

# Gastroesophageal Reflux: A Critical Review of Its Role in Preterm Infants

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**ABSTRACT.** There is widespread concern about gastroesophageal reflux (GER) in preterm infants. This article reviews the evidence for this concern. GER is common in infants, which is related to their large fluid intake (corresponding to 14 L/day in an adult) and supine body position, resulting in the gastroesophageal junction's being constantly "under water." pH monitoring, the standard for reflux detection, is of limited use in preterm infants whose gastric pH is >4 for 90% of the time. New methods such as the multiple intraluminal impedance technique and micromanometric catheters may be promising alternatives but require careful evaluation before applying them to clinical practice. A critical review of the evidence for potential sequelae of GER in preterm infants shows that 1) apnea is unrelated to GER in most infants, 2) failure to thrive practically does not occur with GER, and 3) a relationship between GER and chronic airway problems has not yet been confirmed in preterm infants. Thus, there is currently insufficient evidence to justify the apparently widespread practice of treating GER in infants with symptoms such as recurrent apnea or regurgitation or of prolonging their hospital stay, unless there is unequivocal evidence of complications, eg, recurrent aspiration or cyanosis during vomiting. Objective criteria that help to identify those presumably few infants who do require treatment for GER disease are urgently needed. *Pediatrics* 2004;113:e128–e132. URL: <http://www.pediatrics.org/cgi/content/full/113/2/e128>; *lower esophageal sphincter, regurgitation, treatment indications.*

**ABBREVIATIONS.** GER, gastroesophageal reflux; CMA, cow milk protein allergy; TLESR, transient lower esophageal sphincter relaxation; GERD, gastroesophageal reflux disease; MII, multiple intraluminal impedance; AOP, apnea of prematurity; NICU, neonatal intensive care unit.

Gastroesophageal reflux (GER) is common in preterm infants, occurring on average 3 to 5 times per hour,<sup>1,2</sup> but to what extent is it a clinical problem? A recent survey of current practice estimated that 19% of preterm infants admitted to US teaching hospitals received cisapride.<sup>3</sup> Thus, many neonatologists seem to consider GER indeed a problem, but what is the evidence? This article revisits the pathogenesis of GER in preterm infants and discusses methods for reflux detection, cow milk protein allergy (CMA) as a potential differential diagno-

sis, and clinical problems potentially resulting from GER.

## PATHOGENESIS OF GER IN INFANTS

Reflux may occur when the lower esophageal sphincter relaxes. In an upright adult, gas will exit the stomach during these transient lower esophageal sphincter relaxations (TLESRs), causing belching. In a subject lying supine, however, the gastroesophageal junction is constantly under water, and liquid instead of gas will enter the esophagus. The quantity of the reflux depends on the fluid volume inside the stomach. The volume of fluid given to an infant (180 mL/kg per day) would correspond to a daily intake of ~14 L/day in an adult. GER in an otherwise healthy infant may simply serve as a pop-off valve to cope with this high volume.<sup>4</sup> Thus, GER may be a completely normal phenomenon in infants, and its frequent occurrence in this age group may be merely a result of their age-specific body position and high fluid intake. Whether GER will become clinically relevant will then depend on the quality (eg, pH) and the quantity of the refluxate.

These theoretical considerations were recently confirmed in preterm infants.<sup>5</sup> Using a micromanometric transducer device also incorporating a pH catheter and a feeding tube, Omari et al<sup>5</sup> studied TLESR in 36 preterm infants, 14 of whom had symptomatic GER, ie, GER disease (GERD). They found that both symptomatic and asymptomatic infants had 92% and 94%, respectively, of their reflux episodes associated with TLESR. The latter were triggered by gastric distension (eg, feeding) and abdominothoracic straining (eg, during motion). TLESRs were equally common in infants with and without GERD, the only group difference being a higher proportion of acid GER (16.5% vs 5.9%) in symptomatic infants. Acid GER was reduced by low-volume feeds and shorter feeding intervals. The authors concluded that infants with GERD do not have more TLESRs but some anatomic or sensory variation that increases the likelihood for liquid and/or acid reflux to occur during TLESR.<sup>5</sup>

