GER in Preterm Infants

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Abstract

Gastroesophageal reflux (GER) typically occurs in preterm infants, mostly due to the immaturity of the lower esophageal sphincter and the still impaired esophageal motility. Only in a minority of cases, GER is pathological and known as gastroesophageal reflux disease (GERD).

In symptomatic infants with less than 34 weeks of corrected age, the degree of immaturity is such that any manifestation of GERD should be considered above all an expression of "feeding intolerance" before starting specific treatment. Afterward, food allergies and dysmotility patterns should be ruled out, given the overlapping symptoms. Symptoms usually resolve spontaneously with the growth and maturation of the neonate.

A clinical score could be useful to objectively evaluate symptoms and monitor therapeutic response, but Multichannel intraluminal impedance and pH monitoring (MII-pH) represents the gold standard to discriminate GER from GERD. It also allows establishing relationships between symptoms and GER. Recently, further steps were taken to obtain reference values in infants, analyzing MII-pH traces obtained in infants with negative results.

Other diagnostic tools (such as upper gastrointestinal contrast study and sonography) could be useful to assess gastric morphology and emptying but should not be routinely used to diagnose GERD.

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Firstly, a conservative approach must be used, improving feeding tolerance and stopping xanthines as soon as possible. Hydrolyzed protein formulas could reduce esophageal acid exposure and improve gastric emptying, but they should be administered only for a brief period since they are hypocaloric.

Secondly, no studies demonstrated a symptom reduction in preterm and full term infants after treatment with proton pump inhibitors (PPIs). Considering the higher risk of necrotizing enterocolitis, nosocomial infections, and mortality described for infants exposed to ranitidine, due to acid suppression, PPIs should be reserved only for patients with documented reflux esophagitis or acid-GER-related symptoms.

Keywords

Premature infants · Apnea of prematurity · Feeding intolerance

Introduction

Gastroesophageal reflux (GER), the passage of gastric contents into the esophagus, is a physiological phenomenon in the neonate, especially if born preterm [1]. A physiological GER frequency of about 2–4 events per hour has been detected in neonates [2].

Among factors contributing to GER in preterm infants, there are the prolonged lying position and the relatively large fluid intake (180 mL/kg per day would correspond to a daily intake of about 14 L/day in adults). However, most events are due to the immaturity of the lower esophageal sphincter (LES) with transient LES relaxations (TLESRs) and the still impaired esophageal motility typical of this age group [3].

GER events can be classified, according to esophageal pH recorded during the event, as acid (pH < 4), weakly acidic (pH 4–7), or weakly alkaline (pH > 7) [4].

In preterm infants, GER events are mainly nonacid due to the buffering effect of frequent milk feeds [2, 5]. Only in a minority of preterm infants, GER is pathological and known as gastroesophageal reflux disease (GERD) [6, 7]. This occurs when the acidity of refluxes, their number, and duration increase excessively and interfere with growth and life habits. This may also depend on the presence of risk factors such as the presence of gastric tube, respiratory distress, and bronchopulmonary dysplasia. [8].

In symptomatic infants with less than 34 weeks of corrected age, the degree of immaturity is such that any manifestation of GERD should be considered above all an expression of "feeding intolerance" (FI). Therefore, pharmacological therapies aimed directly at the resolution of GERD should not be considered the first-line treatment, but it is advisable before implementing all the procedures aimed at improving feeding tolerance [9].

Although a possible association between GER and apneas of prematurity (AoP) has been frequently hypothesized and continues to be a topic of significant debate and investigation, there is still a lack of evidence supporting a temporal association

