Gastro-oesophageal reflux disease in infancy: a review based on international guidelines

Robert N Lopez[1], Daniel A Lemberg[2]

Summary

- Gastro-oesophageal reflux (GOR) in infancy is common, physiological and self-limiting; it is distinguished from gastro-oesophageal reflux disease (GORD) by the presence of organic complications and/or troublesome symptomatology.
- GORD is more common in infants with certain comorbidities, including history of prematurity, neurological impairment, repaired oesophageal atresia, repaired diaphragmatic hernia, and cystic fibrosis.
- The diagnosis of GORD in infants relies almost exclusively on clinical history and examination findings; the role of invasive testing and empirical trials of therapy remains unclear.
- The assessment of infants with vomiting and regurgitation should seek out red flags and not be attributed to GOR or GORD without considered evaluation.
- Investigations should be considered to exclude other pathology in infants referred with suspected GORD, and occasionally to confirm the diagnosis.
- Management of GORD should follow a step-wise approach that uses non-pharmacological options where possible and pharmacological interventions only where necessary.

Across the age spectrum, gastro-oesophageal reflux (GOR) is defined as the passage of gastric contents into the oesophagus. This normal physiological event can be associated with effortless regurgitation (ie, the expulsion of oesophageal contents proximal to the pharynx), which affects 40% of infants,[1] or vomiting. GOR in infancy (ie, in children aged ≤ 12 months, as defined by the World Health Organization[2]) usually has its onset before 8 weeks of life, with 90% of infants affected experiencing resolution of regurgitation by one year of age.[3] By contrast, gastro-oesophageal reflux disease (GORD) is distinguished by the presence of organic complications such as oesophageal inflammation or narrowing, pulmonary or upper airway aspiration, or troublesome symptomatology.[4]

The diagnosis of GORD in infants relies almost exclusively on clinical history and examination findings. The role of more objective measures (ie, invasive tests and empirical trials of therapy) within the diagnostic paradigm remains unclear. The range of presentations attributable to GORD largely overlaps with normal infant behaviour, including excessive crying, back-arching, regurgitation and irritability (Box 1). It has been shown that use of the label GORD influences parental expectations regarding pharmacological treatment.[5] Furthermore, GORD has been shown to negatively affect maternal–infant bonding during feeding.[6] Thus, it is imperative for medical professionals to be able to distinguish GORD from physiological GOR to ensure optimal infant and maternal health.

Certain subgroups of infants, including those with a history of prematurity, neurological impairment, repaired oesophageal atresia, repaired diaphragmatic hernia, and cystic fibrosis, are more predisposed to develop GORD.[7]

The presence of GOR in an otherwise well and thriving infant requires recognition and reinforcement as a normal event. Regurgitation and episodic vomiting as a result of GOR seldom commences before the second week or after the sixth month of life.[7] Parents and caregivers should be reassured that regurgitation in this context is normal, rendering treatment both unnecessary and potentially harmful. The presence of poor feeding, apparent distress, chronic cough, hoarseness, or a single episode of pneumonia, in the absence of overt regurgitation, does not warrant investigation or treatment for GORD.[7] By contrast, recurrent aspiration pneumonia, particularly in premature infants or those with neurological disability, may be a manifestation of refluxate being aspirated into the lungs. Similarly, recurrent otitis media could be considered as a possible complication of GORD.[8]

Criteria for referral to specialist or subspecialist providers will vary depending on the experience of a primary care physician and the available local resources, for example. One guideline suggests that referral to a paediatric gastroenterologist should occur (where available) before the institution of acid suppression.[9] This review provides an overview of a safe and simple approach to this common presentation based on a distillation of evidence-based international guidelines.

1 Signs and symptoms of possible gastro-oesophageal reflux disease (GORD) in infants

- Excessive crying or distress*
- Back-arching or posturing*
- Regurgitation*
- Recurrent aspiration pneumonia
- Frequent otitis media
- Apnoea†
- Feeding difficulty†
- Poor growth†

*Often constitutes normal infant behaviour. †Only rarely manifestations of GORD; rule out other causes first. ◆

Methods

We conducted an EMBASE, MEDLINE and PubMed search for guidelines on the management of GORD in infancy. Three guidelines addressing the management of GORD in paediatrics, including infants, were identified: the 2009[10] (which was disregarded) and 2018[9] editions of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines, and the 2015 National Institute for Health and Care Excellence guidelines.[7] Reference lists from both guidelines were also reviewed for studies of particular significance.