One factor that increases this likelihood is a feeding tube. Using the multiple intraluminal impedance technique, a pH-independent method for reflux detection (see below), we studied the frequency of GER with and without an 8-French nasogastric tube passing through the lower esophageal sphincter. We found that the frequency of GER almost doubled when the tube ended inside the stomach instead of the esophagus, ie, when lower esophageal sphincter competence was likely impaired.<sup>6</sup>

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A traditional view has been that infants with GERD have delayed gastric emptying, allowing more time for reflux to occur after a meal. Recently, however, both Omari et al<sup>5</sup> and Ewer et al<sup>7</sup> showed that gastric emptying was not delayed in infants with GERD. This finding has practical consequences as it questions the rationale for prokinetics in the treatment of GERD. After the recent withdrawal of cisapride, there is now increasing interest in the use of erythromycin, which binds to neural motilin receptors and stimulates antral contractions and, in lower doses, induces antral migrating motor complexes, which are important for gastric emptying.<sup>8</sup> Although 2 recent randomized, controlled trials reported a more rapid achievement of full oral feeds in infants who were treated with erythromycin (10–12 mg/kg per day),<sup>9,10</sup> there remain several concerns with this practice, including the potential to induce cardiac arrhythmias, pyloric stenosis, or septicemia from multiresistant organisms.<sup>9</sup> Also, a recent developmental study on the effects of erythromycin on migrating motor complexes showed that these were induced only in infants with gestational ages of 32 weeks or older.<sup>11</sup> Delayed feeding advancements resulting in prolonged parenteral nutrition, however, are a problem mainly in infants who are born well before 32 weeks' gestation. Thus, the role of delayed gastric emptying in promoting GER and the potential usefulness of erythromycin in treating the physiologically slow gastrointestinal motility in this age group remain at present unclear.

#### METHODS FOR REFLUX DETECTION

Reflux detection requires continuous measurements; that 1 or 2 reflux episodes occur during a 10-minute radiologic, scintigraphic, or sonographic investigation does not allow any conclusion as to whether a patient has GERD.<sup>12</sup> For this reason, pH monitoring has become the "gold standard" for reflux detection. With the introduction of antimony pH electrodes, this technique has become easy to use and also allows measurements at multiple sites, eg, in both the stomach and the esophagus, or above the lower esophageal sphincter and at the pharyngeal level.<sup>13</sup> The main disadvantage of pH monitoring is that it relies on gastric acidity: GER cannot be detected when gastric pH is >4. This is relevant in infants, particularly those who are born preterm, who may have gastric pH values >4 for >90% of the time, making it almost impossible to detect GER by this technique.<sup>13,14</sup>

A potential solution to this dilemma is the multiple intraluminal impedance (MII) technique, which has recently become commercially available. This technique is based on the intraluminal measurement of electrical impedance between a number of closely arranged electrodes during a bolus passage. Electrical impedance is defined as the ratio between voltage and current and is inversely proportional to electrical conductivity.<sup>15</sup> The underlying principle of MII is to record changes in impedance in the gastrointestinal lumen that are caused by the passage of a bolus, with air having a low conductivity and yielding an impedance increase and liquid having a high conduc-

tivity yielding an impedance decrease.<sup>16</sup> On the basis of the temporal sequence of these changes in impedance, it can be identified whether a change in impedance is caused by a bolus moving in an antegrade (eg, swallow) or a retrograde (reflux, belching) direction. The technique has been used to study upper and lower gastrointestinal motility in adults.<sup>17</sup> In infants, it has been used mainly for GER detection, for which it has been shown to be extremely sensitive, detecting bolus volumes as small as 0.1 mL, and to yield reproducible results.<sup>18,19</sup> Its major drawback is that analysis is currently extremely time-consuming, but semiautomatic analysis tools, which may solve this problem, are under development.<sup>20</sup> A recent review of this technique is available.<sup>15</sup>

An additional potential alternative is the micromanometric feeding assembly combined with an antimony micro pH electrode developed by Omari et al.<sup>5,21</sup> This assembly, however, requires a catheter across the lower esophageal sphincter, which may interfere with sphincter competence, increasing the likelihood of GER.<sup>5</sup>

A practical approach to reflux detection was recently suggested by James and Ewer<sup>22</sup>. These authors performed acid tests in oropharyngeal secretions. Litmus testing for acid (1 or more positive acid tests) was found to have 89% sensitivity and 80% specificity compared with 24-hour pH monitoring. The authors suggested that the demonstration of 2 or more positive acid tests in oropharyngeal secretions is sufficient to initiate positional treatment in infants with symptoms suggestive of GERD.<sup>23</sup> The scientific evidence for this suggestion, however, remains scant, but given the prevailing uncertainty regarding the diagnosis of GERD, it may be a reasonable compromise.

