**Gastro-oesphageal reflux in infants; what are we treating?**

James J Ashton1,2, R Mark Beattie1

1. Department of Paediatric Gastroenterology, Southampton Children’s Hospital, Southampton, UK
2. Department of Human Genetics and Genomic Medicine, University of Southampton, Southampton, UK

Correspondence to-

Professor R Mark Beattie

Department of Paediatric Gastroenterology,

Southampton Children’s Hospital,

University Hospitals Southampton

Tremona Road

Southampton

SO16 6YD

UK

Mark.beattie@uhs.nhs.uk

The authors declared no conflicts of interest

JJA is funded by an Action Medical Research, research training fellowship.

Frequent regurgitation of stomach contents into the oesophagus, leading to symptoms such as crying and vomiting after feeds affects up to 50% of infants under the age of three months with a natural history of resolution in most cases [1]. The transition point between gastro-oesphageal reflux (GOR), which is extremely common and gastro-oesphageal reflux disease (GORD) is not always straightforward, reflecting a disease spectrum rather than two specific entities. The recently published guidelines from the joint working group of European and North American societies for paediatric gastroenterology, hepatology and nutrition (ESPGHAN and NASPGHAN) are helpful and address specific clinical questions which are relevant to the clinician in practice including the diagnosis, differential diagnosis, investigation, therapeutics and prognosis [2]. The need for this and other guidance including appraisal of the evidence for treatments (2014, Cochrane) and national institute for health and care excellence (NICE) guidance (2015) is crucial in a condition where there are multiple opinions on when, how and what to treat [3,4]. Despite this, the utility of these documents in clinical practice is uncertain, with the increase in prescription of pharmacological treatments seemingly driven largely by the pressure to ‘do something’ and personal experience [5,6].

Definition, Symptoms and Diagnosis

Reflux of gastric contents into the oesophagus in infancy is both common and largely self-limiting. Progression of simple GOR to GORD is defined as ‘reflux leading to troublesome symptoms and/or complications, such as oesophagitis or stricturing’ [2]. The troublesome nature of this definition centres on who is finding the symptoms troubling. Frequently it is the parents who are concerned, whilst the infant is growing well, has only transient discomfort and is otherwise thriving. It is important for the clinician to offer treatment when it is likely to be helpful and impact on symptoms and prognosis. It is crucial not to over treat if the therapies are not likely to be effective. However it is important to recognise the wide differential in children with reflux symptoms and that the evidence base for specific medical treatment is only in children with confirmed GORD [2–4].

The diagnosis of GOR is largely clinical, a full history and examination with the absence of ‘red flag’ symptoms is enough to make a diagnosis (table 1). GORD in infancy can be considered in the context of GOR without improvement following simple intervention.

The ESPGHAN/NASPGHAN and NICE guidelines are clear about investigation of GOR in infants. There is no place for routine pH/impedance, endoscopy, ultrasound and barium contrast studies [2,4]. The use of pH probes/impedance, endoscopy and manometry should be reserved for assessment of improvement of symptoms and correlation of troublesome symptoms with acid reflux in select cases only, although some would use these investigation more frequently to make a diagnosis [7].

Therapies

Non-pharmacological interventions should be the first line according to both ESPGHAN/NASPGHAN and NICE. Simple strategies such as feed thickeners, assessment of volume intake (to avoid overfeeding) and adjustment of feed frequency/volume. Positional therapies may provide some benefit but should not be used in sleeping infants.

A 2-4 week trial on extensively-hydrolysed (or amino acid) formula, or exclusion of diary from the maternal diet is second line management [2].

In contrast to older children there is no support for use of long-term alginates, H2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs) or domperidone in infants with straightforward reflux. NICE and the 2014 Cochrane review are cautious with recommending H2RA/PPI unless there is overt regurgitation, feeding difficulty, distressing behaviour or faltering growth [3,4], i.e. symptoms suggestive of GORD. However evidence suggests that up to 40% of paediatricians would routinely start a H2RA or PPI in a crying or unsettled infant, or in visible regurgitation, with less than 2% of general paediatricians in Europe adhering completely to the 2009 reflux publication from ESPGHAN/NASPGHAN [8]. The presence of GORD/Reflux oesophagitis is an indication for step up therapy including H2RA, PPI’s and potentially jejunal feeding or surgical intervention such as fundoplication in the most severe cases.

The evidence base for the efficacy of PPI’s is confined to children with severe reflux despite their widespread use. Over the last 10 years there has increasing concern regarding their side effects including respiratory and gastrointestinal infections and nutrient malabsorption which have led to regulators being more cautious around safe use in the infant population [9,10].

