# Gastroesophageal reflux (GER) in preterms: current dilemmas and unresolved problems in diagnosis and treatment

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**SUMMARY: Kültürsay N. Gastroesophageal reflux (GER) in preterms: current dilemmas and unresolved problems in diagnosis and treatment. Turk J Pediatr 2012; 54: 561-569.**

**Gastroesophageal reflux (GER) is a common physiologic phenomenon in preterm infants. Many infants remain asymptomatic, and the diagnosis of GER is difficult since clinical signs and symptoms are nonspecific. Diagnosis can also be difficult due to technical limitations. None of the currently available agents has been proven to prevent regurgitation. The efficacy and safety of gastroesophageal reflux disease (GERD) therapy have not been studied systematically in preterm infants. Therefore, clinicians must consider the risks and benefits of therapy. Preventive measures should be the first-line intervention. Prone, head upward and left-side positioning may reduce symptoms, but infants must be discharged home in the supine position. Thickening of feeds may be harmful in preterm infants. Frequent small-amount or continuous-drip feeding, short-term trial of hypoallergenic formula and probiotics are among the proposed treatments. Infants with severe symptoms and those who do not respond to the conservative and medical treatment need further diagnostic evaluation and very rarely a Nissen fundoplication.**

***Key words: gastroesophageal reflux, preterms, diagnosis, treatment.***

"Gastroesophageal reflux" (GER) is retrograde and involuntary passage of stomach contents into the esophagus, whereas "gastroesophageal reflux disease" (GERD) is defined as GER associated with clinical signs and symptoms. The fluid reflux is limited mostly to the distal esophagus. Fluid reaching the proximal esophagus and mouth cause regurgitation and/or vomiting (spilling-spitting up)[1].

## Incidence:

Gastroesophageal reflux (GER) is quite common during infancy, especially in preterm infants[2]. Regurgitation with occasional projectile vomiting is the most common presentation of infantile GER. Up to 70% of healthy 3-4-month-old infants regurgitate. Frequent regurgitation, defined as >3 times per day, occurs in about 25% of infants during the first months of life[3].

The increased risk of GER in preterm infants is thought to be due to immature or impaired anatomic and physiologic factors that typically limit reflux. Since the reflux is mostly not acidic, the real incidence is not known. In a radionuclide study, the incidence of GER was 71.2% in a symptomatic group of preterm infants and 61.1% in asymptomatic preterm infants[4]. It has been reported that 25% of preterm infants are discharged home with GERD medications[5].

Most infants with GER remain asymptomatic and do not require further evaluation or intervention. GER resolves on its own by one year of age due to elongation of the esophagus, a more upright posture, increased tone of the lower esophageal sphincter (LES), and a more solid diet[6].

## Risk factors and mechanisms:

Risk factors for GER are prematurity, asphyxia, sepsis, bronchopulmonary dysplasia (BPD), neurodevelopmental delay, congenital and acquired gastrointestinal anomalies (congenital diaphragmatic hernia, fistula, omphalocele), orogastric tubes, and drugs commonly used in preterm infants such as xanthines, dopamine and beta-adrenergics[7].

The LES is a 1-cm long high pressure segment that consists of intrinsic smooth muscles of the esophagus and skeletal muscle of the diaphragm. Functional development of the LES takes place within 45 days after birth, and the LES pressure is normally between 10 to 55 mmHg. GER occurs when it decreases to less than 5 mmHg.

The most common mechanism of GER in the preterm infant is transient relaxation of the LES[7]. During an episode of transient LES relaxation, the pressure of the LES is reduced spontaneously to less than the intragastric pressure, forming a common cavity between the stomach and esophagus. Because the intragastric pressure typically exceeds the intra-esophageal pressure, gas or liquid contents resting in the fundus of the stomach can reflux into the esophagus. Increased intraabdominal pressure and decreased baseline LES pressure are also associated with GER and may play a more significant role in infants who have respiratory or neurological disease. Respiratory problems in formerly preterm newborns have been shown as strong predictors of GERD and reactive airway disease in the toddler ages[8]. Delayed gastric emptying, immaturity of esophageal motility and gastric tubes are other mechanisms causing GER in preterms[2].