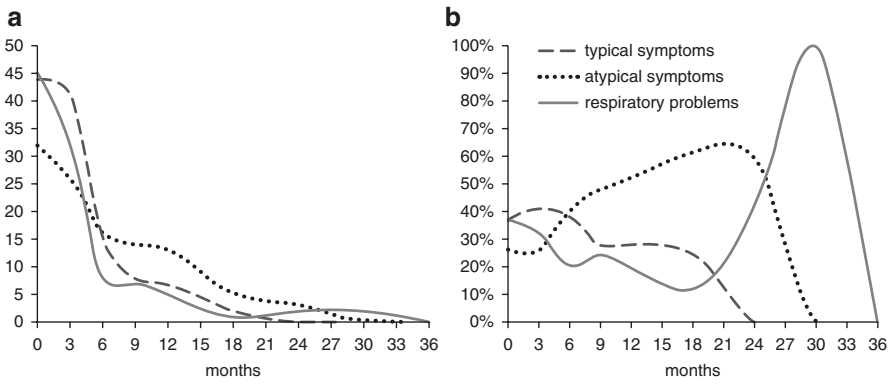

Fig. 6.1 Frequency of GERD symptoms by symptom category during follow-up. (**a**) Absolute frequencies. (**b**) Normalized frequencies [2]

or even a causal relationship. Indeed, in clinical practice, apneas are frequently detected during postprandial periods when the majority of GER events typically occur [10]. Cresi et al. reported that these episodes are associated with reflux only in 12% of cases. In these infants GERD is severe and reflux acts as a trigger to elicit apnea. Therefore, they should not be treated with drugs or dietary therapy for GERD, without specific diagnostic tests.

In symptomatic infants with more than 34 weeks of corrected age, GERD symptoms can be depending on food allergies (such as cow's milk allergy—CMA) as well as dysmotility patterns and feeding intolerance. Moreover, CMA and GERD may manifest similar symptoms in infants making the diagnosis challenging [11]. These associations, if confirmed by clinical and instrumental examinations, may be worthy of treatment.

Furthermore, clinicians should consider that GERD symptoms tend to change over time and usually resolve spontaneously with the growth and maturation of the newborn, as shown by Cresi et al. in Fig. 6.1 [2].

Diagnosis

Clinical Evaluation

Clinical evaluation is the main tool leading to the diagnostic suspicion of GERD and sometimes to a diagnosis. GERD symptoms in preterm can be classified as:

- Typical/Gastrointestinal (excessive regurgitation, vomiting);
- Atypical (irritability, bowing and feeding difficulties, sleep disturbances, failure to thrive);
- Respiratory (apnea and desaturation, cough, laryngeal stridor, worsening of lung disease) [2].

However, a clinical score could be useful to better and objectively evaluate symptoms and monitoring effects of introduced therapies. Although no questionnaires showed a high sensitivity and specificity for GERD in infants [12], the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) is a validated tool to monitor the evolution of symptoms during an intervention trial [13].

Multichannel Intraluminal Impedance and pH Monitoring (MII-pH)

Nowadays, Multichannel intraluminal impedance and pH monitoring (MII-pH) represents the gold standard to discriminate GER from GERD [6].

MII-pH can detect GER and discriminate episodes not only by pH values but also by duration and proximal extent. MII-pH also allows to establish relationships between symptoms and GER, if associated with a precise clinical diary or cardiorespiratory monitoring, such as symptom index (SI: number of GER related symptoms out of the total number of symptom episodes x 100; positive if ≥50%) and symptom association probability (SAP: the likelihood that the patient's symptoms are related to GER, computed analyzing consecutive 2-min segments through Fisher contingency table; positive if ≥95%) [4].

As MII-pH is an invasive test, for ethical reasons it cannot be performed on healthy infants, making it challenging to obtain traditional reference values for MII-pH parameters, i.e., from a normal, healthy population. However, further steps were recently taken to obtain reference values, analyzing MII-pH traces obtained in neonates and infants with negative results [14].

Furthermore, MII-pH can be used to determine the effectiveness of adopted treatments.

There are still three main limitations to using MII-pH in preterm infants: (1) there are no specific MII-pH probes for infants with a weight less than 1500 g; (2) its feasibility is limited during noninvasive ventilation; (3) there are no reference values for tube-fed infants (apart from data reported by López-Alonso et al. in a little sample of 21 preterm newborns fed by a modified nasogastric tube [15]).

Other Diagnostic Tools

Upper gastrointestinal contrast study could be useful to identify anatomical problems that cause GER but it should not be used to diagnose GERD, because of its low sensitivity [16]. Furthermore, it does not provide information on the quality and quantity of refluxes and involves the use of radiation. It can be reserved for those going for surgery and those with negative MII-pH results but strong clinical suspicion of GER [17].

