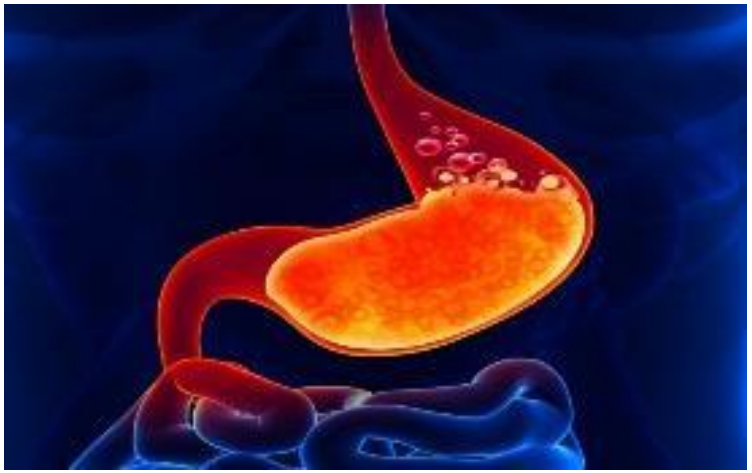
In the name of God

Gastroesophageal Reflux in Newborns



دکتر آرش بردبار

فوق تخصص نوزادان

دانشیار دانشگاه علوم پزشکی ایران

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Jenny Bellodas Sanchez, MD, Sudarshan R. Jadcherla, MD. FEBRUARY 2021 Vol. 22 No. 2

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Gastroesophageal Reflux Disease in the NICU Neonate: Controversies, Current Understanding and Future Directions.

Kathryn A. Hasenstab, BS BME, Sudarshan R. Jadcherla, MD, FRCPI, DCHAGAF. DOI: https://doi.org/10.1016/j.clp.2020.02.004

INTRODUCTION

Over the years, GER & GERD has remained a controversial topic for clinicians especially in newborns because of:

1- many of these symptoms may have multi-systemic etiologies related to prematurity, chronic lung disease, and neuropathology, among others, rather than solely GER

2-The consequences of empiric therapies in this fragile infant population can be detrimental

3- the uncertainty of treatment efficacy in symptomatic neonates

4- In addition, the American Academy of Pediatrics (AAP) through the "Choosing Wisely in Newborn Medicine" initiative highlighted routine use of anti-reflux medications in symptomatic GER in preterm infants as one of the top 5 therapies of debatable usefulness

5- variability in approaches among multi-disciplinary providers

And …….

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 (ESPGHAN) define *Regurgitation*, *GER*, *GERD* and *Refractory GERD*

Regurgitation: Visualization of gastric contents, does not require medical intervention, and does not have negative long-term consequences

GER: The passage of gastric contents into the esophagus with or without regurgitation and vomiting

GER disease (GERD): GER leading to troublesome symptoms that affect daily functioning

Refractory GERD: No response to medical therapy after 8 weeks

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. **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.

To date, no other consensus-based definition for GERD has been proposed for the pediatric population in general and infants in particular

and so

The exact incidence and prevalence of GERD in infants remains uncertain

In preterm infants, GERD diagnosis rates across US NICUs varying widely from 2-88%

Jadcherla SR, Slaughter JL, Stenger MR, Klebanoff M, Kelleher K, Gardner W. Practice Variance, Prevalence, and Economic Burden of Premature Infants Diagnosed With GERD. Hosp Pediatr. 2013;3(4):335-341

Such wide diagnostic rate variation is likely because of:

*the subjective definition of GERD especially in nonverbal infants

*symptom-based definition in whom defining "troublesome" is a difficult task not only to hospitalists and subspecialists, but also to primary caregivers and parents

It is of utmost importance to formulate an objective definition using clinical, diagnostic, and/or therapeutic evidence-based findings

PHYSIOLOGY OF GER IN INFANTS

Multiple factors may predispose infants to GER, especially during the first 4-6 months of age:

Physiological factors:

1-Transient LES relaxation (TLESR). This is the most relevant mechanism of GER in infants, as it is in adults

2- Hypotonic LES

3- Swallowed induced LES relaxation (SLESR)

