CLINICAL REVIEW

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Managing gastro-oesophageal reflux in infants

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Transient, inappropriate relaxation of the lower oesophageal sphincter may permit contents of the stomach to pass into the oesophagus (gastro-oesophageal reflux).[1] This usually presents as regurgitation or vomiting and is common in infants, when it is usually mild and self limiting, and requires no specific treatment.[1] Gastro-oesophageal reflux disease (GORD) in infants describes reflux of gastric contents that causes troublesome symptoms or complications.[2] GORD is sometimes wrongly diagnosed in healthy infants with troublesome but harmless symptoms of "physiological" gastro-oesophageal reflux.[3] This has led to increasing, potentially inappropriate, use of acid reducing drugs.[3 4] Furthermore, few of the drugs used to treat infants with GORD are licensed for this use, a situation that *DTB* criticised 12 years ago.[1] Here we consider GORD in infancy (that is, in those aged 0–12 months), the treatments available, and when these are needed.

About gastro-oesophageal reflux

Some reflux occurs in most infants, particularly in those who are preterm.[5 6] The condition is more marked in those with slow gastric emptying or disorders of upper gastrointestinal motility due to severe neurodevelopmental impairment (such as cerebral palsy) or cows' milk hypersensitivity or allergy.[1 7 8] When reflux in infants causes troublesome symptoms (such as poor weight gain, unexplained crying, distressed behaviour) or complications (such as oesophagitis or respiratory problems), it is classified as GORD.[2] Oesophagitis may present with irritability, clinical features mimicking colic (crying, drawing the legs up towards the abdomen), features of pain after feeding, and, possibly, haematemesis or melaena.[9 10] Sometimes, the oesophagitis disrupts oesophageal motility, reduces sphincter tone further, and so makes reflux even more likely.[1] Possible associations exist between GORD and asthma, pneumonia, bronchiectasis, and apparent life threatening events in infants, but causality has not been established.[2 11] In preterm infants, reflux is associated with episodic apnoea resistant to standard treatment and with exacerbation of bronchopulmonary dysplasia.[1 12]

Diagnosis of GORD

The diagnosis of GORD is often made clinically.[2] However, no symptom or cluster of symptoms reliably predicts complications or identifies infants likely to respond to treatment. Investigations are rarely needed, but they can be useful to document pathological reflux or its complications. However, there is a lack of reliable diagnostic tests.[13]

Intraluminal oesophageal pH monitoring is generally accepted as the optimal test for diagnosing GORD.[13] A probe is inserted into the oesophagus to measure the frequency and duration of oesophageal acid exposure.[2] The use of multiple intraluminal impedance—which shows the movement of fluids, solids, and gases—together with pH monitoring is superior to pH monitoring alone.[2 14] Suspected oesophagitis is best confirmed by endoscopy with biopsy.[15] Barium swallow and meal studies and oesophageal manometry lack sensitivity and specificity for reflux in infants but can be used to detect underlying anatomical abnormalities or the mechanisms of GORD.[2 16 17] Scintigraphy with meals labelled with radioactive technetium-99 sulphur colloid, to assess aspiration into the lungs, and ultrasonography are not recommended for the routine diagnosis of GORD in infants.[2]

Treatment principles

For most infants with reflux, reassuring the parents that the condition will resolve without treatment is all that is needed.[1] Overfeeding is a common cause of reflux in infants, so this possibility needs to be explored, but with the caveat that prolonged severe reduction in feeding volume could cause nutritional problems. If regurgitation is frequent and other

SUMMARY POINTS

- Gastro-oesophageal reflux is common in infants, particularly preterm babies, younger infants, and those with neurodevelopmental disorders
- Reflux is usually self limiting and without complications. Occasionally, it is associated with troublesome symptoms or complications (such as respiratory disorders or suspected oesophagitis), when it is known as gastro-oesophageal reflux disease (GORD)
- Parental education and reassurance, changes in feeds, thickening of fluids, or an alginate combination should be tried first for managing GORD. Infants whose symptoms are unresponsive, or those with complications, should be referred to specialist paediatric services for investigation
- An H_2 receptor antagonist to reduce acid secretion may be needed to control the condition, but there is little evidence to support such therapy. Ranitidine, which is licensed for use from 6 months of age, is now recommended by the *BNF for Children* as the most suitable such drug for infants
- If an H_2 receptor antagonist is unsuccessful, the next step is treatment with omeprazole (unlicensed in infants) or surgery
- No other drugs are licensed or recommended for GORD in infants

causes of vomiting have been excluded, growth should be monitored, ideally through the use of parent-held records. If there is clear evidence of faltering growth, intervention should be considered. The main aims of treatment are to alleviate symptoms, promote normal growth, and prevent complications.

