to respond to esophageal provocation and presence of adaptative reflexes determine the pathophysiological basis for GERD.
- Risk factors and tests for determining GERD presence and severity need to be considered before attributing GERD diagnosis.
- Medical or surgical treatment should not be based solely on clinical signs or parental/provider perceptions.
- The label of GERD diagnosis even in healthy infants increases the interest in using prescribed or non-prescribed medications.
- The consequences of acid-suppressive medications to manage presumed GERD are severe and have long-term repercussions.

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