Prolonged gastric tube use and feeding intolerance increase the risk for GERD, but antenatal and postnatal corticosteroids, caffeine, duration of mechanical ventilation, and oxygen therapy are not related to GERD risk in very low birth weight (VLBW) preterms with BPD[9]. Clinical predictors of abnormal esophageal pH monitoring in preterm infants have been found as vomiting, regurgitation, apnea, female gender, and acute respiratory distress syndrome (RDS), but not BPD and use of caffeine[10].

Feeding periods are associated with a greater number of refluxes per hour, most of which are weakly acidic; however, the acid exposure is significantly greater during fasting periods[11].

**Clinical signs and symptoms:**

Irritability, generalized behavioral discomfort, vomiting, posturing, grimacing, worsening of lung disease, failure to achieve full feeds, failure to thrive, longer hospitalization, and apnea, bradycardia and desaturation attacks are mostly accepted to be related to GER[2] (Table I). However, most of the time, there is no correlation between symptoms, and the diagnosis is problematic[12].

**Apnea and GER**

General belief is for apnea becoming a symptom or consequence of GER[13]. However, studies on this relationship have reported conflicting results, and data on this discussion are currently not enough to come to a definitive conclusion[13-15].

Inhibition of a normal respiratory pattern by fluid stimulation of the larynx has been shown in animal studies, though not yet confirmed in humans[16]. Data from human studies show that most often apnea precedes a reflux episode and that reflux does not cause apnea[17,18]. From a clinical point of view, the use of anti-reflux medications for improvement of apnea, bradycardia and desaturation episodes is not supported by scientific evidence[19]. Immaturity is the primary problem that leads to both GER and apnea of prematurity (AOP). Both of these clinical problems can occur in the same patient group. Time may be the best and safest therapy in this maturational problem.

**Diagnosis:**

Diagnosis is usually performed based on clinical signs and suspicion of GER. None of the test methods are solely reliable in GER diagnosis.

**Table I.** Clinical Signs and Symptoms of GERD in Preterm Infants

| |
|---|
| Irritability |
| Generalized behavioral discomfort |
| Vomiting |
| Posturing |
| Grimacing |
| Worsening of lung disease |
| Failure to achieve full feeds |
| Failure to thrive |

Investigation is reserved for infants in whom complications have arisen[20].

**1-Esophageal pH monitoring**

Esophageal pH monitoring through transnasal passage of a microelectrode containing a pH sensor into the lower third of the esophagus facilitates 24-hour monitoring after placement is confirmed by radiology. It is a reference diagnostic method for older infants and children. Reflux index is the percentage of time with a pH <4 during the recording. Postprandial milk buffering may lead to underestimation of GER. This technique has limited use in preterms having mostly non-acid reflux due to low acidic gastric pH and also because of the difficult application and long test time.

**2-Technetium scintigraphy**

A nuclear medicine scintigraphy study, often commonly referred to as a "milk scan", allows detection of esophageal reflux events, measurement of gastric emptying time, and detection of aspirated gastric contents in the lungs. However, this technique is more likely to miss reflux events than continuous pH or multiple intraluminal impedance (MII) monitoring.

**3-Multiple Intraluminal Impedance (MII)**

The MII technique depends on electrical resistance changes to current flow between two electrodes due to retrograde passage of fluid or gas inside the esophageal catheter. MII detects acid and non-acid GER if a sequential drop to less than 50% of baseline impedance is detected starting from the LES. MII also differentiates GER from antegrade swallows. The presence and extent of reflux can be observed. However, test time is long, and probe stabilization difficulty and lack of normative data in neonates make it impractical for neonates[21].

