Gastroesophageal reflux in the 21st century

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Purpose of review
Gastroesophageal reflux (GER) remains a common, challenging problem for clinicians, with differentiation of normal development from disease a particular issue. This review updates clinicians on advances in diagnosis of GER, relationship to other problems, and current practice in management.

Recent findings
Development and understanding of multichannel intraluminal impedance-pH monitoring has given insights into the relationship of GER to symptoms. Medical treatment has changed little. Avoidance of overmedicalizing normal development is the major issue for clinicians. Laparoscopic fundoplication is established as equivalent to open fundoplication. Newer endoscopic techniques have only limited use in children to date.

Summary
Major changes in pediatric GER relate to understanding of physiology and relationship of GER to symptoms. The major challenge for clinicians involve differentiation of normal from abnormal GER, and applying the most relevant management.

Keywords
gastroesophageal reflux, gastroesophageal reflux disease, multichannel intraluminal impedance-pH monitoring, overuse of medication

INTRODUCTION

Gastroesophageal reflux (GER) remains a clinical challenge. It is common and a significant burden. In the USA, GER disease (GERD) is the leading primary care gastrointestinal diagnosis, and the commonest reason for upper gastrointestinal (UGI) endoscopy [1▪]. A nationwide Swedish working-age adults study identified GER symptoms as a common cause of work absences [2▪].

BURDEN

There are few pediatric-specific data on GER and GERD prevalence. French researchers estimated that 10% of all children had GER and 6% experienced GERD [3▪▪]. A register of 10 394 patients seen by general practitioners and pediatricians documented the occurrence of GER or GERD. Extrapolating the findings to reflect population demographics, it was estimated that 24.4% of infants aged 0–23 months, 7.2% of children 2–11 years, and 10.7% of adolescents aged 12–17 years had symptoms of GER, and GERD was present in 12.6% of infants, 4.1% of 2–11-year-olds, and 7.6% of 12–17-year-olds [3▪▪].

Drug prescription is an indirect measure of disease prevalence. In the USA, off-label proton pump inhibitor (PPI) prescriptions account for 1.6% of prescriptions for infants 0–23 months of age [4▪]. A claims database incorporating 1.3 million children documented a 12.3% rate of diagnosis of GERD in infants 0–1 year of age, and a 0.93–1.26% incidence rate for other pediatric age groups [5].

GASTROESOPHAGEAL REFLUX AND GASTROESOPHAGEAL REFLUX DISEASE

Differentiation of GER and GERD is an important issue. An international consensus statement notes that, with person-centered, symptom-based criteria, the definition of GERD as 'troublesome GER symptoms or complications' frequently relies upon parental perceptions and anxiety, which do not

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KEY POINTS

- GER is a normal physiological and behavioral event, which rarely persists and evolves to GERD.
- Multichannel intraluminal impedance-pH monitoring has increased ability to recognize relationship of symptoms to GER.
- Physicians contribute to demand for unnecessary treatment.
- Laparoscopic fundoplication achieves equivalent results to open fundoplication.
- New endoscopic antireflux surgery has potential in children, but requires further assessment.

always reflect symptom severity or disability, and this definition is unreliable under the age of 8 years [6].

PRESENTATION AND DIAGNOSIS

Multichannel intraluminal impedance-pH (MII-pH) monitoring has improved diagnostic ability, with its ability to detect nonacid GER, and aid in determining relationships of GER to extraesophageal symptoms, and in measuring GER in treatment-unresponsive patients [7▪▪]. Testing can be undertaken while patients continue PPIs. Recently published MII-pH criteria define normal values for infants and children: fewer than 70 GER episodes in children over the age of 12 months, and fewer than 100 episodes in children under a year of age [7▪▪]. New statistical measures increase the diagnostic utility of MII-pH testing: the Symptom Index (number of GER-associated symptoms as a proportion of the total number of symptoms) is abnormal if more than 50% and the Symptom Sensitivity Index (SSI) (number of GER symptom-associated events as a proportion of all GER events) is abnormal if more than 10%. The Symptom Association Probability assesses the temporal association of symptoms with episodes of GER (significant if >0.95) [7▪▪,8]. There are, however, pitfalls in interpretation of MII-pH monitoring. Automated analysis is inadequately validated. Visual inspection and review of automated assessments is recommended, but interpretation is inconsistent, even by experts [9▪]. Clinical services need to develop their own review process and consistency to optimize outcomes for children.

