

Gastro-Esophageal Reflux in neonates: A Challenge in Feeding New Borns and Preterms

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Abstract: Gastro-esophageal reflux (GER) is a physiologic phenomenon in infants and usually resolves by 6-12 months of age. Symptomatic GER, that is gastro-oesophageal reflux disease (GERD) is as frequent as 1 in 300 infants and results from significant reflux producing a detrimental physical change such as poor weight gain, mucosal ulceration or chronic respiratory symptoms. Neonates with GERD can present with a wide spectrum such as frequent vomitings, feeding intolerance, hypoxia, apneic spells, recurrent episodes of pneumonia etc. Patients with significant neurological deficit suffer from serious sequelae secondary to GER. In a patient with GER who is thriving and healthy no diagnostic or therapeutic maneuvers are required. In patients with GERD, available diagnostic studies are barium swallow, endoscopy and esophageal biopsy, scintigraphy and pH monitoring (gold standard). Treatment options for pediatric GERD include lifestyle changes (small frequent feeding & thickened feeds), pharmacological (prokinetics, antacids, H2 receptor antagonists and proton pump inhibitors) and surgery. Recently, percutaneous endoscopic gastrostomy (PEG) has been made available as an option for feeding babies with GERD.

Introduction

The term gastroesophageal reflux (GER) refers to the presence of gastric contents in the esophagus proximal to the stomach. This is physiologic occurrence that takes place more often during infancy and decreases with advancing age. The prevalence of GER peaks between 1 month to 4 months of age and usually resolves by 6 to 12 months of age. No gender predilection or definite peak age of onset beyond infancy has been established. A normal newborn infant who spits up with burps, continues to feed well grows well and thrives with no respiratory or other systemic features is considered to have physiological reflux.

Pathologic reflux or gastroesophageal reflux disease (GERD) is usually significant enough to produce a detrimental physical change, such as poor weight gain, mucosal ulceration, or chronic respiratory symptoms not due to known causes. Gastric regurgitation is seen in two-third of infants while GERD is seen 1 in 300 infants.

Physiology

Factors that contribute to GERD in neonates and infants include, but are not limited to :

- Abnormal physiology of lower esophageal sphincter; non descent of lower end of esophagus into the abdomen, poorly developed crura of diaphragm with defective angulations.
- Limited gastric volume and delayed gastric emptying time.
- Increases in gastric pressure due to abdominal breathing.
- Transient lower esophageal sphincter relaxations.
- Gravitational effects due to positioning.
- Upper or lower esophageal sphincter dysfunction/in-coordination.
- Drugs that are commonly used in newborns that decrease lower esophageal sphincter tone e.g. Xanthines.

Clinical Presentation

Most infants have some reflux in the newborn period, and spitting

or vomiting during the first year of life is common. The neonate with GERD can present with a wide spectrum of presentations such as:

- Frequent vomitings, which may be projectile.
- Effortless drooling of milk from the mouth.
- Feeding intolerance.
- Increased tracheal secretions.
- Hypoxia with desaturation.
- Cyanotic episodes secondary to upper airway obstruction by pharyngeal regurgitation.
- Apneic spell with bradycardia: Instead of a pure obstructive apnea pattern, a mixed pattern of both obstructive and central types generally predominates.
- Recurrent episodes of pneumonia.
- Stridor
- Acute life threatening event.
- Abnormal behaviour and posturing with the tilting of the head to one side and bizarre contortions of the trunk referred as Sandifer's syndrome.
- Esophagitis: Leads to mucosal ulcerations, strictures, vomiting and poor feeding.

Diagnostic Evaluation

As most infants with symptoms of GER are thriving and healthy, they require no diagnostic or therapeutic maneuvers other than a careful history and physical examination, with appropriate reassurance to the parents if anxiety is present. Infants and older children who have significant neurologic deficits or psychomotor retardation often have significant GER and may suffer from serious sequelae secondary to GER.

The diagnostic studies available are :

Upper GI Barium Swallow : This study should be readily performed if history and physical examination suggest that an anatomic obstruction in the intestinal tract is likely.

Specific anatomic intestinal abnormalities that may give rise to symptoms of GER include esophageal strictures, pyloric stenosis;

gastric outlet obstruction from a variety of conditions like gastric web and malrotation; or even more distal intestinal obstruction, such as intestinal web, stenosis or atresia. The barium swallow is a sensitive way of detecting reflux but has a very low specificity rate.