Lifestyle and dietary changes

The prevalence of physiological gastro-oesophageal reflux is similar in breast fed and formula fed infants.[18] Some infants with allergy to cows' milk protein experience regurgitation and vomiting indistinguishable from that associated with primary gastro-oesophageal reflux.[7 8 19 20] In these infants, vomiting frequency decreases substantially after the elimination of cows' milk protein from the diet (usually within two weeks), and reintroduction causes recurrence of symptoms.[2] Use of extensively hydrolysed or amino acid formula milks for up to four weeks may help to reduce troublesome symptoms.[8 21] Since ingested cows' milk protein passes into human breast milk in small quantities, breast fed infants with regurgitation and vomiting may benefit from a trial of withdrawal of cows' milk from the maternal diet.[19] However, the symptoms of infant gastro-oesophageal reflux are rarely severe enough to justify stopping breast feeding.[2]

Short-term (7–10 days) nasogastric feeding is sometimes used in infants with GORD (but no complicating disorders) who do not gain weight.[22] Nasojejunal feeding may be useful in infants with pneumonia related to gastro-oesophageal reflux to prevent recurrent aspiration.[2]

Thickening milk

A systematic review pooled data from 14 randomised controlled trials of thickened feeds involving a total of 877 otherwise healthy infants aged ≤2 years with gastro-oesophageal reflux.[23] It found that, compared with standard milk formulas, formulas thickened with carob bean gum, corn starch, rice starch, cereal, or soy fibre increased the percentage of infants with no regurgitation (risk ratio 2.91, 95% confidence interval 1.73 to 4.91), reduced the number of daily episodes of regurgitation and vomiting (weighted mean difference −1.37, −2.53 to −0.02), and increased daily weight gain (weighted mean difference 3.68, 1.55 to 5.81). No thickening agent seemed more effective than any other, and no serious unwanted effects were seen. The reviewers concluded that thickened food was "only moderately effective" for gastro-oesophageal reflux in healthy infants.

Some products can be used to thicken milk and are prescribable on the NHS as borderline substances (as detailed in Appendix 2 of the *BNF for Children*). These include the carob seed flour thickener Instant Carobel ("for thickening feeds in the treatment of vomiting") and the starch based thickeners Thick & Easy, Thixo-D, and Vitaquick ("for thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive"). Parents should use teats with large holes and be shown how to increase feed viscosity without blocking the teat. Other drinks may also be thickened. Excessive calorie intake is a potential problem with starch based thickeners such as rice cereal and corn starch, which are not recommended unless there is accompanying faltering growth.[24] The allergenicity of commercial thickening agents is uncertain because of lack of data.[2]

Commercial anti-regurgitant formula feeds containing processed rice, corn or potato starch, guar gum, or locust bean gum are available. One potential advantage of these formulas over standard formulas with added thickener is that the former are designed to have a caloric density, osmolality, protein, calcium, and fatty acid content appropriate to an infant's nutritional needs. Also, they do not require teats with large holes nor substantially increased sucking effort. Two such formulas, Enfamil AR and SMA Staydown, are available on NHS prescription for "significant gastro-oesophageal reflux." However, according to Appendix 2 of the *BNF for Children*, they are not to be used "for a period of more than 6 months" or "in conjunction with any other feed thickener or antacid products."