Differential diagnoses and the role of investigations

The unwell infant with poor growth should never have their symptoms and signs ascribed solely to GORD (Box 2). Similarly, projectile, blood-stained or bilious vomiting, or vomiting that

[1] Queensland Children's Hospital, Brisbane, QLD. [2] Sydney Children's Hospital, Sydney, NSW. daniel.lemberg@health.nsw.gov.au • doi: 10.5694/mja2.50447

2 Red flags suggesting causes other than gastro-oesophageal reflux disease

- Systemic illness
- Haematemesis
- Projectile vomiting
- Bilious vomiting
- Onset after 6 months of age
- Persistence beyond 12–18 months of age
- Bulging fontanelle
- Macrocephaly/microcephaly
- Seizures
- Diarrhoea
- Rectal bleeding
- Abdominal distension

has its onset after 6 months of age and/or persists beyond 12–18 months of age should raise the spectre of alternate pathology, including pyloric stenosis and intestinal malrotation. Infant vomiting in the context of a bulging fontanelle, macrocephaly or microcephaly, variable level of responsiveness, or seizures should prompt investigation for intracranial pathology.

Apparent life-threatening events and apnoeas are only rarely caused by GORD.[11,12] In the absence of supporting evidence for GORD, investigations in these infants should focus on other causes of apnoea, rather than on silent or occult reflux[7] — the retrograde passage of gastric contents into the oesophagus not associated with overt regurgitation perceptible to caregiver or observing health professional. However, specialist investigation, such as a pH impedance study, may be considered by a paediatric gastroenterologist if general paediatric review has not elucidated a cause for an infant presenting with apnoeas.[7] Infants with persistent back-arching or features suspicious for Sandifer syndrome — GOR in association with episodic torticollis with neck extension and rotation — should be similarly referred for gastroenterology, and possibly, neurological review.

The presence of GOR on an upper gastrointestinal tract contrast (usually barium) study has no clinical significance. Nevertheless, the test is useful to rule out anatomical abnormalities such as hiatus hernia, malrotation, intrinsic or extrinsic oesophageal compression and duodenal obstruction. In established GORD treated with fundoplication, barium imaging has a crucial role in the evaluation of the integrity of a wrap. A modified barium swallow study, or videofluoroscopic swallow study, should be considered in the setting of recurrent aspiration,[13] as it may help in identifying infants with impaired swallowing causing direct aspiration — as distinct from reflux aspiration. Ultrasonography has no role in the routine diagnosis of GORD, but it is a useful modality to exclude other causes of infant vomiting, such as pyloric stenosis and renal or biliary tract pathology.[9]

The correlation between endoscopic appearance of the oesophagus and the presence of GORD is imperfect. A finding of erosive oesophagitis strongly suggests GORD, but a normal oesophagus (even histologically) cannot exclude it as a diagnosis.[14–16] Upper gastrointestinal tract endoscopy has a role in the exclusion of conditions that can mimic GORD, such as eosinophilic oesophagitis and infective oesophagitis, and conditions that can complicate GORD, such as strictures and Barrett oesophagus.[7,9]

There is a limited role for oesophageal pH studies in the routine diagnosis of GORD. Their performance and subsequent interpretation of results require subspecialist training. Therefore, decisions pertaining to if and when they need to be done should involve a paediatric gastroenterologist. One measure of oesophageal acid exposure is the Reflux Index, which in infants has been defined as pH below 4 for more than 10% of the study period.[17] Disadvantages include its inability to detect non-acid reflux — a common occurrence in infants — and a lack of clarity with regards to the appropriate time frame to consider symptomatology and reflux correlation. In the absence of impedance testing, pH studies may have a role in assessing the association between acid events and symptoms and also in evaluating the efficacy of acid suppression therapy.[9]