Conclusions

The distinction between GOR and GORD is important and prompt and correct treatment is essential. The only successful long-term strategy for treating GOR in infants is growth, and this should be reinforced early and often. Parental education and expectation management is key to good outcomes- ‘if you or I were to drink milk all day, lie on our backs and cry a lot we would have reflux’. Weaning and neurodevelopment require time but are effective in the vast majority of cases. Often the most difficult thing in medicine is to do nothing, but in infant GOR all guidelines point to therapeutic inactivity as the ultimate cure.

Selected key points for paediatricians/primary care physicians from new guidance [2]-

1. Do not use barium contrast, ultrasound, endoscopy or manometry to diagnose GORD
2. In infants do not use a trial of PPIs or H2RAs as a diagnostic test for GORD.
3. In infants PPIs/H2RAs should be reserved for oesophagitis and not used for crying/distress or visible regurgitation
4. Do use a 2- to 4-week trial of extensively hydrolysed protein-based (or amino-acid based) formula in infants suspected of GORD after optimal non-pharmacological treatment has failed
5. Do use thickened feeds for treating visible regurgitation/vomiting in infants with GORD
6. Avoid overfeeding in infants by calculation of milk intake and adjustment of volume
7. Do not use anta-acids/alginates for chronic treatment in infants
8. Do not use domperidone, metoclopramide in treatment of GORD in infants
9. Do not use other prokinetics (such as erythromycin) in the routine treatment of GORD in infants
10. Do provide parental education and support as part of the treatment of GORD

Table 1- ‘Red Flag’ signs and symptoms in children with reflux in infancy, adapted from NICE guidelines 2015 [4].

|  |
| --- |
| **Red flags in gastro-oesophageal reflux** |
| **Gastrointestinal** | **Systemic** |
| Frequent, forceful (projectile) vomiting | Appearing unwell. Fever |
| Bile–stained vomit | Bulging fontanelle |
| Haematemesis | Rapidly increasing head circumference (more than 1 cm per week)Persistent morning headache, and vomiting worse in the morning |
| Onset of regurgitation and/or vomiting after 6 months or persisting after 1 year | Altered responsiveness, for example, lethargy or irritability |
| Blood in stool | Infants and children with, or at high risk of, atopy |
| Abdominal distension, tenderness or palpable mass |  |
| Chronic diarrhoea |  |

References

1 Nelson SP, Chen EH, Syniar GM, *et al.* Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 1997;**151**:569–72.http://www.ncbi.nlm.nih.gov/pubmed/9193240 (accessed 26 Apr 2018).

2 Rosen R, Vandenplas Y, Singendonk M, *et al.* Pediatric Gastroesophageal Reflux Clinical Practice Guidelines. *J Pediatr Gastroenterol Nutr* 2018;**66**:516–54. doi:10.1097/MPG.0000000000001889

3 Tighe M, Afzal NA, Bevan A, *et al.* Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database Syst Rev* 2014;:CD008550. doi:10.1002/14651858.CD008550.pub2

4 Gastro-oesophageal reflux disease in children and young people: diagnosis and management | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/ng1 (accessed 26 Apr 2018).

5 Khoshoo V, Edell D, Thompson A, *et al.* Are we overprescribing antireflux medications for infants with regurgitation? *Pediatrics* 2007;**120**:946–9. doi:10.1542/peds.2007-1146

6 Long HA, Solski L, Rebuck JA, *et al.* Infantile Gastroesophageal Reflux: Adherence to Treatment Guidelines in the Hospital Setting. *J Pediatr Pharmacol Ther* 2018;**23**:41–7. doi:10.5863/1551-6776-23.1.41

7 Drug and Therapeutics Bulletin. Managing gastro-oesophageal reflux in infants. *BMJ* 2010;**341**:c4420. doi:10.1136/BMJ.C4420

8 Quitadamo P, Papadopoulou A, Wenzl T, *et al.* European Pediatricians’ Approach to Children With GER Symptoms. *J Pediatr Gastroenterol Nutr* 2014;**58**:505–9. doi:10.1097/MPG.0b013e3182a69912

9 Higginbotham TW. Effectiveness and Safety of Proton Pump Inhibitors in Infantile Gastroesophageal Reflux Disease. *Ann Pharmacother* 2010;**44**:572–6. doi:10.1345/aph.1M519

10 van der Pol RJ, Smits MJ, van Wijk MP, *et al.* Efficacy of Proton-Pump Inhibitors in Children With Gastroesophageal Reflux Disease: A Systematic Review. *Pediatrics* 2011;**127**:925–35. doi:10.1542/peds.2010-2719