**4-Combined multichannel intraluminal impedance and pH monitoring (MII-pH)**

Combined multichannel intraluminal impedance and pH monitoring (MII-pH) is emerging as a useful tool to study both acid and non-acid GER in preterms[22]. A large systematically standardized data collection of MII-pH measurements in 700 children showed that 45% of the patients with abnormal GER would not have been recognized by 24-hour pH measurement alone. MII-pH is superior to pH monitoring alone in detecting GER[23,24]. MII-pH helps to detect acid reflux that may be missed in the smallest infants due to delayed clearance[25].

**5-Esophageal manometry (measurement of sphincter dynamics)**

Manometry classically reveals information about esophageal pressure patterns and sphincter function, but does not inform about bolus flow. This technique is very rarely used in newborns. The combination of MII with manometry may help to evaluate esophageal function and motility together with liquid and air flow[24].

**6-Endoscopy and biopsy**

Endoscopy and biopsy to show esophagitis is not used in preterms. Techniques used to detect GER in older infants and children, including endoscopy and esophageal manometry, are rarely employed in neonates because of size limitation. The need to perform biopsy to diagnose esophagitis is almost non-existent[3].

**7-Ultrasonography**

Studying 21 preterms with significant GER with a reflux index >5 and 10 control newborns, ultrasonography was positive for GER in 8 patients (25.8%). Sonography was negative in 23 newborns (74.2%), 13 of whom were positive on pH monitoring and may therefore be considered as false-negatives. With respect to continuous 24-hour pH monitoring, sonography showed a specificity of 100%, but a very low sensitivity of 38%, with a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 43%. Sonography should not replace 24-hour pH monitoring for detecting GER in preterm infants[26].

**8-Barium passage**

Upper gastrointestinal studies are performed in infants with severe GER to evaluate congenital anomalies in esophageal, gastric, and intestinal anatomy that may cause reflux or vomiting. The procedure is performed under non-physiologic conditions that may provoke reflux that is not clinically important. On the other hand, upper gastrointestinal studies may miss clinically significant GER because the period of fluoroscopic monitoring is brief, typically less than five minutes.

**9-Pepsin assay**

Pepsin assay is a useful tool for correlation

of reflux with airway disease and is a reliable diagnostic marker of extraesophageal reflux (EER). Pepsin assay may identify tracheal pepsin as an indicator of GER and is related to the pulmonary signs and symptoms in preterm patients with BPD[27].

**Differential diagnosis:**

Since commonly accepted GER symptoms such as excessive irritability and crying, food refusal, cough, apnea, choking, and gagging may also be caused by food allergies/intolerances, infections, or functional gastrointestinal disorders such as infantile colic or constipation, the differential diagnosis with these problems is important.

Problems other than GER must be investigated when there is bilious vomiting, gastrointestinal bleeding, diarrhea, constipation, fever, lethargy, abdominal tenderness, distension, or hepatomegaly[2].

**Treatment**

Conservative, pharmacologic and surgical treatments are considered in order.

**1.Conservative treatment**

**a-Positioning**

Positioning infants in a 30° upward prone or left lateral position is mostly preferred by neonatologists since it is known to cause less reflux in older children and adults. In healthy preterm infants, GER is predominantly liquid, and right-side positioning is associated with increased triggering of transient LES relaxation and GER despite accelerating gastric emptying[28]. Feeding infants in the right decubitus position, followed by the left decubitus position one hour later caused faster gastric emptying and less liquid reflux[29].

In a study of eight healthy preterm infants (mean post-menstrual age of 36.1 weeks), more episodes of LES relaxation and GER occurred when infants were placed in a right versus left lateral position[30]. To date, the only non-pharmacological intervention proven to reduce reflux is the positioning of infants on their left side after feeding[31]. The fewest number of acidic and non-acidic GER episodes (4.4 and 0.3%) were observed in the prone position, followed by left lateral positioning (7.5 and 0.7%), supine (17.6 and 1.3%) and right lateral positioning (21.4 and 1.2%)[32]. Placing premature infants in the prone or left lateral position in the postprandial period is suggested as a simple intervention to limit acid GER. However, supine compared with prone sleeping neither increases clinically important acid GER nor obstructive apnea episodes associated with acid GER in asymptomatic, convalescent, prematurely born infants[33].