Multichannel intraluminal impedance (MII), routinely done in combination with pH monitoring, can detect acid and non-acid refluxate of either liquid or gas at different levels of the oesophagus. This specialised test is not universally available and lacks true normal reference ranges. Furthermore, there are variations in the performance and interpretation of the test, with no large studies proving that pH-MII testing influences clinical outcomes. Notwithstanding, pH-MII could be considered in cases where the association between symptoms and GOR remains unclear as well as in patients with recurrent aspiration pneumonia, otitis media, unexplained apnoeas, epileptiform events, upper airway inflammation, or Sandifer syndrome and in patients being considered for fundoplication.[9]

3 Summary of key recommendations

Recommendation	Strength of recommendation based on GRADE[20]
Food thickeners, and changes in feed volumes or frequency could be considered for infants with GORD[7,9]	Weak
Tube feeding, gastric or transpyloric, could be considered when GORD in infants is adversely affecting growth, especially in the neurologically impaired or the neonate[7,9]	Weak
GORD symptoms may be indistinguishable from CMPI and treatment for the latter should be considered over acid suppression, particularly in infants with a family history of atopy[7,9]	Weak Trial of dairy exclusion recommended before trials of pharmacological therapy, as per NASPGHAN guideline[9] — a recommendation supported by the authors of this review NICE guideline[7] recommends CMPI be considered particularly in infants with a family history of atopy
A trial of alginates could be considered in infants with GORD who present with problematic regurgitation or vomiting[7,9]	Weak — as per NICE guideline[7] and supported by authors of this review NASPGHAN guideline discourages chronic use of alginates[9]
Trials of PPIs and H_2RAs should be reserved for infants with GORD, with frequent assessment as to the ongoing need for these medications[7,9]	Strong
Baclofen could be considered after paediatric gastroenterology review for infants with refractory GORD[7,9]	Weak

CMPI = cow's milk protein intolerance; GORD = gastro-oesophageal reflux disease; H_2RA = histamine-2 receptor antagonist; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NICE = National Institute for Health and Care Excellence; PPI = proton pump inhibitor. ◆

Some infants with cow's milk protein intolerance (CMPI) may exhibit regurgitation and vomiting that is clinically indistinguishable from (or resistant to treatment for) GORD.[18] CMPI occurs more commonly in patients with an atopic predisposition and affects up to 7% of all infants.[18] Non-IgE mediated CMPI is a clinical diagnosis based on symptom improvement with exclusion of dairy, and symptom recurrence on subsequent dairy reintroduction.

Non-pharmacological management

A number of options pertaining to the constitution or administration of bottle feeds in the context of infant GORD have been studied. Many of these studies are of low quality and have a disparity of diagnostic and outcome definitions,[19] but despite these limitations, certain conclusions can be drawn.

Reduction of feed volume, often with a concomitant increase in feed frequency, is a measure worth trialling in infants with GORD. Both guidelines[7,9] acknowledge the lack of evidence for this recommendation but justify its inclusion on the basis of collective experience and the relative low risk of this intervention (Box 3). However, special attention needs to be paid to ensure there is no nutritional compromise to the infant secondary to inadequate caloric or fluid provision. Therefore, this measure is best implemented under medical and dietetic supervision. While there is evidence that left lateral,[21,22] head elevation[23] and prone[24] positioning reduces acid reflux on a pH study, the overwhelming benefit of supine positioning during sleep, including a reduction in the incidence of sudden infant death syndrome, means that positioning therapy has no role in management of the infant with GORD during sleep. However, positioning may have a role in the management of the awake, supervised infant and should be advised with caution.[7,9]

While thickeners do not reduce the frequency of acid and non-acid reflux episodes,[25] they result in fewer episodes of regurgitation[26–28] and vomiting.[26,29] Cereal-based (preferably with low or no arsenic) and commercially available thickeners, such as cornstarch, xanthan gum (for patients over one year of age) and carob bean (for infants > 42 weeks' gestation), are generally safe. In infants with frequent regurgitation, a trial of thickened feeds for at least 2 weeks could be considered. These trials are best conducted with medical oversight and where access to dietetic intervention is readily available.

For infants with poor growth and regurgitation, in whom other causes of suboptimal growth have been excluded, enteral tube feeding could be considered if non-pharmacological and medical management have proved unsuccessful. Tube feeding is best commenced within a multidisciplinary setting to ensure adequacy of oral intake, with regular monitoring of growth and ongoing stimulation to promote appropriate development of oral motor skills. Frequent assessments should be performed to ensure that weaning infants off tube feeding is done as soon as practicable.

