Gastro-esophageal Reflux in Neonates

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Definition

The term gastroesophageal reflux (GER) is merely descriptive and refers to the presence of gastric contents in the esophagus proximal to the stpmach. Reflux of gastric contents is a physiologic occurrence that takes place more often during infancy and decreases with advancing age. Although virtually all infants have some degree of GER, the severity of symptoms ranges widely from an occasional burp to persistent emesis.

Incidence & Prevalence

Regurgitation has been reported in 40-65 % of healthy infants but decreases to 1% by one year of age. Hrabovsky & Mullett (1), reported the incidence of GER in their preterm population as 2.8% (22 cases out of 760 admissions). The current literature does not offer any other citations of percentage of occurrences in the preterm population.

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.

Types

In general, reflux can be divided into

a). Physiologic,

b). Symptomatic or pathologic.

Physiologic GER describes the normal newborn infant who spits up with burps, continues to feed well, grows well and thrives with no respiratory or other systemic features.

Symptomatic reflux called Gastroesphageal reflux disease (GERD) includes those infants who have some spectrum of observable events that lead one to suspect GER is present. Symptoms include (2)

- frequent vomiting (> 2 times a day for more than 2 days/week), which may be effortless drooling of formula from the mouth or projectile vomiting,
- increasing tracheal secretions,
- hypoxia or desaturations,
- recurrent episodes of pneumonia,
- stridor,
- recurrent cough or wheezing,
- apneic and/or bradycardic episodes,
- irritability with feeding

Pathologic reflux is usually significant enough that it produces 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-thirds of infants while GERD is seen 1 in300 infants.

GER	GERD
1) Regufigitation with normal wt gain	i) Regurgitation with poor wt gain
2) No signs or symptoms of esophagitis	2) Persistent irritability, pain in infants, dysphagia, pyrosis in children
3) No significant respiratory symptom	3) Apnea and cyanosis in infants swheezing, recurrent aspiration chronic cough, stridor
4) No neurobehavioral symptoms	4) Neck tilting in infants

Physiology of upper gastrointestinal tract motility

The muscular layers of the upper gastrointestinal tract distal to the mid-esophagus are composed of smooth muscle and are not, therefore, under voluntary control. The esophagus functions as a muscular tube. Peristaltic waves of contraction are responsible for the forces that transport an ingested food bolus through the body of the esophagus and ultimately past a relaxed lower esophageal sphincter into the stomach. The external circular muscle layer is primarily responsible for the generation of force identified as a peristaltic wave and the maintenance of lower esophageal sphincter tone.

The lower esophageal sphincter at the distal end of the esophagus has attracted the greatest amount of interest in attempts to explain why newborns and infants seem to have a greater tendency to GER than do older children or adults. The lower esophageal sphincter is an area of thickened circular muscle that is tonically contracted at rest. A network of neurons that are coordinated to ensure that relaxation occurs at the appropriate time integrates the relaxation that occurs at the end of an esophageal peristaltic sequence. This tonically contracted zone is relatively independent of neurotransmitters in the generation of tone at rest in the basal state (3) however, neural input is important in the production of the inhibitory neurotransmitters that are responsible for relaxation of the lower esophageal sphincter. These neurotransmitter agents are non-cholinergic, non-adrenergic, and current investigations suggest vasoactive intestinal peptide and nitric oxide as likely candidates. Normal LES pressure in preterms is < 5 mmHg and in term babies it is 23 mmHg. Adult pressures are double the pressure at birth in term babies and are attained at 1-2 months of age; The possible explanations for pathologic reflux include a decreased basal tone, either persistently or episodic, in the lower oesophageal sphincter; or in appropriate relaxation of the lower oesophageal sphincter. Recent evidence from animal models suggests that newborn gastric muscles may function differently than adult gastric musculature (4). These differences may give risk to more retrograde peristalsis in the newborn. Beside these, there are several factors that could contribute to GER disease in neonates and infants (table 1)

Table-1 - Factors that contribute to GER disease in neonates and infants include, but are not limited to:

- Abnormal physiology of LES: Non descent of lower end of esophagfls into the abdomen, poorly developed cruri of diaphragm with defective angulation;
- 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/ uncoordination; and
- Drugs that are commonly used in newborns that decrease lower esophageal sphincter tone e.g Xanthines