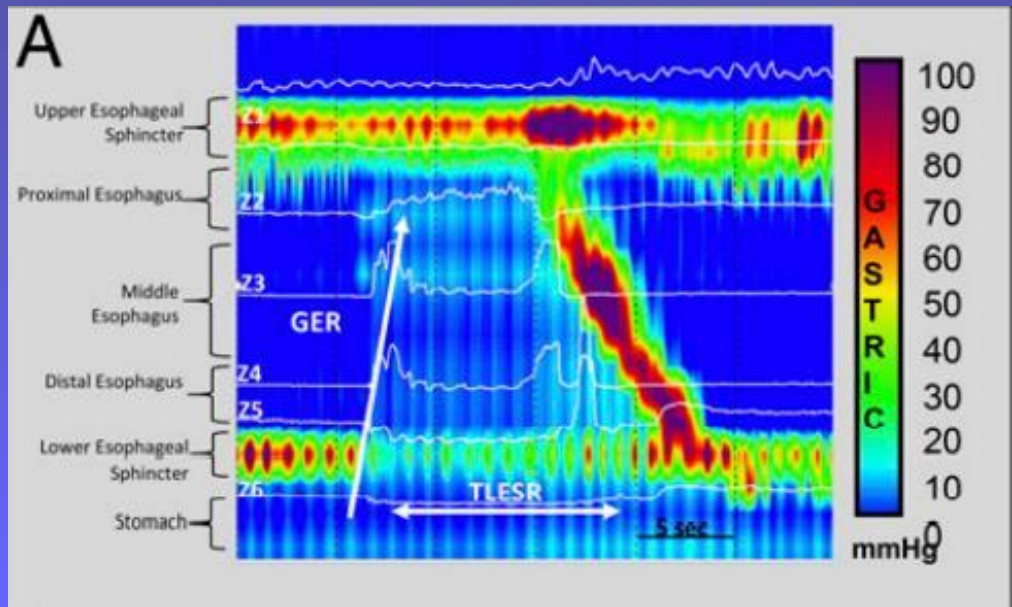
4- Abdominal strain

Transient LES Relaxation (TLESR)

TLESR is the most common mechanism of GER in both term and preterm infants

It consists of a sudden brief drop in LES pressure at or below intragastric pressure

This facilitates the retrograde passage of gastric contents into the esophagus



TLESR occurs as a physiologic mechanism that enables proximal gastric venting, hence its increased frequency in the early postprandial period

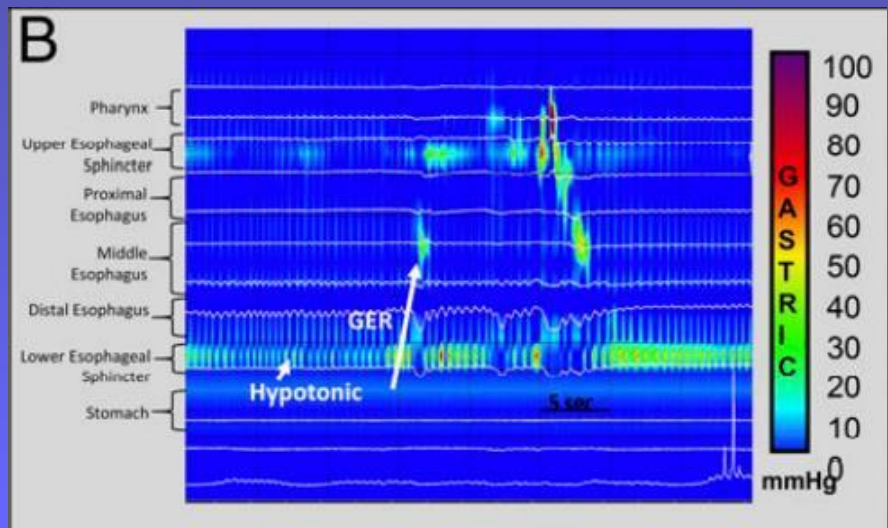
TLESRs are common in healthy infants but increased in those with GERD, and are impacted by body position with lateral left sidelying position being favorable to decreased TLESR frequency

