

Appendix A: Summary of evidence from surveillance

2018 surveillance of gastro-oesophageal reflux disease in children and young people: diagnosis and management (2015) NICE guideline NG1

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a final decision on the need to update each section of the guideline.

Diagnosing and investigating GORD

- 1.1.1 Recognise regurgitation of feeds as a common and normal occurrence in infants that:
- is due to gastro-oesophageal reflux (GOR) – a normal physiological process in infancy
 - does not usually need any investigation or treatment
 - is managed by advising and reassuring parents and carers.
- 1.1.2 Be aware that in a small proportion of infants, GOR may be associated with signs of distress or may lead to certain recognised complications that need clinical management. This is known as gastro-oesophageal reflux disease (GORD).
- 1.1.3 Give advice about GOR and reassure parents and carers that in well infants, effortless regurgitation of feeds:
- is very common (it affects at least 40% of infants)
 - usually begins before the infant is 8 weeks old
 - may be frequent (5% of those affected have 6 or more episodes each day)
 - usually becomes less frequent with time (it resolves in 90% of affected infants before they are 1 year old)
 - does not usually need further investigation or treatment.

1.1.4 When reassuring parents and carers about regurgitation, advise them that they should return for review if any of the following occur:

- the regurgitation becomes persistently projectile
- there is bile-stained (green or yellow-green) vomiting or haematemesis (blood in vomit)
- there are new concerns, such as signs of marked distress, feeding difficulties or faltering growth
- there is persistent, frequent regurgitation beyond the first year of life.

1.1.5 In infants, children and young people with vomiting or regurgitation, look out for the 'red flags' in table 1, which may suggest disorders other than GOR. Investigate or refer using clinical judgement.

Table 1 'Red flag' symptoms suggesting disorders other than GOR

Symptoms and signs	Possible diagnostic implications	Suggested actions
Gastrointestinal		
Frequent, forceful (projectile) vomiting	May suggest hypertrophic pyloric stenosis in infants up to 2 months old	Paediatric surgery referral
Bile-stained (green or yellow-green) vomit	May suggest intestinal obstruction	Paediatric surgery referral
Haematemesis (blood in vomit) with the exception of swallowed blood, for example, following a nose bleed or ingested blood from a cracked nipple in some breast-fed infants	May suggest an important and potentially serious bleed from the oesophagus, stomach or upper gut	Specialist referral
Onset of regurgitation and/or vomiting after 6 months old or persisting after 1 year old	Late onset suggests a cause other than reflux, for example a urinary tract infection (also see the NICE guideline on urinary tract infection in children) Persistence suggests an alternative diagnosis	Urine microbiology investigation Specialist referral
Blood in stool	May suggest a variety of conditions, including bacterial gastroenteritis, infant cows' milk protein allergy (also see the NICE guideline on food allergy in children and young people) or an acute surgical condition	Stool microbiology investigation Specialist referral
Abdominal distension, tenderness or palpable mass	May suggest intestinal obstruction or another acute surgical condition	Paediatric surgery referral
Chronic diarrhoea	May suggest cows' milk protein allergy (also see the NICE guideline on food allergy in children and young people)	Specialist referral

Systemic		
Appearing unwell Fever	May suggest infection (also see the NICE guideline on feverish illness in children)	Clinical assessment and urine microbiology investigation Specialist referral
Dysuria	May suggest urinary tract infection (also see the NICE guideline on urinary tract infection in children)	Clinical assessment and urine microbiology investigation Specialist referral
Bulging fontanelle	May suggest raised intracranial pressure, for example, due to meningitis (also see the NICE guideline on bacterial meningitis and meningococcal septicaemia)	Specialist referral
Rapidly increasing head circumference (more than 1 cm per week) Persistent morning headache, and vomiting worse in the morning	May suggest raised intracranial pressure, for example, due to hydrocephalus or a brain tumour	Specialist referral
Altered responsiveness, for example, lethargy or irritability	May suggest an illness such as meningitis (also see the NICE guideline on bacterial meningitis and meningococcal septicaemia)	Specialist referral
Infants and children with, or at high risk of, atopy	May suggest cows' milk protein allergy (also see the NICE guideline on food allergy in children and young people)	Specialist referral

1.1.6 Do not routinely investigate or treat for GOR if an infant or child without overt regurgitation presents with only 1 of the following:

- unexplained feeding difficulties (for example, refusing to feed, gagging or choking)
- distressed behaviour
- faltering growth
- chronic cough
- hoarseness
- a single episode of pneumonia.