Clinical Presentation

Although many older children with GER complain of symptoms, such as heartburn, that are quite similar to those of adults, neonates and infants often present with a different spectrum of clinical manifestations. As noted previously, all infants have some degree of reflux in the newborn period, and spitting or vomiting during the first year of life is common. It must be remembered that infants who suffer from significant regurgitation or vomiting might be responding to disease process outside the gastrointestinal tract. It is, therefore, important to perform a careful history and physical examination to ensure that no easily definable anatomic, metabolic, infectious, or neurologic cause for GER is present.

The neonate with GER can present with a wide spectrum of presentation such as:

- Frequent vomitings which may be projectile
- Effortless drooling of milk from the mouth

- Feeding intolerance
- Increased tracheal secretions
- Hypoxia with desaturations
- Cyanotic episodes secondary to upper airway obstruction by pharyngeal regurgitation.
- Apneic spells with bradycardia : Instead of a pure obstructive apnea pattern, a mixed pattern of both obstructive and central types generally predominates.
- Recurrent cough or wheezing
- Reccurent episodes of pneumonia
- Stridor
- Acute life threatening event (ALTE)

In the infant, the spectrum of GER is different and includes:

Projectile non-bilious vomiting- A natomic disorders, such as pyloric stenosis, often have a typical history of projectile nonbilious vomiting following eating. Bilious emesis usually indicates more distal obstructions, such as congenital webs, atresias, or malrotations.

Spitting up- The vast majority of infants with GER who are symptomatic of spitting up during the first year of life resolve their overt symptoms between the ages of 9 and 24 months.

Airway disease: This includes reccurent stridor, aspiration pneumonia, wheezing and chronic cough. It's especially seen in infants with neurological disease.

•*Esophagitis :* This leads to mucosal ulcerations .strictures, vomiting and poor feeding. Blood loss, from erosive esophagitis in these children is not uncommon leading to iron deficiency anemia.

•*Abnormal behavioral and posturing* with the tilting of the head to one side and bizarre contortions of the trunk have been noted in many children who have symptoms/of reflux. These symptoms are often referred to as Sandifer's syndrome. This movement is perhaps a protective mechanism of an infant with acid reflux causing esophagitis. The use of pH probes may be helpful in determining which children are having abnormal behavioral problems because of GER. GER is occasionally associated with a variety of head and neck complaints that occur in children, such as recurrent otalgia and dental erosions in older children.

Relationship between GER and respiratory symptoms

The cause-and-effect relationship between GER and respiratory symptoms in infants is often difficult to determine. Although it has been demonstrated in some patients with recurrent respiratory symptoms that GER occurs into the proximal esophagus (5), experience suggests that prevention of GER doe's not necessarily result in resolution of all respiratory tract disease.

Many case reports of upper respiratory tract disorders are being associated with GER in children (6). It is thought that aspiration of esophageal contents causes inflammation and edema resulting in stridor or that neural reflexes cause laryngospasm.

The possible rote of GER in apnea and bradycardia has been of great interest because of the life-threatening nature of these disorders. Although studies sometimes show that infants with a history of apnea have greater-than-normal amounts of GER, the correlation of apneic episodes with GER usually does not exist (7).The association between asthma, bronchitis or pneumonia with GER is often equally difficult to document. Although case reports have attempted to demonstrate the presence of GER in these disorders (8) it is often unclear whether GER is an etiologic agent or secondary to increased respiratory effort or coughing.The presence of pneumonia in patients who have neurologic impairment and[7] psychomotor retardation is well established and aspiration of esophageal contents must **be** considered strongly in this patient population. The use of macrophages may be helpful in detecting which children have respiratory symptoms on the basis of aspiration of gastric contents (9)

Conditions associated with increased risk of GERD

This include

- Repair of Tracheal-oesophageal fistula
- Neurologic impairement and delay
- Hiatus hernia

- Bronchopulmonary dysplasia
- Asthma
- Cystic fibrosis

Diagnostic Evalution

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

Specific anatomic abnormalities that may give rise to symptoms of GER include oesphageal 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 webs, stenosis, or atresia. Many of these intestinal tract anomalies can be readily picked up by a contrast study of the upper gastrointestinal tract. This study should be readily performed if history and physical examination suggest that an anatomic obstruction in the intestinal tract is likely. Although many radiologists believe that they can quantitate the degree of GER on a barium swallow or an upper gastrointestinal tract study, most clinicians do not find these tests particularly helpful.