Sonography should not replace 24 h MII-pH monitoring for detecting GER in preterm infants but is suitable to study the activity and characteristics of the pylorus and gastric emptying time in infants with vomit [18].

Use of Proton Pump Inhibitors as a Diagnostic Test

A trial with proton pump inhibitors (PPI) for a week ("PPI test") with careful monitoring of symptoms could be diagnostic in preterms with severe symptoms and unresponsive to first level treatments, in which MII-pH is still not feasible (low birth weight, noninvasive ventilation, tube feeding, etc.). However, no studies clearly demonstrated a symptom reduction in preterm and full term infants after treatment periods ranging from 2 to 4 weeks [19].

Use of Extensively Hydrolyzed Protein Formula as a Diagnostic Test

The use of an extensively hydrolyzed protein formula (eHPF) could be evaluated for reducing esophageal acid exposure in preterm infants with feeding intolerance and symptoms of GER after 34 weeks of corrected age, due to its buffering property and effects on gastrointestinal motility [20].

Corvaglia et al. reported a significant reduction in the number of GERs detected by pH monitoring in a sample of preterm infants with symptoms of feeding intolerance (large gastric residuals, abdominal distension, and constipation) and GER (frequent regurgitations and/or postprandial desaturations) nourished with an eHPF, when compared to their peers managed with standard preterm formula (SPF) [21].

Treatment

Conservative Approach

Improvement of Feeding Tolerance

The definition of FI varies and different strategies to improve feeding tolerance should be addressed. An excessive volume of meals may overwhelm the capacity of neonatal gut; thus, a reduction in the volume of meals fractioning them in smaller but more frequent meals could be useful to optimize enteral nutrition [22].

Slow advancement of enteral feed volumes is historically considered as a safe strategy to improve feeding tolerance, but current evidence actually indicates that advancing enteral feed volumes slowly (daily increments up to 24 mL/kg) compared with faster rates (30–40 mL/kg/day) probably does not reduce the risk of necrotizing enterocolitis, death, or feed intolerance in very preterm or very low birth weight (VLBW) infants. Even if advancing enteral feeding at a faster rate seems safe in terms of feeding tolerance [23], no specific data on how it can influence GER is reported. Therefore, feeding strategy should be the same as for healthy preterm infants while fractioning meals and monitoring GER as a sign of feeding intolerance.

How to administer feeding is another area of uncertainty: infants receiving continuous nasogastric milk feeding, using an infusion pump, every 2 or 3 h, may reach full enteral feeding slightly later than their peers receiving slow intermittent feeding

[24]. Intermittent bolus milk feeds may be administered by a syringe to gently push milk into the infant's stomach (push feed). Alternatively, milk can be poured more physiologically into a syringe attached to the tube and allowed to drip in by gravity (gavage feed). To date, there is still not enough literature to determine whether the use of push compared with gavage feeding results in a more rapid establishment of full gavage feeds without increasing side effects in this category of neonates [25].

Furthermore, routine monitoring of gastric residual (GR) in preterm infants gavage-fed is a common practice, in the absence of real advantages. This practice should be abandoned, considering that avoiding routine GR monitoring has been postulated that can reduce late-onset sepsis and promote an earlier achievement of full enteral feeding and an earlier discharge from the hospital [26].

In addition to feeding strategies also body positioning can play a role in improving feeding tolerance. Indeed, different postures can influence gastric emptying and GER. The prone or left lateral position in the postprandial period is a simple intervention to limit GER in preterm infants. Corvaglia et al. analyzed MII-pH traces in a cohort of premature infants, showing a lower esophageal acid exposure in these positions [27].

Probiotics may be an useful tool in improving early feeding tolerance in preterm infants, but it is difficult to assess the real impact due to heterogeneity of administered species and in available studies [28].

The administration of xanthines for AoP (caffeine) should be stopped as soon as possible in neonates with clinical suspicion of GER, given the detection of pepsin (a reliable marker of gastric aspiration) in tracheal aspirates from preterm ventilated neonates during xanthine therapy, due to its effect on LES relaxation [29].

Use of Hydrolized Protein Formula

Extensively hydrolyzed protein formulas (eHPFs) are often used in these infants due to their effects on gastrointestinal motility, gastric emptying time, and GER episodes [21].