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

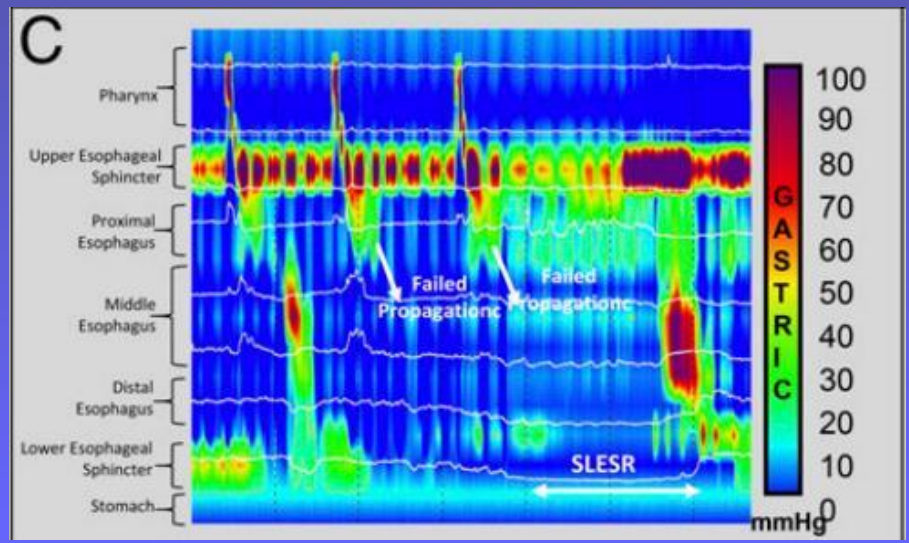
Hypotonic LES may be the result of impairment of either vagal excitatory innervation or myogenic contractile activity

Some study performed in children with esophagitis and a history of birth asphyxia found hypotonic LES as the main mechanism of GER



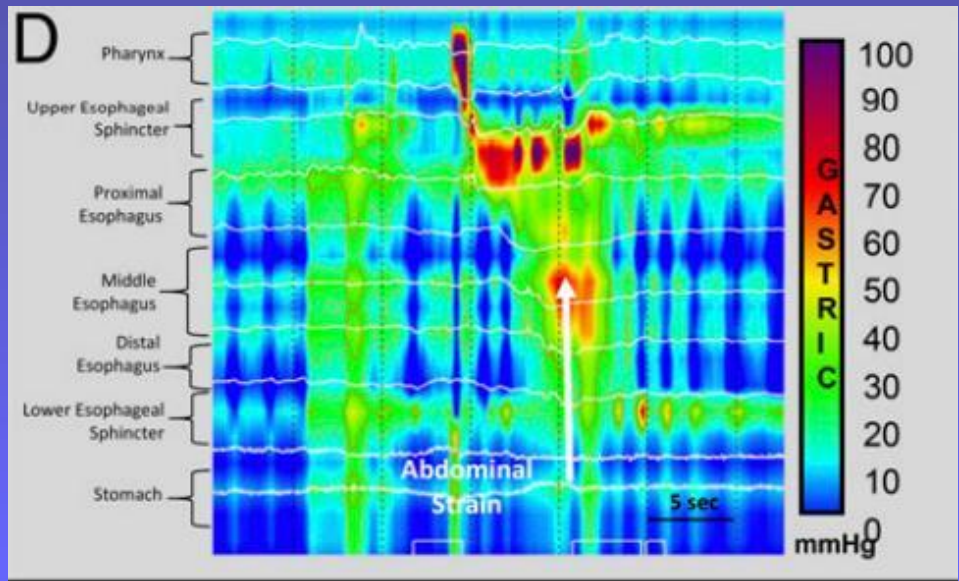
Swallow-associated LES Relaxation (SLESR)

Swallow-associated LES relaxation (SLESR) is LES tone relaxation that occurs as a physiologic response to swallowing



Abdominal Strain

Abdominal strain is the sudden increase in intra-abdominal pressure that exceeds LES pressure, leading to an involuntary relaxation of the GEJ



Anatomic and Developmental factors:

1- Infants have a shorter esophagus and LES, leads to smaller esophageal capacity, facilitating rapid backflow of gastric content into the esophagus

2- Postprandial esophageal motor activity is primarily non-peristaltic in 73% of premature neonates, which may contribute to ineffective esophageal clearance of refluxate material

3- small stomach size and capacity resulting in faster gastric distention and increased intragastric pressure

4- frequent feedings per day (average of 6–8 times per day)

5- an exclusively liquid diet

6- high fluid intake per kilogram per day

7- prolonged periods in the supine position

Anatomic and developmental changes occur as infants get older, usually by 12 months of age:

1- the total longitudinal dimension of the esophagus and LES increase, causing the LES to go from being in the intrathoracic compartment to an intra-abdominal location

2- during this period, the stomach becomes larger

3- the introduction of solids begins along with longer feeding intervals

4- infants spend more time in an upright position

5- Postnatal maturational in esophageal peristalsis greater peristaltic velocity with older postnatal age in preterm infants

This facts may provide an explanation for the decreased GER prevalence during the second half of infancy

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.