1.1.7 Consider referring infants and children with persistent back arching or features of Sandifer's syndrome (episodic torticollis with neck extension and rotation) for specialist assessment.

1.1.8 Recognise the following as possible complications of GOR in infants, children and young people:

- reflux oesophagitis
- recurrent aspiration pneumonia

- frequent otitis media (for example, more than 3 episodes in 6 months)
 - dental erosion in a child or young person with a neurodisability, in particular cerebral palsy.
- 1.1.9 Recognise the following as possible symptoms of GOR in children and young people:
- heartburn
 - retrosternal pain
 - epigastric pain.
- 1.1.10 Be aware that GOR is more common in children and young people with asthma, but it has not been shown to cause or worsen it.
- 1.1.11 Be aware that some symptoms of a non-IgE-mediated cows' milk protein allergy can be similar to the symptoms of GORD, especially in infants with atopic symptoms, signs and/or a family history. If a non-IgE-mediated cows' milk protein allergy is suspected, see the NICE guideline on [food allergy in children and young people](#).
- 1.1.12 When deciding whether to investigate or treat, take into account that the following are associated with an increased prevalence of GORD:
- premature birth
 - parental history of heartburn or acid regurgitation
 - obesity
 - hiatus hernia
 - history of congenital diaphragmatic hernia (repaired)
 - history of congenital oesophageal atresia (repaired)
 - a neurodisability.
- 1.1.13 GOR only rarely causes episodes of apnoea or apparent life-threatening events (ALTEs), but consider referral for specialist investigations if it is suspected as a possible factor following a general paediatric assessment.
- 1.1.14 For children and young people who are obese and have heartburn or acid regurgitation, advise them and their parents or carers (as appropriate) that losing weight may improve their symptoms (also see the NICE guideline on [obesity](#)).
- 1.1.15 Do not offer an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of GORD in infants, children and young people.
- 1.1.16 Perform an urgent (same day) upper GI contrast study for infants with unexplained bile-stained vomiting. Explain to the parents and carers that this is needed to rule out serious disorders such as intestinal obstruction due to mid-gut volvulus.

- 1.1.17 Consider an upper GI contrast study for children and young people with a history of bile-stained vomiting, particularly if it is persistent or recurrent.
- 1.1.18 Offer an upper GI contrast study for children and young people with a history of GORD presenting with dysphagia.
- 1.1.19 Arrange an urgent specialist hospital assessment to take place on the same day for infants younger than 2 months with progressively worsening or forceful vomiting of feeds, to assess them for possible hypertrophic pyloric stenosis.
- 1.1.20 Arrange a specialist hospital assessment for infants, children and young people for a possible upper GI endoscopy with biopsies if there is:
- haematemesis (blood-stained vomit) not caused by swallowed blood (assessment to take place on the same day if clinically indicated; also see table 1)
 - melaena (black, foul-smelling stool; assessment to take place on the same day if clinically indicated; also see table 1)
 - dysphagia (assessment to take place on the same day if clinically indicated)
 - no improvement in regurgitation after 1 year old
 - persistent, faltering growth associated with overt regurgitation
 - unexplained distress in children and young people with communication difficulties
 - retrosternal, epigastric or upper abdominal pain that needs ongoing medical therapy or is refractory to medical therapy
 - feeding aversion and a history of regurgitation
 - unexplained iron-deficiency anaemia
 - a suspected diagnosis of Sandifer's syndrome.
- 1.1.21 Consider performing an oesophageal pH study (or combined oesophageal pH and impedance monitoring if available) in infants, children and young people with:
- suspected recurrent aspiration pneumonia
 - unexplained apnoeas
 - unexplained non-epileptic seizure-like events
 - unexplained upper airway inflammation
 - dental erosion associated with a neurodisability
 - frequent otitis media
 - a possible need for fundoplication ([see below](#))
 - a suspected diagnosis of Sandifer's syndrome.