Positioning of infants

One systematic review, including five randomised studies that assessed the effect of positioning infants with gastro-oesophageal reflux, found that the designs of the trials were too dissimilar to make any comparisons between positions.[25] The authors concluded that elevating the head of the crib so that the baby's head is always uppermost when lying supine is not justifiable, and that the prone position must not be used in infants because of the risk of sudden infant death syndrome. Placing premature infants in the left lateral position in the postprandial period can reduce gastro-oesophageal reflux.[26 27] However, lying on the side is an unstable position for infants, and using pillows to maintain it is not recommended.[28]

Drug treatments for GORD

Many of the drugs used to treat GORD are not licensed for this use in infants. Furthermore, comparisons between drug treatments for GORD in children have been hampered by limited and heterogeneous evidence from small trials with inadequate controls.[29]

Alginate combinations

The aim of alginate combinations is to increase the viscosity of gastric contents and form a protective coating over the distal oesophagus.[30] In a double blind, randomised, placebo controlled trial involving 88 infants with gastro-oesophageal reflux, Gaviscon Infant (powder in sachets containing sodium alginate 225 mg and magnesium alginate 87.5 mg, but no aluminium) was effective in reducing the number of vomiting or regurgitation episodes at 14 days (the primary outcome measure) from a median of 8.5 to 3.0 (*v* from 7.0 to 5.0 with placebo, P=0.009), but not the severity of vomiting.[31] Another double blind, randomised, placebo controlled trial of Gaviscon Infant involving 20 infants with gastro-oesophageal reflux found no difference in the number of reflux events.[32]

Gaviscon Infant is licensed for use from birth.[33] However, the summary of product characteristics states that in premature infants or infants <1 year old it should be used only under medical supervision. It is contraindicated in those with known or suspected impairment of renal function, where excessive water loss is likely, or when there is intestinal obstruction. Also, it should not be given with other preparations that contain thickening agents. The licensed dose of Gaviscon Infant for children weighing <4.5 kg is one

dose (half of a dual sachet) mixed with each feed (or water, for breast-fed infants), and for those weighing ≥4.5 kg is two doses. It should not be administered more than six times in 24 hours.

Drugs to reduce gastric acid secretion

Infants with severe GORD—such as those who are unresponsive to dietary and lifestyle changes or to an alginate combination, or those with complications such as suspected oesophagitis or a respiratory disorder—need to be referred to a paediatrician for further investigation and possibly treatment to reduce gastric acid secretion (such as with H_2 receptor antagonists or proton pump inhibitors).[30]

H_2 receptor antagonists

In one non-blinded randomised controlled trial in 33 children aged 2–42 months with GORD and reflux oesophagitis, cimetidine (20 mg/kg/day) for 12 weeks was as effective as high doses of antacid in reducing reflux and oesophagitis as assessed clinically (P<0.05) and by pH monitoring and endoscopy.[34] In a randomised placebo controlled trial involving 35 infants aged 1.3–10.5 months with gastro-oesophageal reflux, oral famotidine 1.0 mg/kg reduced crying time (P=0.027) and regurgitation frequency (P=0.004) and volume (P=0.01), while famotidine 0.5 mg/kg reduced regurgitation frequency only (P=0.04).[35] We could find no randomised controlled trials of ranitidine for GORD in infants.

In the UK, the only two H_2 receptor antagonists licensed for treating GORD in children are cimetidine and ranitidine. The summary of product characteristics for cimetidine states that, for those aged <1 year, the drug has not been fully evaluated but that an oral dose of 20 mg/kg daily in divided doses "has been used."[36] However, cimetidine is not considered suitable for inclusion in the *BNF for Children* by the Paediatric Formulary Committee and is rarely used in practice.[30] The summary of product characteristics for ranitidine gives an intravenous infusion regimen for infants aged >6 months.[37] The *BNF for Children* recommends an oral dose of ranitidine of 1 mg/kg three times daily (up to a maximum of 3 mg/kg three times daily) for infants aged 1–6 months and 2–4 mg/kg twice daily for those aged 6–12 months, or a slow intravenous injection dose of 0.5–1 mg/kg every 6–8 hours for neonates and 1 mg/kg every 6–8 hours for infants aged ≥1 month.[30] Unwanted effects of H_2 receptor antagonists in infants include gastrointestinal disturbances such as diarrhoea, rash, agitation and irritability, head rubbing and headache, and somnolence.[30 35] Reassessment is necessary if symptoms persist after four to six weeks of treatment with ranitidine.[30]