In infants with refractory regurgitation in spite of enteral tube feeding and in those at risk of reflux aspiration events, transpyloric feeding should be considered.[7,9] Transpyloric or jejunal feeding has been shown to be comparable to antireflux surgery in the cohort of children with neurological disability with regards to reducing the risk of extra-oesophageal complications, such as aspiration pneumonia.[30] Similar benefits have been shown in neonates with episodes of apnoea and bradycardia who were fed via a transpyloric tube.[31,32]

The infant presenting with GORD symptoms who has not responded to non-pharmacological measures and modifications of feed consistency or administration should have a diagnosis of CMPI considered before commencement of pharmacological options for GORD. Management of CMPI would involve a 2–4-week trial of dairy exclusion.[9] In breastfed infants, this will involve the mother observing an elimination diet, whereas formula-fed infants should be trialled initially on an extensively hydrolysed formula or, if there is no improvement, on an amino acid-based formula. Clinical improvement usually occurs within 2 weeks of dairy exclusion,[18] with a recurrence of symptoms upon allergen reintroduction confirming the diagnosis.

Pharmacological management

Alginates and antacids are medications that contain either sodium or potassium bicarbonate, or aluminium, magnesium or calcium salts, which are designed to neutralise acid and treat dyspepsia or heartburn. Alginates have been shown to have a favourable effect on the symptoms of regurgitation when compared with no intervention, thickeners or placebo.[33,34] There is no evidence to suggest that the use of alginates is associated with increased adverse effects,[34] although the quality and quantity of available evidence are low. A 1–2-week trial with aluminium-free formulations would appear safe[7,9] and may result in reduced regurgitation. This could be recommended in problematic cases where non-pharmacological measures have had suboptimal effect. Aluminium-containing antacids should not be used, while the sodium and calcium content of different formulations needs to be taken into account when used in infants, particularly in those with cardiac or renal comorbidities.[7,9]

Studies looking at the use of proton pump inhibitors (PPIs) to treat infants with GORD apply different definitions of GORD based on pH monitoring, endoscopic findings, clinical symptoms and a GOR questionnaire. No study has demonstrated that PPI use is associated with an improvement in symptoms such as crying, cough, back-arching or regurgitation.[35–40] None of these studies showed an increase in the side-effect profile between PPI use and placebo in infants with GORD, except for one which reported a higher number of serious adverse events in the PPI group compared with the placebo group (10/81 [12%] *v* 2/81 [2%] respectively; $P = 0.032$); however; non-serious adverse events and treatment-related adverse events were similar between groups.[36] There is some evidence to suggest that histamine-2 receptor antagonists (H_2RAs) use may be associated with less regurgitation and vomiting (but no change in other symptoms of GORD), with no increase in side-effect profile compared with placebo.[41–43] However, the lack of high quality evidence means that the routine use of H_2RAs in infants with GORD cannot be recommended.

The available evidence on head-to-head comparisons between PPIs, H_2RAs, topical agents (eg, sucralfate) and hydrolysed formula is inconclusive. There are no studies comparing the efficacy of one PPI over another for the treatment of infants with GORD. In summary, there is no compelling evidence to suggest that one class of drug or intervention consistently and reproducibly performs better in the management of infants with GORD. Primarily adult literature suggests the superiority of PPIs over H_2RAs in healing endoscopically proven erosive oesophagitis.[44–46] Recommended dosages for some commonly used PPIs in children are omeprazole (1–4 mg/kg/day), lansoprazole (2 mg/kg/day), esomeprazole (10 mg/day for infants < 20 kg, and 20 mg/day for infants > 20 kg), and pantoprazole (1–2 mg/kg/

day).[9] Similarly, the recommended dosages for H_2RAs in children are cimetidine (30–40 mg/kg/day), nizatidine (10–20 mg/kg/day), and famotidine (1 mg/kg/day).[9] Prescribed daily doses should not exceed maximum adult doses.