MII-pH monitoring helps understand the relationship between GER, infantile apnea, oxygen desaturation, and bradycardia, which esophageal pH studies failed to demonstrate consistently [10,11]. MII-pH studies, however, show that weakly acidic GER is implicated in apnea of prematurity. MII-pH monitoring and polysomnography, the 30 s before and after GER events, were studied in 54 infants with recurrent apnea. Fifteen percent of pathological apneic events occurred in association with nonacid GER, typically more after GER events [12]. This relationship is still questioned by some because of methodological issues and older evidence of the lack of a real association [13]. It is prudent to consider the possibility of GER contributing to apnea of prematurity, while remembering that these infants are vulnerable to other stimuli as well.

Kahrilas *et al*. [14▪] systematically reviewed treatment of chronic cough with acid suppression, finding tentative evidence of a relationship between chronic cough and GER, although the direction of the relationship is uncertain, as cough may induce GER. A retrospective review of pediatric MII-pH studies failed to confirm a relationship between cough and GER [15]. Analysis of the time preceding and following episodes of cough during MII-pH studies in 106 children showed 28–78% of cough episodes were preceded by GER in 83 patients. Weakly acid GER was responsible for 22% of GER-associated cough, and was more likely to be the stimulus in infants. Acid GER as a trigger increased with increasing age, accounting for 94% of GER-related triggers in children older than 6 years. Cough preceded only 2.4% of GER events [16▪▪].

Refluxate components other than acid contribute to extraesophageal disease. Rosen *et al*. [17▪] reported 50 children undergoing bronchoalveolar lavage (BAL), UGI endoscopy, and MII-pH study. Pepsin-positive BAL was more common in individuals with more nonacid GER. An Indian study documented elevated levels of pepsin in middle-ear effusions of children undergoing middle-ear surgery [18]. Bile acids are found in airways of individuals with chronic lung disease, and more than 50% of patients with cystic fibrosis. The presence of bile acids was associated with higher concentrations of neutrophil elastase and worse lung disease [19▪]. Both pepsin and bile acids can promote an inflammatory response and exaggerate airways disease [20].

MEDICAL MANAGEMENT

GER treatment is aimed at symptom control, mucosal healing, complication prevention, and minimizing harm from medications. The traditional paradigm of a stepwise approach starting with parental education and support in uncomplicated GER and then sequentially nonpharmacological modifications of lifestyle, pharmacological management, and surgical interventions in severe GERD is the preferred model of care [21▪].

LIFESTYLE MODIFICATION

Parental education regarding normal infant physiology, behavior, and development remains central to managing GER. Recent studies confirm the natural history of GER [22,23]. Italian primary care physicians assessed 2462 infants, collecting clinical information and completing the Infant Gastroesophageal Reflux Questionnaire (I-GERQ). Twelve percent of patients met Rome II diagnostic criteria for infant regurgitation, most in the first 6 months of life. One quarter had resolved by age 6 months, and a further 60% by 12 months of age. Breastfeeding was associated with more rapid resolution of regurgitation. At follow-up, only one child had developed GERD [22]. An Indonesian study of 130 babies followed to 1 year of age found 80% regurgitating at least once daily at 1 month, but only 10% regurgitating daily by 12 months. Fully breastfed infants regurgitated less frequently than partially breastfed infants [23].

Lifestyle modifications for infantile GER include thickening of feeds, postural change, avoiding overfeeding, and in certain situations a time limited trial of hypoallergenic formula [24▪,25].