The barium swallow is a sensitive way of detecting reflux but has a very low specificity rate because many infants and neonates who have little or no clinical symptoms of reflux experience reflux of some barium into the esophagus. The barium swallow is not helpful also in terms of evaluating rates of gastric emptying, because barium is physiologically inert and does not activate any of the normal duodenal receptor mechanisms that tend to modulate gastric emptying function.

Barium swallow showing reflux upto upper part of oesophagus

Extended pH probe monitoring

This is considered as the gold standard for diagnosis (10). It's carried out by introducing thin flexible probes into the distal oesophagus which can detect the pH of the secretions around. Evidence of acidic pH suggests that there is reflux of gastric contents into the oesophagus . They are unable to determine the volume of reflux material into the distal esophagus, but they are able to detect the frequency of episodes of reflux, the time it takes for an episode of acid reflux to be cleared, and, over a given period of time, the frequency of episodes of acid reflux in 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. A 24-hour pH probe study can obtain fairly reproducible information on the amount of reflux that is occurring in an infant. There have been attempts to reproduce the validity of the 24-hour pH probe by reducing the amount of time to 12 hours or even to 4 hours. In many instances, however, it may be important to monitor the sleeping and nonsleeping period because infants who have significant reflux during the sleep phase may have altered esophageal clearance of reflux gastric contents. The recent availability of a more portable recording apparatus allows children to be monitored for GER in a more physiologic setting with normal dietary intake.

Recent research literature cites pH monitoring as 100% sensitive and 94% specific (11).

Definition of a reflux episode varies from a drop in pH less than or equal to 4 lasting at least 8 seconds (11) to at least 15 seconds (12) The number of reflux episodes considered as normal has not been well established. A descriptive study of 509 healthy full term babies who were being screened for risk of SIDS because they were siblings of SIDS infants, has been published (13) and presents data from 24 hour pH monitoring of these asymptomatic infants. This may be as close as we can get to a good study of what is "normal" for physiologic reflux in infants. 95% of these infants had a reflux index (percentage of total investigation time with pH < 4) of 10, with 72 reflux episodes documented, 9 of which were longer than 5 minutes duration, with the longest duration 41 minutes. This study also reports some norms that are age related and may be helpful in the interpretation of pH probe studies. What imy be more important is the clinical events that occur when reflux happens. It may be valuable in associating a specific time-related clinical problem with GER or evaluating specific pharmacologic or surgical therapy for problems with GER. 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.

One problem of pH probe monitoring is that they are often unable to detect acid reflux during the postprandial period because many ingested foodstuffs buffer the gastric acidity for varying periods of time and thereby alter the ability of the pH probe to detect reflux episodes. Some researchers have suggested the^ use of relatively low-buffering food during at least one feeding during pH probe study.(14)

Endoscopy **and** Esophageal **Biopsy**

The increased use of small fibreoptic endoscopes in recent years has resulted in many infants and neonates with symptoms of GER undergoing 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 2 kg. Its usefulness in diagnosing esophagitis may prelude the need to perform a pH probe study. Although inflammatory cells, such as lymphocytes and polymorphic nuclear 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 (15). One or more of epithelial eosinophils are considered sufficient to establish the presence of GER in an infant.

Manometry

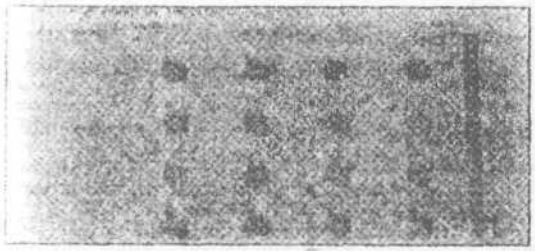
Initially, there was great hope that the measurement of changing oressure profiles in the upper gastrointestinal tract and changes in basal lower esophageal sphincter tone would be of great value in evaluating GER during infancy. Manometric studtes are difficult to perform in the unsedated infant, however, and have proven to be of little clinical use for patients and remain primarily a research tool. Manometry has been more helpful than any other modality in understanding more about the pathophysiology of GER in infants. Although initial reports suggested that many infants with GER had decreased lower esophageal sphincter pressure, later studies have suggested basal or tonic lower esophageal sphincter pressure in the majority of infants who have GER is within the normal range. Careful studies of large populations of adults have shown that inappropriate relaxation of the lower esophageal sphincter may be the primary etiologic agent for most GER. There have been indications that similar events occur during infancy (16).