Extended pH monitoring : This is considered as the gold standard for diagnosis (1). Recent research literature cites pH monitoring as 100% sensitive and 94% specific (2). 24 hours monitoring is felt to be necessary to establish an accurate record. Definition of a reflux episode varies from a drop in pH less than or equal to 4 lasting at least 8 seconds (2). to at least 15 seconds (3). Interpretation of pH probe results need to be considered with clinical symptoms and should only be done by a certified Pediatric Gastroenterologist familiar with the infant's clinical history and symptoms.

pH probes are restricted by their ability to detect only episodes that cause a change in the esophageal pH. They are able to detect the frequency of episodes of acid reflux in the distal esophagus, the time it takes for an episode of acid reflux to be cleared and over a given period of time but are unable to determine the volume of reflux material into the distal esophagus. This has allowed standardized norms to be published, which permits one to know how often reflux occurs in a particular age group.

Endoscopy and Esophageal Biopsy : The increased use of small fiber-optic endoscopes in recent years has resulted in many infants and neonates with symptoms of GER undergo an endoscopic procedure. This technique allows direct visualization of the esophageal mucosa and biopsy to determine the severity of reflux esophagitis. It is performed in infants more than 2kg. Its usefulness in diagnosing esophagitis may prelude the need to perform a pH probe study.

Although inflammatory cells, such as lymphocytes and polymorphonuclear cells have been seen in reflux esophagitis, these cells can be observed under normal conditions, and eosinophilic infiltrates have been found to be far more specific indicators of reflux esophagitis in infants (4). However, markedly increased eosinophilic epithelium (>15 eosinophils/hepf) suggest the diagnosis of eosinophilic esophagitis. Eosinophilic esophagitis is commonly associated with milk protein allergy and may not respond well to acid suppressant therapy.

Manometry : Manometric studies are difficult to perform in the un-sedated infant and have proven to be of little clinical use to patients and remain primarily a research tool.

Technetium Scintigraphy : After ingestion of the radionuclide labeled formula/meal, the neonate/infant is placed under a gamma counter. This allows seeing the reflux of the radionuclide into the esophagus and can also detect pulmonary aspiration of radionuclide. It is also possible to calculate how much radionuclide empties from the stomach over a given period of time. This test has the advantages of being noninvasive, low in radiation, and widely available. In practice, however, the value of this test in documenting and quantitating GER is small. The sensitivity is reported to be 59-93% with differences ascribed to techniques.

Table : Advantages/disadvantages of diagnostic procedures for GERD children.

Study	Advantages	Disadvantages
1. Upper GI (Barium)	Readily available	Inadequate screening

	Evaluates upper GI structures	Results-Operator dependent
2. 24hr pH probe	Quantifies reflux Evaluates atypical symptoms monitors therapy	Requires overnight hospitalization Requires special equipment and personnel
3. Endoscopy with biopsy	Evaluates persistent GERD, H.pylori infection, allergic enteropathy	Invasive & requires sedation
4. Technetium Scan	More sensitive than pH probe Picks up pulmonary aspirations	Non physiologic settings Does not rule out anatomic obstructions Cannot quantify GER

Management

Feeding Issues : As in adults, treatment options for pediatric GERD include lifestyle changes, pharmacological and surgery. Conservative medical management refers to positioning, thickening of feeds and small volume feeds. Recent literatures question the efficacy of any of these measures, and generally are performed on infants with mild or suspected GER, who do not have any pathologic disease.

Positioning : The traditional therapy of placing a child in an infant seat to reduce the amount of GER has not been shown to be effective either by clinical observation or by pH probe studies that have quantified the amount of GER. Seated position should be minimized because it provokes reflux by increasing intra-abdominal pressure. A head-elevated prone position resulted in both fewer and briefer episodes of reflux (5) but there is a possible increased risk of sudden infant death syndrome. Therefore, soft bedding material should be avoided in this setting. Medical therapy should be initiated before diagnostic evaluation or vice-versa. The medical therapy should be initiated before diagnostic evaluation or vice-versa. The pharmacological therapy includes prokinetics and antacids.

Metoclopramide and a related agent, domperidone, mildly increase resting lower esophageal sphincter pressure and somewhat increase gastric emptying under many conditions. Domperidone has marginal benefits at best and is not widely used to treat GER during infancy. The dose recommended is 0.2 mg/kg/dose to be given every 6-8 hourly. Metoclopramide has been used much more widely in US; however, few studies have demonstrated its effectiveness in widespread use for treatment of GER during infancy. It has a high range of side effects, the occurrence rate of which ranges from 11% to 34%. Although drowsiness and restlessness are the most common side effects, the most troublesome is an extrapyramidal reaction that seems to occur with increased frequency in children.