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
gastrointestinal

Aerodigestive

- Cough
- Sneezing
- Grunting
- Stridor
- Wheezing
- Aspiration
- Oral aversion
- Swallowing problems
- Feeding difficulty

Behavioral

- Back arching
- Irritability
- Crying
- Sleep disturbances

GERD-like signs & symptoms

Gastrointestinal (GI)

- Spitting
- Regurgitation
- Emesis
- Poor oral intake

Cardiorespiratory

- Apnea
- Bradycardia
- Desaturations
- Choking
- Tachypnea

the aerodigestive tract, nerves, its functions, and potential responses to GER

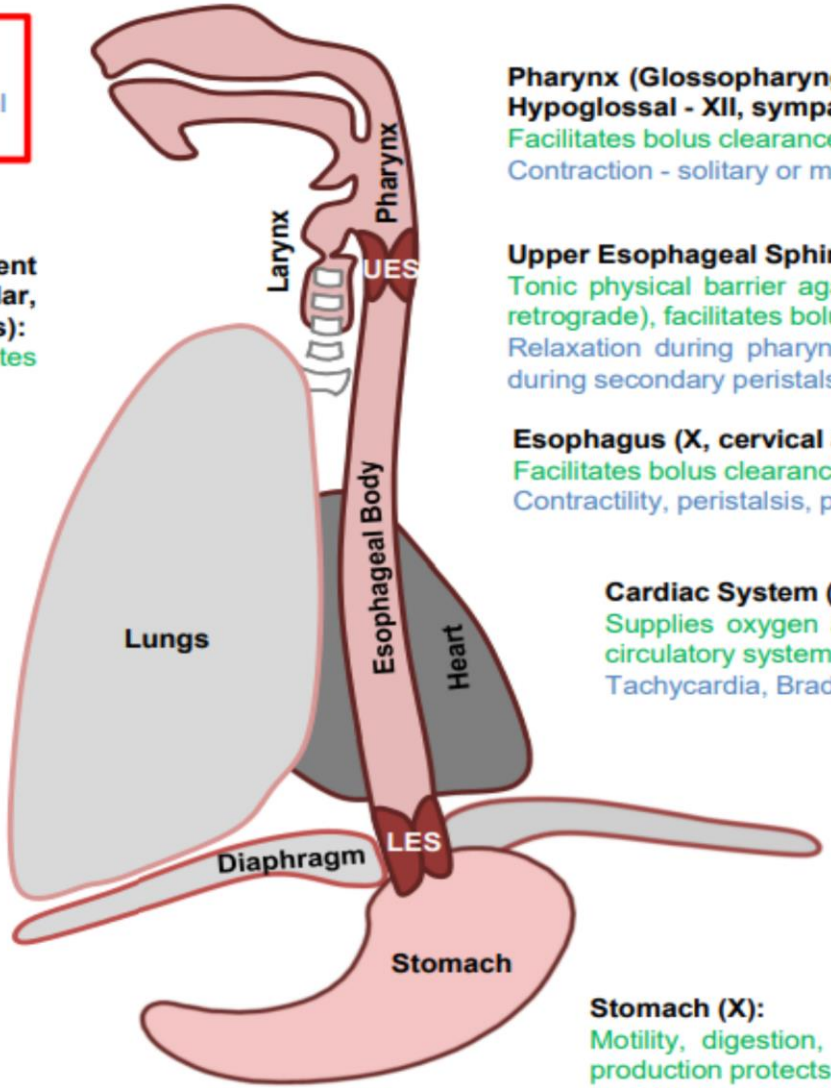
LEGEND

Region (Nerves):
Function of Region
Reflexes evoked upon esophageal provocation as in GER

Larynx (Superior and recurrent laryngeal nerves, X, Mandibular, Facial, C1 - C2, sympathetic nerves):
Protects lower airways facilitates respiration and phonation.
Glottal closure, stridor