Thickening of formula, typically with carob bean gum or rice starch, has a modest effect upon GER. Despite reduction of emesis and improved weight gain, there is no decrease in acid exposure of the esophagus [25,26]. Use of amylopectin feed thickener in preterm neonates resulted in a decrease in the frequency of acid, but not nonacid, GER in 24 neonates, and did not decrease apnea [27▪].

The effect of posture on GER has recently been re-explored. A specially designed 'bed' supporting infants in a prone, 40°, head elevated position was assessed using the I-GERQ, in an open trial in 30 infants (median age 1.5 months) with frequent GER. Eight infants (27%) ceased using the bed within 48 h because of increasing distress. Normalization or significant improvement of I-GERQ score occurred in 64%. This bed may have some limited application [28]. A Korean study assessed the 30° head elevated position during the postprandial period and documented a decrease in the number of GER episodes per hour, and respiratory symptoms, during the head elevated period [29▪]. The effects of postural change upon GER in preterm infants are complex. The prone and left lateral positions (LLPs) reduce GER episodes compared with the supine position. Van Wijk *et al.* [30] previously suggested using the right lateral position (RLP) for the first postprandial hour, changing to the LLP to promote gastric emptying and reduce liquid GER. Recently, this group has documented in a crossover study of healthy preterm infants that transient lower esophageal sphincter relaxation (TLESR) is triggered with lower feed volumes in the RLP (10.6 ml) compared with the LLP (21 ml) [31]. At present, evidence supports care in the supine head elevated position, and further work is required to determine the clinical utility of the LLP [24▪,25].

Evidence regarding mode of feeding and GER is limited. An open observational study of 35 neonates with feeding problems compared GER parameters in tube-fed and orally fed infants [32]. Prolonged feeding duration was associated with fewer GER events and more rapid bolus clearance. An open study of children being treated for congenital heart disease confirmed enhanced weight gain with transpyloric feeding, presumed to be secondary to improved GER control [33].

In a subset of children, GER symptoms may be a manifestation of cow's milk protein intolerance. These babies often have other allergic manifestations [25]. Borrelli *et al.* [34▪▪] studied 17 infants and young children aged 6–24 months, with known cow's milk allergy and suspected GER. During MII-pH monitoring, participants received an amino acid-based formula (AAF) for the first 24 h and then cow's milk. They demonstrated a significant increase in the number of weakly acid GER episodes and in the proximal extent of GER after cow's milk challenge. A 2–4-week trial of hypoallergenic formula is recommended in these situations. If there is no response, normal formula is reinstituted [35]. This strategy should not be contemplated in fully breastfed infants [24▪].

There are limited data regarding other dietary modification in children, but, based upon adult data, avoidance of prebedtime eating, fatty meals, caffeine, chocolate, carbonated beverages, alcohol, tobacco, and spicy foods may be helpful. Passive smoking is a risk factor for esophagitis in children. Weight management is an important part of treatment in obese children with GER [25].

PHARMACOLOGICAL THERAPY

Surface protective agents usually contain alginate or sucralfate. Alginates are thought to generate CO_2 after interaction with acid, forming a raft atop gastric contents and acting as a buffering agent and physical barrier to reflux. Evidence of clinical benefit is variable [35]. A study of sodium alginate in 28 preterm neonates confirmed a decrease in the number of acid, but not nonacid GERs, and no change in apnea frequency [34▪▪,36]. Sucralfate (combined sucrose, aluminium, and sulphate) forms a gel that binds to exposed mucosa in an acidic environment and promotes healing of esophagitis in adults, but there are no pediatric efficacy or safety data.

Antacids neutralize gastric acid. Most products contain magnesium and aluminium hydroxide or calcium carbonate. Validated in adults, they can be used in older children and adolescents for quick symptom relief [37]. Potential side-effects include aluminium toxicity and milk alkali syndrome, and, because safer and more convenient alternatives exist, chronic antacid therapy is not recommended for children [35].