Cisapride, a 5HT agonist, is a relatively new agent used to treat GER. The mechanism of action is thought to work primarily by enhancement of release of neurotransmitters, which seem to stimulate smooth muscle contraction throughout the intestinal tract. Most of the side effects observed with cisapride are related to the gastrointestinal tract (abdominal cramps and diarrhea) but it is also known to cause fatal arrhythmias. It is of paramount importance to get an ECG before starting the patient on Cisapride and a QTc interval of more than 0.44 is a contraindication to start the drug. Clinical trials suggest that it may have some benefit in treating

GER in infants (7), although results are not dramatically impressive. We give it at a dose of 0.2 mg/kg/dose every 8 hourly. Contraindications to use of cisapride are the use of other drugs that may increase the QTC like erythromycin and antifungals etc. Most side effects reported in literature have been in those babies where very high doses have been given or in those who have underlying cardiac rhythm abnormalities.

Bethanechol, a muscarinic agonist, has been shown to increase basal lower esophageal sphincter pressure in many patients; however, researchers have had difficulty in showing whether it has any effect in reducing GER (8). It has a high frequency of undesirable side effects and it's rarely used in neonates.

Erythromycin, a macrolide antibiotic has been used as a prokinetic agent in the management of GER. Erythromycin has structural similarity to peptide hormone motilin, (9) it increases the motor activity in stomach and intestine. Various studies have shown that this drug is safe and effective in facilitating enteral feeding in newborn babies with feeding intolerance and may also shorten the course of hyper-alimentation. It has been shown to increase the gastric emptying in a dose response manner, its efficacy has been compared with metoclopramide in various clinical studies(10). In GER it has been used in the dosage of 3-5 mg/kg/day in 2-3 divided doses. There has been some anecdotal reports of association of erythromycin with occurrence of hypertrophic pyloric stenosis.(11)

Histamine-2 Receptor Antagonists : Initial H2 receptor antagonist introduced was cimetidine which has been shown to be effective in children with mild to moderate esophagitis. But this drug is associated with adverse effects like diarrhea, tachypnea, bradycardia, granulocytopenia, thrombocytopenia and gynaecomastia. Cimetidine per se as well as one of its metabolite impairs the hepatic clearance of drugs because of its inhibitory action on CYP2D6. Widely used H2 receptor antagonist-ranitidine has fewer overall central nervous system and anti-androgenic side effects. It inhibits both basal as well as stimulated gastric secretions (decreases volume, acid and pepsin content); it is 4-10 times more potent than cimetidine. Very limited data are available regarding pharmacokinetics and pharmacodynamics in newborn period. It has been used in the dosage of 1 to 2mg per kg per dose two to three times daily (2 to 6mg per kg per day). Safety of Ranitidine in children has been well proven but caution is to be exercised in neonates with renal or hepatic impairment. Famotidine has no significant role in management of GERD in childhood population.

Proton Pump Inhibitors (PPI): PPIs are used in infants with recurrent vomiting and failure to thrive, and/or irritability that have not responded to H2-RAs, child with frequent heartburn or chest pain, the child with feeding resistance of dysphagia, the child with asthma, the child with recurrent pneumonia and GERD and the infant with apparent life-threatening Event (ALTE). PPIs decrease acid secretion by inhibition of the H⁺, K⁺, -ATPase in the gastric parietal cell canaliculus and are more potent suppressor of acid secretion than H2-RAs. *Omeprazole*, Cap: 10,20 40 mg, doses 0.7-3.3mg/kg/day; *Lanzoprazole*, Cap: 15,30mg dose 0.4-4mg/kg/day. Medical therapy should be re-evaluated after 2 months

Surgical Treatment of GERD

Surgery should be used, as a last resort in the management of GER, in a baby near term or weighing 2kg. Indications include:

- Recurrent aspiration pneumonia
- Recurrent failures to remain extubated
- Poor weight gain
- Persistent vomiting
- Esophageal bleeding leading to anemia
- Esophageal stricture/ulcerations

Dalt et al¹² reports little success in medical management of GER in infants with pH probe study results of >20 episodes of reflux longer than 5 minutes or reflux time > 27%. The procedure of choice is a Nissen fundoplication. There has been a high incidence of delayed gastric emptying in infants needing fundoplication (13), therefore, a technetium gastric emptying study or milk scan may be considered prior to fundoplication in order to rule out the need for concurrent pyloroplasty.

Success rate based on symptom relief in pediatric patients ranges from 57-92%. Mortality ranges from 0.4-7% and complications range from 2.2-45%. The most common complications are breakdown of fundoplication, small bowel obstruction, gas blot syndrome, infections, atelectasis or pneumonia, perforation, persistent esophageal stricture, and esophageal obstruction.

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