Respiratory System (Phrenic, X via anterior and posterior pulmonary plexuses):
Facilitates respiration
Cough, bronchospasm

Diaphragm (Phrenic):
Rostral diaphragm primarily for respiration, crural diaphragm for respiration and contributes to LES function.
Inhibition during LES relaxation



Pharynx (Glossopharyngeal - IX, Vagus - X, Hypoglossal - XII, sympathetic nerves):
Facilitates bolus clearance
Contraction - solitary or multiple

Upper Esophageal Sphincter, UES (IX, X):
Tonic physical barrier against aspiration (anterograde or retrograde), facilitates bolus clearance
Relaxation during pharyngeal swallowing, or contraction during secondary peristalsis and/or presence of GER

Esophagus (X, cervical and thoracic sympathetic trunk):
Facilitates bolus clearance, buffers acid
Contractility, peristalsis, pain

Cardiac System (X, sympathetic plexuses):
Supplies oxygen and nutrients to organs via circulatory system
Tachycardia, Bradycardia

Lower Esophageal Sphincter, LES (X):
Tonic physical barrier against gastric contents, facilitates bolus clearance
Relaxation during swallowing (pharyngeal swallowing and secondary peristalsis). TLESRs and SLESRs are potential mechanisms of GER

Stomach (X):
Motility, digestion, absorption, acid production protects against infection
Increased intrabdominal pressure is a potential mechanism for GER

Complications

-Reflux esophagitis
-Strictures
-Recurrent aspiration pneumonia
-recurrent otitis media

Red flags suggesting potential conditions other than GERD requiring further investigation

-Vomiting: pyloric stenosis, urinary tract infection, intracranial pathologies
-Fever: infection
-Bile-stained vomit: intestinal obstruction is a strong consideration
-Hematemesis: gastrointestinal bleeding
-Bloody stools: Cows milk protein allergy, bacterial, acute surgical condition
-Abdominal distension: intestinal obstruction, dysmotility, anatomic abnormalities
-Chronic diarrhea: milk protein allergy

GER and Apnea

For many years, apnea has been thought to be a consequence of GER in preterm infants, likely because of higher prevalence of both conditions in the postprandial period

However, various studies failed to show temporal or causal association between GER (acid and nonacid) and apnea in premature infants

de Ajuriaguerra M, Radvanyi-Bouvet MF, Huon C, Moriette G. Gastroesophageal reflux and apnea in prematurely born infants during wakefulness and sleep. Am J Dis Child. 1991;145(10):1132–1136

Di Fiore J, Arko M, Herynk B, Martin R, Hibbs AM. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. J Perinatol. 2010;30(10):683–687

Omari TI. Apnea-associated reduction in lower esophageal sphincter tone in premature infants. J Pediatr. 2009;154(3):374–37

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 and show contradictory results

Sindel BD, Maisels MJ, Ballantine TVN. Gastroesophageal reflux to the proximal esophagus in infants with bronchopulmonary dysplasia. Am J Dis Child. 1989;143(9):1103–1106

Borrelli O, Battaglia M, Galos F, et al. Non-acid gastro-oesophageal reflux in children with suspected pulmonary aspiration. Dig Liver Dis. 2010;42(2):115–121

Farhath S, He Z, Nakhla T, et al. Pepsin, a marker of gastric contents, is increased in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. Pediatrics. 2008;121(2):e253–e259

Chen PH, Chang MH, Hsu SC. Gastroesophageal reflux in children with chronic recurrent bronchopulmonary infection. J Pediatr Gastroenterol Nutr. 1991;13(1):16–22

Akinola E, Rosenkrantz TS, Pappagallo M, McKay K, Hussain N. Gastroesophageal reflux in infants < 32 weeks gestational age at birth: lack of relationship to chronic lung disease. Am J Perinatol. 2004;21(2):57–62

Current Diagnostic Testing Modalities for GERD and its potential advantages and disadvantages in infants