TechnetiumTc Scintigraphy

The ingestioh of radionuclide-labeled formula allows the performance of a nuclear medicine scan known as gastroesophageal scintiscan. 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 studies are difficult to reproduce, and

frequent images, perhaps as frequent as every 30 to 60 seconds, are necessary to accurately quantitate the amount of reflux that occurs into the distal esophagus (17). It also has the disadvantage of being performed over a relatively short period of time in a rather nonphysiologic setting. The sensitivity is reported to be 59 - 93% with differences ascribed to technique.



Tc scan showing Reflux.

In theory, the esophageal scintiscan has an advantage over the traditional pH probes because it can detect postprandial reflux when an esophageal pH probe may not be able to detect reflux because the gastric contents are buffered by ingested food.

Some researchers have also suggested that the gastroesophageal scintiscan may be useful in detecting pulmonary aspiration of radionuclide. Although some investigators have claimed that it has sufficient sensitivity to be clinically useful. However most attempts to document the aspiration of this radionuclide have not been uniformly successful, most likely because of technical limitation of the technique(18).

STUDY	ADVANTAGES	DISADVANTAGES
1) Upper GI (Barium)	Readily available Evaluates upper GI structures	Inadequate screen for GERD Results-operator dependent
2) 24 hr pH probe	Quantification of reflux	Requires overnight hospitalization
	Evaluates atypical symptoms	Requires special Equipment and personnel
	Monitors medical treatment	
3) Endoscopy with biopsy	Evaluates persistent GERD H.pylori infection, allergic Enteropathy.	Invasive & requires sedation
4) Technetium	More senstive than Ph probe	Non physiologic settings
	Detect smaller volumes	Does not rule out anatomic Obstructions
	Picks up pulmonary aspirations	Cannot quantify GER

Management

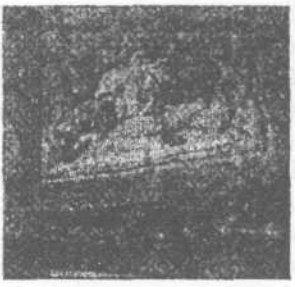
Conservative

Conservative medical management refers to attention to positioning, thickened feedings and small volume feeds. Recent literature questions the efficacy of any of these measures, and generally are performed on those 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 quantitated the amount of GER that occurs in various positions. Some evidence indicates that placing the infant in a head-elevated prone position resulted in both fewer and briefer episodes of reflux (19) but that the decreases in reflux time are small, and the possible increased risk of sudden infant death syndrome for children in this position has led to less enthusiasm for its use. Complete upright and prone position is beneficial in infants and neonates with GERD. Soft bedding material should be avoided in this setting. Prone positioning is not routinely recommended as the first- line management of simple regurgitation without evidence of GERD. Placing these infants in the supine position is routinely recommended. Seated position should be minimized because it provokes reflux by increasing intra-abdominal pressure.



Position of baby with GER

Small frequent feeds

Many infants often can be treated effectively with small or more frequent feedings. Continuous infusions, either by nasal, gastric, or even postduodenal tubes, have been shown to be successful in getting adequate weight gain and may allow surgical intervention to be avoided in infants in whom the risk is unacceptably high.

Thickened Feedings

Thickening the child's food (e.g., rice cereal in formula) to reduce the clinical symptoms of children with GER has long been an accepted practice. This assumption has been tested with pH probe data, and thickened feedings (e.g., apple juice thickened with rice cereal) were found to have no effect on reflux time unless the child was in a head-elevated prone position after the feeding (20). However, although infants with GER who are given thickened feedings might not have significantly reduced reflux time as measured by a pH probe, other criteria, such as episodes of emesis, time spent crying, and time spent awake, may be reduced. In addition, their effects may often result in the therapeutic success of thickened feedings (21).