Patients fed with standard formula reach faster a gastric pH below 4 during gastric emptying [30], explaining the decrease in acid refluxes observed after meals with eHPFs by Corvaglia et al. [21].

Hydrolysis of lactose can improve feeding tolerance in some cases, although evidence is still lacking (and further studies are needed to compare lactase-treated feeds and placebo) [31].

However, the nutritional characteristics of hydrolyzed formulas are not adequate for preterm infants [32], since they are hypocaloric. Therefore, they should be reserved for severe cases and only for a brief period (1–2 weeks).

Medications

First-Line Treatments

Commercial thickened formulas provide controlled concentrations of different thickening agents (locust bean gum/carob flour, tapioca, potato, rice, corn starch),

reducing the frequency and severity of regurgitations: they are indicated in formula-fed infants with persisting symptoms despite reassurance and verify of appropriate feeding volume intakes [33]. However, a possible association between thickened feedings and necrotizing enterocolitis has been identified in preterm infants [34]. Therefore, they are not suitable for premature infants. They should be taken into consideration only in case of dysphagia (on logopedic indication), or in cases of GERD with poor growth secondary to excessive regurgitation and vomiting.

Alginate-based formulations, acting as physical protection of the gastric mucosa, are commonly employed to treat GERD. In the presence of gastric acid, sodium alginate precipitates to form a low-density but viscous gel, while sodium bicarbonate, usually contained in these formulations, is converted to carbon dioxide, with a buffering and thickening effect [35]. Sodium alginate (Gaviscon Infant®) seems to significantly reduce acid GER episodes, with the advantage of a nonsystemic mechanism of action and a favorable safety profile [36]. No effects on GER-related apneas were detected by Corvaglia et al. using MII-pH [37].

Second-Line Treatments

Despite lack of evidence and increasing safety concerns, Slaughter et al. warned about the increase in prescription of Histamine-2 (H2) Receptor Antagonists (H2RA) and proton pump inhibitors (PPIs) to extremely preterm neonates and those with congenital anomalies, often continuing them also through discharge [38].

H2RA (i.e., ranitidine) compete with histamine for the H2 receptor in the parietal cells in the stomach, reducing hydrochloric acid secretion and buffering intragastric pH.

Terrin et al. reported that the risk of NEC, nosocomial infection, and mortality were significantly higher in the infants exposed to ranitidine [39].

Nevertheless, H2RA was frequently prescribed for infants in whom GER is clinically diagnosed. However, the finding that ranitidine spontaneously breaks down to a cancer-causing chemical caused its removal from the market in the US and other countries in 2020.

Proton pump inhibitors (PPIs, i.e., omeprazole, esomeprazole, etc.) dramatically reduce gastric acidity, inhibiting the last step of gastric acid secretion in the parietal cells regardless of the stimulus for acid secretion. Data on the safety and efficacy of PPIs in preterm neonates are few and controversial [35] and their use is still off-label for infants.

Omari et al. yielded a reduction in the frequency of acid GER events and esophageal acid exposure using omeprazole in preterm infants, although without significant changes in the number of symptomatic events [40]. Similarly, Orenstein et al. reported no significant changes in typical GER symptoms among term and preterm infants treated with lansoprazole or placebo. On the contrary, serious adverse events, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo [41].

To date, there are no studies that examined the association between PPIs and necrotizing enterocolitis in preterm infant, but all are based on H2RA [42]. However, acid suppression is higher in patients who receive PPIs [43], causing the disruption

of gut ecosystem and enhancing thus the growth of pathogens that could be pivotal in the pathogenesis of NEC [44].

Therefore, PPIs should be reserved only for patients with documented reflux esophagitis or acid-GER-related symptoms.

Regarding the use of prokinetics (i.e., erythromycin, domperidone, etc.), there is still no evidence of the positive effects on GERD in preterm infants. They can be used to improve gastric emptying, intestinal mobility, and feeding tolerance only in selected cases and in cases of documented LES incontinence (enhancing its tone) [45]. Indeed, prolongation of QTc interval is a well-known side effect of prokinetics; cardiac monitoring or at least serial ECGs should be performed before and during administration [46].

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