Upper GI

Advantages

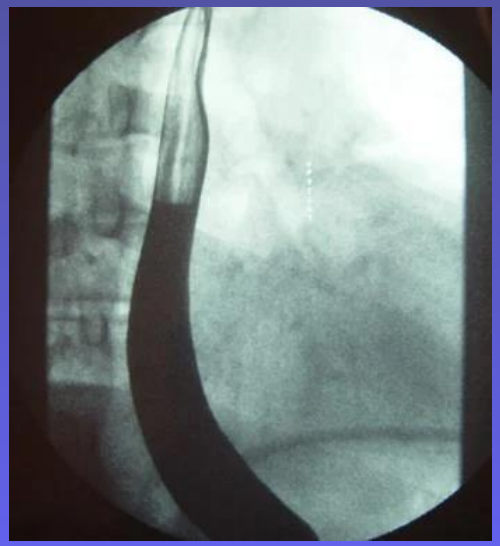
- Targets foregut anatomical considerations (hiatal hernia, malrotation, pyloric stenosis, intestinal stricture, achalasia, and tracheo-esophageal fistula)

- Useful for those undergoing Gastrostomy or antireflux surgery and evaluation of extraesophageal symptoms

Disadvantages

- Not supported to diagnose GERD

- Radiation exposure



Ultrasonography

Advantages

Targets foregut anatomical considerations (Pyloric stenosis or gastric dysmotility, other diagnoses triggering vomiting such as non GI causes like renal or liver origins)

Disadvantages

Limited value with GERD evaluation

Esophagogastroduodenoscopy (EGD)

Advantages

Can be performed with/without biopsy, targets esophagitis (erosive, microscopic, eosinophilic), GERD complications or conditions mimicking GERD

Disadvantages

Normal endoscopy does not rule out GERD

Not supported to diagnose GERD in infants

Biomarkers

Advantages

Utilizes salivary pepsin to determine cause of extraesophageal symptoms

Disadvantages

Lack of normal values, insufficient to diagnose extraesophageal reflux disease

Unknown if it correlates with severity of symptoms

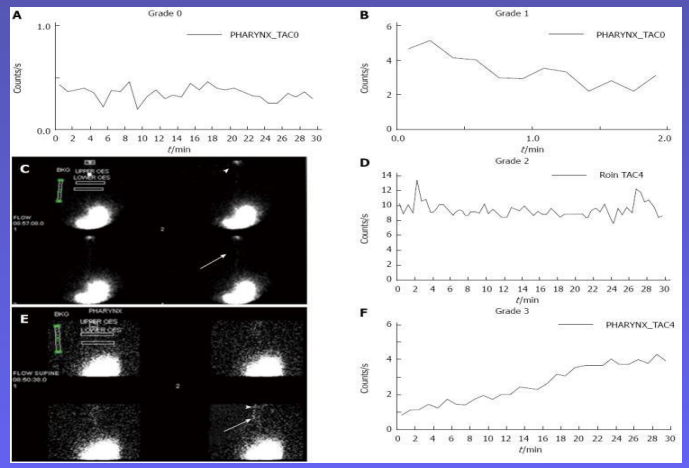
Scintigraphy

Advantages

Targets gastric emptying and GERD, can detect possible aspiration of refluxate

Disadvantages

Lack of standardization, not supported for diagnosis of GERD in infants



Pharyngoesophageal Manometry

Advantages

Targets GI motility (dysmotility) and/or LES function (outlet obstruction, hiatal hernia, TLESRs, hypotonicity) and assesses mechanisms

Detailed evaluation of aerodigestive protection (peristalsis, UES, LES, airway responses) in response to simulated reflux and cause of aerodigestive and cardiorespiratory symptoms such as cough and pathologic apnea

Personalized approaches using concurrent technologies (impedance, cardiorespiratory monitoring, video-fluoroscopy, ultrasonography

Fundoplication and post-surgery LES evaluations

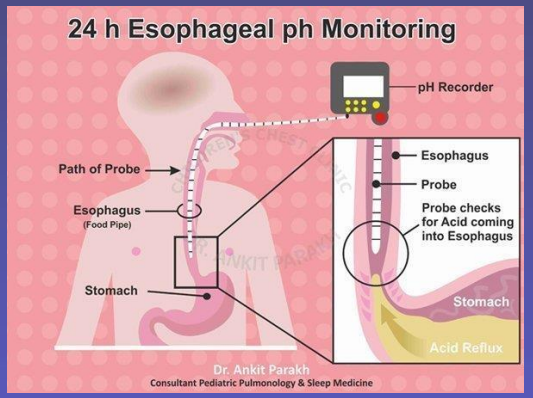
Disadvantages

Not supported to diagnose GERD in infants
Requires specialized equipment and expertise
Labor intensive

pH-metry

Advantages

Determines pathologic esophageal acid exposure (acid- GERD)
Acute symptom correlation with acid reflux episodes
Can evaluate acid suppressive therapy efficacy