Parents must be reassured that most infants and neonates with regurgitation and GER respond well to conservative management. Parents should be informed of the widespread prevalence of functional GER in early infancy, especially among 1- 4 months of age. Observation of feeding behaviors and the interaction between the parent and infant is important, and revised instructions on feeding techniques may be necessary.

Literature from the west suggests that allergy to cow's milk may manifest with symptoms similar to those of GER and a two week trial of casein hydrolysate formula is usually considered in their scenario if the infant does not show improvement with conservative measures.

Pharmacologic Management

The widespread nature of GER in infants has generated considerable interest in developing a specific pharmacologic therapy for this disorder; however, the observation that many episodes of GER are transitory in nature and caused by inappropriate relaxation of the lower esophageal sphincter explains the inability of many therapeutic agents to alleviate symptoms of GER.

If conservative measures fail and other differential diagnosis have been considered and excluded, pharmacologic therapy is warranted.One algorithm allows for a trial of medical therapy before any diagnostic

evaluation is performed.If the pt improves with the use of medications, no further evaluation is necessary. However, if no improvement occurs, a diagnostic work-up should be performed. It is debatable whether medical therapy should be initiated before diagnostic evaluation or vice-versa. The pharmacological therapy includes prokinetics and antacids and agents that suppress gastric and production like H2 receptor antagonists and proton pump inhibitors.

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 (22). It has a high frequency of undesirable side effects, such as cramping and diarrhea and respiratory side effects in infants with asthma. It's rarely used in neonates.

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; 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. Although occasional studies have shown metoclopramide to be somewhat effective in treating GER in the pediatric age group, many researchers have argued that it is either ineffective or that high doses, which may increase the incidence of its side effects, are necessary to cause these therapeutic results (23). The recommended dose is 0.1 mg/kg/dose to 0.2 mg/kg/dose every 8 hourly.

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 seems 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 also known to cause fatal arrythmias. It is of paramount importance to get an ECG before starting the patient, especially preterms, on Cisapride and a QTc interval of more than 0.44 is a contraindication to starting the drug. Other contraindications to use of cisapride are the associated use of other drugs that may increase the QTc interval like erthromycin, 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 abnormalites.

Clinical trials suggest that it may have some benefit in treating GER in infants (24). We give it at a dose of 0.2 mg/kg/dose every 8 hourly.

Erythomycin is nowadays used as a prokinetic for the treatment of GER. It increases the gastric motility at low doses of 3-5 mg/kg/day in two divided doses.

The use of antacids or H2 receptor antagonists (H2RA), Cimetidine and Rantidine certainly can reduce the amount of gastric acid produced in the stomach and may have an effect on peptic esophagitis(25).Side effects include headaches. giddiness.malaise.The dose used is 1-2 mg/kg/dose of Rantidine thrice a day or 10 mg/kg/dose of Cimetidine four times a day .The safety of rantidine in newborns has been well proven.

Efficacy of proton pump inhibitors like Omeprazole for GERD has now been evaluated in pediatric age group and its usually revered for patients who do not respond well to H2RA.In India, however, it is not available in liquid formulation. Lansoprazole is another, drug which is under trial for its use in pediatric age group.

Medical management is appropriate in the infant with moderate reflux symptoms. Medical

therapy should be re evaluated after 2 months.

Surgical Management

Surgery should be used as a last resort in the management of GER. Surgery is generally not contemplated until the baby is near term or weighing 2 kg.

The indications for surgical intervention include:

- Recurrent aspiration pneumonia
- Recurrent ALTE (Acute life threatening episodes)
- Recurrent failures to remain extubated
- Poor weight gain
- Persistent vomiting
- Esophageal bleeding leading to anemia
- Esophageal stricture / ulcerations.

Publication of data from Dalt et al (11) 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%. Surgery is more often required in patients with neurological deficits and GERD. The procedure of choice is a Nissen fundoplication. There has been a high incidence of delayed gastric emptying in infants needing fundoplication (26), 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. Ideally, manometric and oesophageal motility studies are warranted.

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