Caution is necessary when placing infants in non-supine positions because of the risk of sudden infant death syndrome[34]. Because there is no evidence of a preferred position to reduce GER, it is important to model supine positioning prior to discharge in the hospital and to educate families to use the supine sleeping position at home[35].

**b-Feeding regimen**

Overfeeding exacerbates recurrent regurgitation in infants. Frequent feeds with small volumes may help to decrease GER attacks. Breast-feeding has not been proven to cause less GER than formula except in one study. However, since cow's milk intolerance is more frequent in formula- fed infants, a two-week trial of a hypoallergenic formula (protein hydrolysate or amino acid–based) can be considered to exclude intolerance to cow's milk protein as a cause of reflux symptoms in formula-fed infants[34]. Higher protein content of human milk and human milk fortifiers may increase acid reflux in preterm infants[36].

**c-Thickened feeds**

Thickening of feeds with guar gum or cereals or the use of newer milk-based formulas that thicken upon acidification in the stomach reduces the number and height of non-acid reflux episodes and regurgitation, but does not decrease acid reflux events. The use of feeds thickened by rice cereal may be challenging in preterm infants with weak oromotor skills or who are fed by tube feeds. In addition, it remains unclear whether this dietary manipulation is effective in preterm infants[2]. The addition of thickeners may result in changes in formula osmolarity and caloric density, resulting in increased risk of necrotizing enterocolitis and excessive caloric intake[37,38]. Starch thickening of human milk is ineffective in reducing GER in preterm infants[39].

**d-Continuous drip feeding**

Continuous drip feeding reduces vomiting and

reflux symptoms, but chronic use of indwelling tubes that cross the gastroesophageal junction is associated with increased regurgitation and esophagitis. This problem may be avoided by intermittent orogastric tube placement[40].

**e-Transpyloric tube (TPT) feeding**

Transpyloric tube (TPT) in preterm infants bypasses the stomach and, theoretically, reduces the potential for GER. A reduction in apnea and bradycardia episodes was observed with TPT[41]. A review of nine randomized controlled trials (RCTs) concluded that there was no evidence for improved "feeding tolerance" or growth with TPT feeds, but an increased risk for gastrointestinal disturbance requiring cessation of feeds. The studies involved did not evaluate the GER incidence[42].

**f- Probiotics**

Lactobacillus reuteri DSM 17938 at a dose of 1x $10^8$ colony-forming units (cfu) per day reduced gastric distension, accelerated gastric emptying and diminished the frequency of regurgitation[43].

**2. Pharmacologic therapy**

**a. Prokinetic treatment:** Prokinetic drugs increase basal LES pressure, speed clearing of the esophagus and accelerate stomach clearing[2].

**Erythromycin**

Erythromycin increases antral contractility via the motilin receptor and may improve reflux scores and feeding tolerance in preterm infants in a dose of 10 mg/kg/dose orally every 6 hours for two days, followed by 4 mg/kg/dose orally every 6 hours[44]. The increased risk of hypertrophic pyloric stenosis and cardiac arrhythmias should be kept in mind when erythromycin is considered.

**Metoclopramide**

Metoclopramide, recommended as 0.1-1 mg/kg/dose, 4 doses a day before feeds, blocks dopamine and serotonin receptors, and has a-sympathomimetic activity[45]. Adverse effects are seen in up to 34% of children as drowsiness or restlessness, and rarely extrapyramidal reactions. There is limited evidence for the efficacy of metoclopramide in children with GER, and a significant potential adverse effect profile[3,6,20].