Disadvantages

Lack of healthy control data

Not sensitive to non-acid or ascending reflux, and not preferred over pH-MII

pH-impedance (pH-MII)

Advantages

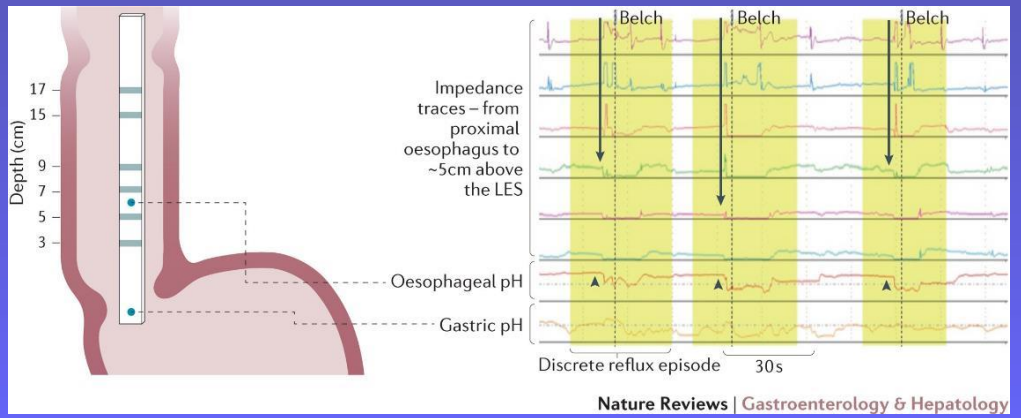
Determines pathologic esophageal acid exposure, and can detects non-acid refluxate and height of refluxate

Distinguishes physical (gas, liquid, mixed) and chemical (acid, weakly acid, weakly alkaline) characteristics of refluxate

Acute symptom correlation with reflux events

Baseline impedance as a surrogate for esophageal inflammation

Determine acid suppressive therapy efficacy



Disadvantages

Limited availability

Lack of control data

Reflux episodes may be underestimated

Time consuming and needs expertise to interpret

Reliance on bedside caregivers dedicated to symptom documentation

Although no gold standard currently exists for the diagnosis of GERD in high-risk infants; pH-impedance is currently the preferred method over pH-metry alone as pH impedance is able to measure additional GER bolus characteristics (anterograde/ retrograde, gas/liquid/mixed, height, clearance times) and symptom correlation via symptom indices

NASPGHAN Guidelines:

- History and physical exam
- Alarm sign/Red Flags -> Testing and Referral
- Feeding modifications (Avoid overfeeding by reducing volume with more frequent feeds, thicken feeds, continue breastfeeding) management if improved
- 2-4 weeks' protein hydrolysate or amino acid based formula, or elimination of cow's milk in mother's diet if breastfed
- Pediatric GI referral. if referral not possible consider 4-8 week trial of acid suppressive therapy and wean if symptoms improve (if no improvement then revisit differential al diagnosis, testing, and short term medication trial)

NICE Guidelines

- Parental education/reassurance

- Determine complicated vs uncomplicated GER, red flags/complications -> Testing/clinical judgement/referral

- Frequent regurgitation

Formula Fed: Feeding history -> reduce feeding volume if excessive -> smaller more frequent feeds -> thickened formula -> 1-2-week alginate therapy
Breast Fed: Breastfeeding assessment -> 1-2- week alginate trial

- 4-week acid suppressive therapy trial in 1) overt regurgitation + unexplained feeding difficulties, distressed behavior, or poor growth, 2) endoscopy proven esophagitis

- Enteral tube feeding for poor growth with overt regurgitation, Jejunal feeds in those with intragastric intolerance or concern for reflux related pulmonary aspiration

Current GERD controversies that remain to be resolved in infants

- True GERD definitions, prevalence, and identification of troublesome symptoms / complications

- Development of diagnostic criteria to define true GERD in nonverbal infants

- Development of effective GERD therapies:

- Conservative therapies
- Thickening is controversial and should be monitored
- Use of acid suppressive therapies and duration
- Role of surgical therapies (fundoplication, tracheostomy, gastrostomy) and transpyloric feeds
- Timing, duration, and definition of therapeutic success