Histamine 2 receptor antagonists (H2RAs) inhibit acid secretion from parietal cells. Although ranitidine is commonly prescribed in children, there are no pediatric randomized controlled trials (RCTs) examining efficacy. Extrapolation of large adult RCTs to older children and adolescents suggests that H2RAs may be effective short-term treatment, and on-demand therapy due to onset of action within 30 min. Short duration of action and development of tachyphylaxis, as early as 14 days after initiation of therapy, limit H2RA use [35,38,39]. Though they are considered safe, some infants may develop irritability, head banging, and headaches with H2RAs [37].

PPIs are potent inhibitors of gastric acid secretion that act by irreversibly inhibiting hydrogen potassium ATPase, the final pathway of gastric acid secretion [40]. Adult RCTs have established the superiority of PPIs over H2RAs in healing esophagitis and maintaining remission [35,41]. Pediatric pharmacokinetic and safety studies suggest PPIs are well tolerated and efficacious, but relatively higher dosage is needed to obtain acid suppression comparable to adults. PPIs do not lose their potency over time, but are unreliable 'on-demand therapy' as time to maximal effect may be 2–8 days [40]. PPIs have been used in children safely and effectively for up to 11 years for treatment of erosive esophagitis, although up to 14% of children will have idiosyncratic reactions, including headache, nausea, diarrhea, and constipation [41,42].

Prokinetic medicines include metoclopramide, domepridone, cisapride, and erythromycin. Though theoretically appealing due to their potential to enhance gastric emptying and increase lower esophageal sphincter (LES) tone, there is inadequate evidence of clinical effectiveness [35,43]. More importantly, these medications are associated with significant and life-threatening cardiac electrical changes. They have no role in the management of uncomplicated GER but may be tried in severe, treatment-resistant patients if closely monitored [24▪,35].

Recognition that nonacid GER may be as important as acid GER has led to attempts to inhibit TLESR, the principal cause of GER. Baclofen, an agonist of the inhibitory neurotransmitter gamma amino-butyric acid (GABA) receptor, reduces TLESR and acid GER [44,45]. Unfortunately, it has significant central nervous system side-effects, including drowsiness, limiting its usefulness [46]. Agents that show some promise in adult studies, but that need further assessment, include arbaclofen (GABA receptor agonists) and the mGluR5 antagonist ADX10059 [25,47,48].

Overuse of medication to manage uncomplicated GER is a significant issue. Crying and posseting are part of normal infant development and behavior, not necessarily related to GER but often conflated into a diagnosis of GERD [24▪,35,49▪]. This is erroneous, potentially dangerous, and leads to futile treatments. The largest RCT to date in infants showed that for symptoms purportedly due to GERD (screaming and back arching), a PPI was no better than a placebo [50].

Part of the physician response to prescribe PPIs may reflect belief in their safety. Evidence to the contrary is accumulating, with reports of risk of infections including acute gastroenteritis and community-acquired pneumonia, necrotizing enterocolitis, candidemia, bacterial enterocolitis, and small bowel bacterial overgrowth. Chronic PPI use is also associated with increased risk of hip fractures and vitamin B12 deficiency [35].

Scherer *et al*. [51▪▪] highlighted the importance of the definition of GERD and the use of the label 'disease' in promoting overmedicalization of GER. They questioned 175 parents, prior to medical consultation, using clinical vignettes with treatment options consistent with current guidelines for treatment of GER and GERD [35]. The study tested the influence of a 'disease' label, and advice that medication was likely to be ineffective in improving GERD symptoms. Parents receiving the 'disease' label were more interested in medication than parents who did not, as were parents with children previously diagnosed with GERD. Parents with a 'disease' label were interested in medication even knowing that it was likely to be ineffective, whereas parents not given a GERD diagnosis and informed of likely ineffectiveness of medication were less interested in medication.