Proton pump inhibitors

In one double blind, randomised, placebo controlled trial including 10 preterm infants with gastro-oesophageal reflux, oral omeprazole 0.7 mg/kg daily for seven days reduced gastric acidity (P<0.0005), oesophageal acid exposure (P<0.01), and the number and duration of acid gastro-oesophageal reflux episodes (P<0.05 and P<0.01, respectively).[38] In another such trial including 162 infants with clinically diagnosed GORD, oral lansoprazole (0.2–0.3 mg/kg daily for infants aged ≤10 weeks and 1.0–1.5 mg daily for those aged >10 weeks) was no more effective than placebo for GORD symptoms. However, more of the infants given lansoprazole developed serious unwanted effects, particularly lower respiratory tract infections (10 *v* 2 infants with placebo, P=0.032).[39]

Omeprazole is licensed for children aged >1 year with GORD with severe symptoms.[30] However, no marketed proton pump inhibitors are licensed for GORD in infants. For omeprazole, the *BNF for Children* recommends an oral dose of 0.7 mg/kg once daily for infants, which can be increased if necessary after 7–14 days to 1.4 mg/kg (maximum 2.8 mg/kg) in neonates (aged <1 month) and to 3 mg/kg (maximum 20 mg) in infants aged ≥1 month. The *BNF for Children* states that lansoprazole may be considered when the available formulations of omeprazole are unsuitable and recommends an oral dose of 0.5–1 mg/kg (maximum 15 mg) once daily in the morning for children weighing under 30 kg. Unwanted effects have been reported in around 2–15% of children taking proton pump inhibitors[40 41] and include gastrointestinal disturbances and headache.[30]

Increasing evidence suggests that acid suppression with proton pump inhibitors or H_2 receptor antagonists may increase rates of gastroenteritis (in infants aged >4 months), candidaemia (in infants in neonatal intensive care), and necrotising enterocolitis (in very low birthweight infants).[42-44]

Other drugs

Antacids directly buffer gastric contents, thereby potentially reducing heartburn and healing oesophagitis. However, evidence of benefit in infants is unclear, and antacids containing aluminium should not be used in infants aged <1 year because accumulation may lead to increased plasma aluminium concentrations.[30] Neither simeticone (activated dimeticone) nor sucralfate (a complex of aluminium hydroxide and sulphated sucrose) has a place in treating GORD in infants.[30]

Motility stimulants increase oesophageal sphincter pressure and stimulate gastric emptying. Cisapride is an example of a motility stimulant that was widely used for infant gastro-oesophageal reflux.[1] However, it has been withdrawn from the market in most countries, including the UK, because it prolongs the QTc interval, increasing the likelihood of sudden death.[45] Domperidone and metoclopramide are dopamine receptor antagonists that have been used to treat GORD, but neither is licensed for this use in infants and both can cause acute dystonic reactions.[1 30] Furthermore, an association between domperidone and prolongation of QTc interval in infants has been reported,[46] and metoclopramide has caused tardive dyskinesia.[30] A systematic review of domperidone identified only four randomised controlled trials in children, which provided "very little evidence" for the drug's efficacy in paediatric GORD.[47] A recent randomised controlled trial found a paradoxical increase in the number of gastro-oesophageal reflux episodes in newborns given domperidone.[48] A systematic review, which included 12 studies of metoclopramide (five blinded and randomised) involving a total of 343 children (aged 0–23 months) with symptoms of gastro-oesophageal reflux, found that the available evidence did not show a clinically significant benefit or any harm with the drug.[49] By contrast, another systematic review (described above) found evidence that metoclopramide reduced the number of daily symptoms (standard mean difference 0.72, 0.98 to 0.45) and reflux index (0.43, 0.72 to 0.14) compared with placebo in infants with GORD.[25]

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Surgery

Surgery may help selected children with severe GORD for whom optimum medical therapy has failed or who have life threatening complications. However, it is thought to have a relatively high failure rate and some complications.[50 51]

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