The available paediatric studies do not suggest an increase in adverse effects while taking PPIs[35–40] or H_2RAs.[41–43] However, some evidence suggests an increased rate of necrotising enterocolitis, respiratory tract infections, urinary tract infections and *Clostridium difficile* infections reported in infants and children treated with either agent.[47] Nevertheless, it is acknowledged that *C. difficile* is not a cause of colitis in infants. The increased risk of adverse sequelae is supported by biological plausibility, as stomach acid serves, among other roles, as a protective barrier against infection.

In summary, PPIs and H_2RAs are not recommended for well infants who present solely with regurgitation, vomiting, crying or distress. However, infants with regurgitation or vomiting in the context of feeding difficulties, distressed behaviour or poor growth should be offered a trial of either a PPI or a H_2RA,[7,9] with patient preference, medication preparation and local availability to serve as a guide in choosing one class over the other. Similarly, erosive oesophagitis warrants treatment with PPI.[7,9] Extra-oesophageal symptoms, such as a chronic cough, occurring in isolation from classic symptoms do not warrant medical management of GORD. Infants commenced on either a PPI or a H_2RA require regular assessment of treatment efficacy, the potential presence of competing pathology, and the ongoing need (or otherwise) for the medicine itself.

Baclofen has proven utility in reducing the frequency of transient lower oesophageal sphincter relaxation and acid reflux while also increasing the rate of gastric emptying[48,49] in adults and children. However, its significant side-effect profile limits its use for the treatment of GORD. But in cases of infants with GORD where all non-pharmacological and conventional pharmacological options have been optimised, a trial of baclofen may be considered after a paediatric gastroenterology review.

There is no evidence to support the widespread use of prokinetic agents such as domperidone, metoclopramide, erythromycin and bethanecol in the treatment of infants with GORD.[7,9] Their side-effect profile dictates that they should only be considered under specialist guidance.

Surgical management

Fundoplication is a surgical procedure whereby the lower oesophageal sphincter pressure is increased, the frequency of transient lower oesophageal sphincter relaxation episodes is reduced, and swallow-induced relaxation pressure is increased. There are different antireflux surgical options, with laparoscopic Nissen fundoplication being largely preferred over open Nissen fundoplication. The evidence in adults in favour of surgery to treat GORD is overwhelming, with a curative rate between 85% and 93%.[50,51] In children, a systematic review found a success rate of 86% in complete relief from GORD symptoms after surgery.[52] Laparoscopic fundoplication is associated with a reduction in reflux symptoms, in oesophageal acid exposure, and in the frequency of acid reflux.[53]

While there are prospective data on the efficacy of antireflux surgery in children with GORD,[53] no such information is available for infants. One study exploring the effectiveness of fundoplication in infancy found a high proportion of unsuccessful cases, although that cohort was biased towards a high proportion of congenital anomalies.[54]

In general, antireflux surgery should be reserved for children with GORD in whom optimal non-pharmacological and pharmacological measures as well as trials of transpyloric feeding have proved unsuccessful or impractical. Therefore, consideration of antireflux surgery will usually occur once a child has progressed through infancy.

Directions for future research

A drawback of the current GORD definition is its reliance on clinical presentation — a unique complexity in the medical management of an infant. Optimal diagnostic criteria for GORD in infancy should incorporate parental reporting, physical assessment, and objective investigation parameters. This would serve to standardise what is meant by GORD in infancy and, as a corollary, make research into this area more rigorous.

A recent systematic review provided data on the prevalence of GORD among the paediatric population.[55] Ten of the 24 included studies had information on GORD in infancy. While confirming that symptoms of GORD affected more than one-quarter of all infants and that this figure decreased with increasing age, the authors bemoaned the scarcity of data from regions other than Asia and the United States. Adult literature points to geographical variation insofar as the prevalence of GORD is concerned.[56] Possible demographic and socio-economic factors that may have an impact on the presentation in infancy of a condition such as GORD, which shares significant overlap with normal behaviour and development, would be an area worthwhile exploring.

Lastly, more rigorous research should be done comparing the management for dairy intolerance versus acid suppression in infants presenting with symptoms of GORD.

Conclusion

GOR in infancy should be distinguished from GORD based on careful assessment, particularly for red flags. If infants are presenting with GOR, parents and caregivers should be appropriately counselled regarding the physiological nature of this entity. On the other hand, infants with GORD should be managed in a step-wise fashion using non-pharmacological measures where possible and pharmacological measures where necessary.

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