SURGICAL MANAGEMENT

Antireflux surgery (ARS) aims to reduce GER without inhibiting swallowing. Recent pediatric GERD guidelines note the lack of evidence regarding patient and procedure selection for ARS [35]. The quality of this evidence is reflected in some practitioners' understanding of ARS indications. Surgeons indicated that they weighed up a range of subjective as well as objective issues in arriving at

preoperative decisions. The authors concluded that some surgeons might feel that they are expected to undertake ARS, regardless of the objective evidence [52]. Given the dearth of prospective studies enabling prediction of optimal therapy, surgery should be restricted to children who have complicated GERD and have failed medical therapy [21▪,24▪].

When PPI treatment is effective, surgery offers no advantage in symptom control. The Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic GERD trial compared maintenance therapy of chronic symptomatic GERD with esomeprazole and standardized laparoscopic ARS in adults responding well to PPI, and found that remission rate and severe adverse events were similar in both groups. PPIs are better at controlling heartburn, but surgery more effectively controls regurgitation, at the cost of some dysphagia (11 vs. 6%) [53].

Fundoplication is now commonly a laparoscopic procedure. An RCT of 88 children comparing laparoscopic procedure and open fundoplication failed to demonstrate differences in outcome, except that laparoscopic procedure required longer operating time, similarly to earlier findings in neonates [54▪,55]. A meta-analysis of 466 children treated with laparoscopic procedure and 255 with open fundoplication in six studies documented earlier feeding, less morbidity, and shorter hospitalization for laparoscopic procedure, with no difference in rate of GERD recurrence at 12 months, concluding that laparoscopic procedure is a safe, effective alternative to open fundoplication [56].

Pediatricians need to be aware of risks of fundoplication. Mortality is generally low, less than 1% [57▪]. Early postoperative complications of bleeding, bowel perforation, pneumothorax, and severe postoperative nausea and vomiting occur in 0–5% of patients. Long-term complications include gas-bloat syndrome (1–85%), dysphagia (3–50%), diarrhea (18–33%), and recurrence of symptoms (10–62%) [57▪,58,59].

An important follow-up study of a single surgeon's experience at a tertiary pediatric center identified 46 of 233 children undergoing ARS dying during a mean follow-up period of 2.8 years. This population included 76 children with cerebral palsy, 71 with congenital syndromes and anomalies, 114 with a gastrostomy, and 18 with a tracheostomy. Children dying were more likely to be underweight, female, and have a gastrostomy and cerebral palsy. Children with cerebral palsy had an 11% 30-day mortality [60].

Endoluminal techniques have the potential to minimize surgical morbidity [61,62,63▪,64▪]. Limited pediatric experience has been reported for the Endocinch procedure (suturing the stomach wall below the LES), the Stretta procedure (radio frequency ablation of the tissue of the LES resulting in scarring), the Enteryx procedure (polymer injection into the LES), and transoral incisionless fundoplication (TIF; the EsophyX device). TIF endoscopically creates a three-quarter wrap of the lower esophagus, and limited experience in adults and children confirms effectiveness and safety of TIF in carefully selected patients. A novel magnetic device placed laparoscopically around the distal esophagus to augment the LES, but still allow passage of swallowed boluses, decreased esophageal acid exposure and allowed a 50% decrease in PPI use in 93% of patients [65▪]. These procedures are not without risk, with reported complications including perforation, bleeding, mediastinal or abdominal abscess, and symptom recurrence [61].

CONCLUSION

The challenge of GER and GERD in the 21st century is the same as it has always been: to differentiate normal development from disease, apply clinical judgment to determine which children need special tests and treatment, and choose therapy that offers the best risk–benefit ratio, at the most reasonable cost. At the heart of these processes is dialogue with families, explaining, educating, and leading them to the best decisions, while remembering *primum non nocere*.

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Conflicts of interest

There are no conflicts of interest.
The article has not been submitted elsewhere.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 639–640).

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