**Domperidone**

Domperidone, recommended as 1 ml/kg/day in 3 doses, is a dopamine D2 receptor blocker that increases motility and gastric emptying, and also decreases postprandial reflux time. It has few adverse effects; however, case reports of extrapyramidal adverse effects exist. The studies with small patient numbers and short-term follow-up need to be confirmed in larger trials.

The ESPGHAN working group on GER concluded that the available data for both domperidone and metoclopramide do not support their use in GERD in children[46]. Similarly, NASPGHAN concluded that the effectiveness of domperidone in children is unproven[20].

Cisapride is a prokinetic that stimulates motility in the lower esophagus, stomach and small intestine by increasing acetylcholine release in the myenteric plexus, controlling smooth muscle. Cisapride has been prescribed to more 36 million children worldwide and recommended as "the drug of choice in chronic and persistent GERD in infants and children" by ESPGHAN. However, it was withdrawn in 2000 because of concerns about fatal cardiac toxicity due to prolonged QT interval. In the Cochrane review, no statistically significant effect on GER was shown[47]. In the United States and Europe, cisapride use is still restricted to a limited access program supervised by pediatric gastrologists.

Bethanechol, a muscarinic receptor agonist, was shown to increase LES tonus, but it can cause bronchospasm in patients with respiratory symptoms. At the moment, there is no evidence to suggest the efficacy of bethanechol in reducing GER in children[6].

Baclofen, a gamma butyric acid receptor agonist, reduced the frequency of transient LES relaxation, decreased acid reflux, and accelerated gastric emptying in a placebo-controlled study in infants. It has neurologic side effects in early adult studies[2,6].

Due to lack of efficacy in large meta-analyses (metoclopramide), potential cardiac side effects (domperidone and cisapride), and neurologic side effects (metoclopramide and domperidone), none of these drugs can be recommended at the moment[6].

**b. Surface agents** Mucosal protectors: These

agents prevent development of esophagitis and related symptoms.

Gaviscon Infant (sodium-alginate sachets): Alginate-based reflux suppressant preparations provide symptom relief by forming a physical barrier on top of the stomach contents in the form of a neutral floating gel or raft. It contains sodium and magnesium alginate and mannitol, acts as a feed thickener and prevents reflux by increasing the viscosity of feeds.

Gaviscon Infant contains 0.92 mmoL Na+/dose and has risk of renal impairment and congestive cardiac failure due to high sodium. It may also increase the risk of intestinal obstruction in infants whose feeds are thickened. Other Gaviscon preparations also contain sodium bicarbonate/ potassium bicarbonate to neutralize gastric acid and may have higher risk due to increased sodium load[6].

Sodium alginate was given four times at alternate meals in 32 symptomatic preterm newborns, and 24-hour MII-pH showed that sodium alginate significantly decreased the number of acid GER, acid esophageal exposure and the number of GER reaching the proximal esophagus, without any influence on non-acid GER[48].

Atasay et al.[49] showed that Na alginate improves GER symptoms (vomiting and weight gain), the number of episodes with pH <4 per 24 hours, the reflux index, the number of episodes >5 minutes with pH <4, and the duration of the longest episode with pH <4 in 27 (83%) of 41 preterm infants when used in a dose of four times/day, 1 ml/kg. No side effect was observed except thickening of stool in 3 patients.

**c. Acid suppression:** Acid suppression agents increase gastric pH and reduce esophageal acid exposure during episodes of reflux[2,3,6,20].

1.For buffering: histamine 2 (H2) receptor antagonists (H2RAs, cimetidine, famotidine, ranitidine, or nizatidine)

2.For reducing secreted gastric acid: proton pump inhibitors (PPIs, e.g., omeprazole and lansoprazole).

**H2-Receptor antagonists (H2RAs):**

Ranitidine (p.o.=2 mg/kg/dose, q8h; IV= for term infants: 1.5 mg/kg/dose, q8h and for preterm infants: 0.5 mg/kg/dose, q12h) may be used in esophagitis but this entity is not reliably diagnosed by symptoms alone in infants[44].