#### CMA AS A DIFFERENTIAL DIAGNOSIS

That recurrent vomiting in a preterm infant can be a symptom of an underlying anatomic, metabolic, infectious, or central nervous disorder is widely known; an extensive review of these underlying conditions is beyond the focus of this article. In addition, vomiting, feeding problems, failure to thrive, and irritability, the leading symptoms of GERD, are characteristic of CMA. This disorder affects between 0.3% and 7.5% of term infants, usually within the first 4 months of life.<sup>24</sup> Recently, it has also been described in preterm infants, who shared the same symptoms and also had the eosinophilic inflammation of the antral mucosa characteristic of CMA in older infants.<sup>25</sup> Although the incidence of CMA at this age is yet unknown, the authors suggested that CMA should be considered in preterm infants with recurrent vomiting and irritability.<sup>25</sup> Confirmation of this diagnosis (and treatment) consists of a trial of cow milk protein-free formula. It has to be kept in mind, however, that some infants are also allergic to hydrolysate and will respond only to an amino acid-based formula. More data on the relevance of this potential underlying diagnosis in preterm infants with recurrent vomiting are required.

## POTENTIAL CLINICAL PROBLEMS RESULTING FROM GER

### Apnea

Problems that are frequently cited in conjunction with GER are apnea, failure to thrive, and airway problems such as recurrent aspiration or wheezing.<sup>26</sup> Preterm infants often exhibit both apnea and GER, and the belief that the latter is an underlying cause of apnea of prematurity (AOP) is evident from the fact that it was the most frequent indication for the widespread use of cisapride in preterm newborns (see above).<sup>3</sup> The evidence for this proposed relationship, however, is largely circumstantial and includes the observation that AOP occurs frequently in the immediate postprandial period,<sup>27</sup> ie, when GER is most likely to occur. It also includes data from animal studies that show that apnea can be induced by the instillation of small amounts of liquid into the larynx, resulting in stimulation of laryngeal chemoreceptors,<sup>28</sup> and the observation that apneas are more likely to occur after episodes of regurgitation.<sup>29</sup> The latter observation is supported further by anecdotal reports of apneic spells occurring immediately after a reflux episode.<sup>30,31</sup> Most studies that attempted to document a temporal relationship between apnea and GER, however, failed to do so.<sup>32-38</sup>

We recently addressed this issue by performing simultaneous recordings of MII and cardiorespiratory signals in 19 preterm infants with AOP. The frequency of apnea occurring within 20 seconds of a reflux episode was not significantly different from that during reflux-free epochs (0.19 vs 0.25/min). The same was true for desaturations and bradycardias, which are often considered more likely than central apneas to be associated with GER. Only 9 (4.8%) desaturations were associated with a reflux episode, and the frequency of desaturation occurring with GER was again not significantly different from that occurring during reflux-free epochs. Also, only 1 of 44 bradycardias occurred within  $\pm 20$  seconds of a reflux episode. Thus, both cardiorespiratory events and GER were common in these infants but were not temporally related.<sup>1</sup>

Similarly, Page and Jeffery<sup>39</sup> observed that preterm infants who were studied at term-equivalent age responded to the pharyngeal infusion of small volumes of 0.9% saline or water during sleep with a volume-dependent increase in swallowing frequency but not with an increased apnea rate. These authors suggested that apnea and bradycardia are predominantly evoked when the larynx rather than the pharynx is stimulated, which does not usually occur during regurgitation of small amounts of liquid.<sup>39</sup> Finally, treatment with cisapride or metoclopramide had no effect on AOP.<sup>40</sup> Infants in these studies,<sup>1,39,40</sup> however, were not selected because they had symptoms suggestive of GER-related apnea. Thus, there may be the occasional infant with such symptoms, as also reported in case studies.<sup>30,31</sup> In the majority of infants with AOP, however, the latter seems to be unrelated to GER and therefore does not justify provision of anti-reflux treatment.

### Failure to Thrive

Failure to thrive, a symptom frequently reported in older infants with GER,<sup>26</sup> seems rare in preterm infants who exhibit this disorder. Khalaf et al,<sup>41</sup> in a cohort study of 150 neonatal intensive care unit (NICU) residents evaluated by a pH study, did not find a significant difference in body weight between infants with and without GER. A recent case-control study from another NICU confirmed these findings. Specifically, weekly weight gain and caloric intake were similar between groups. Nonetheless, infants with GER had a significantly longer hospital stay than those without (99 vs 70 days;  $P < .002$ ).<sup>42</sup> Thus, it seems that the close attention given to weight gain in NICU residents seems to protect against the failure to thrive often seen in older infants with GERD but that physicians are still sufficiently concerned by GER to keep these infants in the hospital for longer periods of time. Whether this concern is justified remains to be proved.

### Airway Problems

GER may undoubtedly cause pulmonary aspiration, but this is usually a dramatic event that is clinically and radiologically apparent. The more controversial issue is whether chronic airway problems may be caused by clinically inapparent or "silent" GER. In one of the first studies that addressed this issue in infants, midesophageal pH, exhaled CO<sub>2</sub>, and breathing movements were measured in six 2- to 12-month-old infants with stridor; 5 of these also had some clinical suspicion of GER. Within 5 to 20 minutes after onset of acid reflux, retractions and stridor were observed in all infants. Stridor improved with medical management (bethanechol, positioning, feed thickeners) in all 5 infants in whom this was attempted.<sup>43</sup> More recent, Bibi et al<sup>44</sup> studied 116 children, aged 3 to 28 months, with flexible bronchoscopy including bronchoalveolar lavage and chest radiography; 54 of these had tracheo- and/or bronchomalacia. Patients with recurrent vomiting and/or feeding-related or unexplained cough (24 in the malacia group, 41 in the control group) underwent pH monitoring and barium radiography. Children with airway malacia were more likely than those without to have GER (70% vs 39%;  $P < .01$ ) and had higher scores for lipid-laden alveolar macrophages in their bronchoalveolar lavage fluid (92-101 vs 52), suggesting reflux-related recurrent microaspirations in the former group. Infants with GER were treated with antireflux therapy, and an improvement in respiratory symptoms was noted.<sup>44</sup>

Several issues remain unclear from these studies. First, assuming a causal relationship, is GER cause or effect of the respiratory symptoms, ie, does it result in airway narrowing via stimulation of airway receptors and/or recurrent aspiration, or do the large intrathoracic pressure swings caused by the upper airway narrowing facilitate GER? Although the respiratory response to GER treatment described above supports the first option, it cannot prove it. It is not even clear whether there is any causal relationship. For example, a recent 1-year follow-up study of

63 infants with GER did not find an increased prevalence of airway problems in this cohort.<sup>45</sup> Also, a comparison between infants with respiratory symptoms suggestive of GER and those with gastrointestinal symptoms only found less GER in the upper esophagus in the respiratory than in the control group (eg, a mean reflux index of 0.95 vs 4.0).<sup>46</sup> Second, are data from older infants and toddlers transferable to preterm infants? The only study that investigated the relationship between airway problems and GER in this age group studied infants with bronchopulmonary dysplasia and found less reflux in the upper esophagus in these than in those without bronchopulmonary dysplasia.<sup>47</sup> Thus, despite the above data from older infants, there is currently no evidence that GER is a significant contributor to chronic airway problems in preterm infants. Why then treat it?

### CONCLUSION

Clearly, there are some preterm infants in whom GER causes serious problems, such as aspiration of gastric contents or recurrent cyanosis, or whose recurrent vomiting is related to CMA. These infants undoubtedly warrant treatment, which should involve a stepwise approach, starting with prone or left lateral positioning (under cardiorespiratory monitoring)<sup>48,49</sup> followed by frequent low-volume feeds,<sup>5</sup> removal of feeding tubes between feeds,<sup>6</sup> feed thickening,<sup>2</sup> possibly histamine-2 receptor antagonists,<sup>50</sup> and finally a trial of cow milk protein-free formula.<sup>25</sup> They should be viewed separately, however, from the vast majority of infants who have physiologic GER and do not require treatment. There is currently insufficient evidence to justify the seemingly widespread practice of treating GER in infants with symptoms such as recurrent apnea and recurrent regurgitation or prolonging their hospital stay. Objective criteria that help to identify those presumably few infants who do require treatment for GERD are urgently needed.

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