Famotidine (0.5 mg/kg) reduced the frequency of regurgitation, and at a dose of 1 mg/kg, reduced crying time in preterm infants[44].

One study of cimetidine in VLBW infants was stopped by the safety monitoring committee because of increased death or severe intraventricular hemorrhage in the cimetidine group[50].

Neither the pharmacokinetic properties of other H2RAs nor their efficacies in the treatment of signs or symptoms of GERD have been evaluated in preterm infants. Because of the risk of heavy-metal toxicity and chronic acid suppression on vitamin or mineral absorption, chronic antacid use in preterm infants is not recommended.

Antecedent H2RA exposure has been proposed to increase the risk of necrotizing enterocolitis and infection[51,52].

**Proton-pump inhibitors (PPIs)**

Proton pump inhibitors (PPIs) increase the pH of gastric contents, decrease the total volume of secretions, and facilitate emptying. PPIs covalently bind and deactivate the H, K-ATPase pumps in the stomach, providing more effective gastric suppression than H2RAs. The pharmacokinetic and pharmacodynamic properties of lansoprazole and omeprazole have been studied only in a small number of neonates[6].

Omeprazole reduces gastric acidity and the duration of acid exposure in preterm infants[53]. A small study of esomeprazole showed a decrease in acidity but not in the frequency, extent or clearance of esophageal boluses in preterm infants and term neonates[54]. In the first few months of infancy, a relative hypochlorhydria exists due to immature parietal cells. Potentiating the hypochlorhydria in neonates further with omeprazole can result in bacterial overgrowth. A double-blinded randomized multicenter trial of infants demonstrated no difference in the reduction of symptoms but serious adverse effects (lower respiratory tract infections) in the lansoprazole group[55]. Lansoprazole is generally recommended as 0.73-1.66 mg/kg/dose, once daily[44].

Pantoprazole (1.2 mg/kg, high dose, once daily) improved pH-metry parameters after ≥5 consecutive daily doses, and was generally well tolerated for ≤6 weeks in neonates, preterm infants, and infants aged 1 through 11 months, with a clinical diagnosis of GERD[56]. Pantoprazole has a shorter half-life than adults but does not accumulate and is well tolerated in preterms[57].

Consequent increases in respiratory infections in critically ill babies have been reported with PPIs[2]. The NASPGHAN consensus statement on GER states that "Proton pump inhibitors (PPIs), the most effective acid suppressant medications, are superior to histamine H2 receptor antagonists in relieving symptoms and healing esophagitis."[20] In older children with GERD, acid suppression is the mainstay of treatment, and the largest evidence base supports the initial use of H2RAs. For infant GERD, ranitidine and omeprazole and probably lansoprazole are safe and effective medications that should provide symptomatic relief and endoscopic and histological healing of esophagitis. More evidence is needed before other H2RAs/PPIs or other antireflux medications can be recommended[2,6].

3. Surgical intervention (fundoplication) is reserved for infants with severe GERD who have failed aggressive medical management. These patients often have major central nervous system and respiratory morbidity, or have suffered a life-threatening event associated with reflux[58].

The best results are obtained in isolated GER, as the recurrence rate of GER in infants with associated anomalies is high[59]. In a metaanalysis, surgical relief of symptoms was given as 86%[60]. The operative complication rate of fundoplication is between 1.6% and 4.6%, and the postoperative complication rate is between 8.2% and 10.6%[61]. GERD-related symptoms can persist in up to two-thirds of children who undergo antireflux surgery. Many of these children continue to receive GERD medical therapy two months following the procedure[62].

## Conclusion

In conclusion, there is no reliable test for GERD diagnosis nor a reliable or effective single treatment at the moment. Careful and noninvasive pretreatment differential diagnosis, conservative approach and preventive methods should be effectively applied before multiple pharmacologic drugs, and treatment must be stopped if not effective. Multidisciplinary follow-up of complicated cases is necessary.

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