- 1.1.22 Consider performing an oesophageal pH study without impedance monitoring in infants, children and young people if, using clinical judgement, it is thought necessary to ensure effective acid suppression.
- 1.1.23 Investigate the possibility of a urinary tract infection in infants with regurgitation if there is:
- faltering growth
 - late onset (after the infant is 8 weeks old)
 - frequent regurgitation and marked distress.

Surveillance decision

This section of the guideline should not be updated.

Risk factors for GORD

2018 surveillance summary

A prospective study (1) surveyed parents of children who had repair of tracheoesophageal fistula or oesophageal atresia to determine the prevalence of GORD after these operations. The mean age of children at the time of survey completion was 8.7 years. Of 381 children whose parents provided information about GORD, 290 (76%) reported having these conditions. The prevalence of GORD was not affected by the type of repair performed.

A systematic review (2) of 6 studies (n=289) assessed whether there is an association between GORD and apnoea in infants. One study found an increase in apnoea after reflux events. The other 5 studies found no association between reflux and subsequent apnoea. Two studies assessing reflux after apnoea found no association.

Intelligence gathering

No additional information related to this section was identified.

Impact statement

Evidence suggesting that children who had repair of tracheoesophageal fistula or oesophageal atresia have a high prevalence of GORD is consistent with current recommendations recognising this association. Although the recommendations refer only to atresia, fistula was recognised in the guideline text as a congenital disorder associated with atresia.

New evidence on the association between reflux and apnoea in infants appears to be inconsistent. The evidence considered in developing the guideline also showed no clear association between reflux and apnoea. This led to the recommendation to consider specialist assessment in children with apnoea, and to consider oesophageal pH monitoring if apnoea remains unexplained.

Overall, these findings are consistent with current recommendations to consider investigations only in children with specific indications.

New evidence is unlikely to change guideline recommendations.

Diagnosis

2018 surveillance summary

A survey of 207 UK neonatal units (3) investigated current practice in investigation and management of GORD. Responses were obtained from 84% of neonatal units. A trial of therapy was the most frequent first action (in 83% of units). Investigations were performed as follows: pH studies in 38%, upper gastrointestinal contrast studies in 19% and multichannel intraluminal impedance and pH in studies 5%. Six units used a threshold for an abnormal pH study and two units used a threshold for an abnormal multichannel intraluminal impedance study. Infants always started treatment without investigation in 32% of units, often in 29%, occasionally in 19% and never in 1%.

A diagnostic study (4) assessed ultrasound compared with barium swallow for detecting severity of GORD in children with suspected GORD (n=51). All participants had barium swallow and then transabdominal ultrasound. The number and duration of reflux episodes in a 5-minute period, the angle of His, mucosal thickness, and intra-abdominal oesophageal length were recorded during ultrasound. Duration and number of reflux episodes seen in ultrasound were significantly higher in patients that had severe reflux with barium swallow. A

reflux duration of 9.5 seconds on ultrasound had sensitivity of 80% and specificity of 60% for severe reflux detected by barium swallow. More than 2 episodes in 5 minutes had sensitivity of 75% and specificity of 58% for severe reflux detected by barium swallow. The angle of His, oesophageal wall mucosal thickness, and the intra-abdominal oesophageal length did not correlate with the severity of reflux.

A cross-sectional study (5) assessed multiple intraluminal impedance plus pH monitoring compared with pH monitoring alone in children with suspected reflux (n=217). GORD was diagnosed in 57% of participants with multiple intraluminal impedance plus pH monitoring and in 34% of participants with pH monitoring alone. Using multiple intraluminal impedance plus pH monitoring as the gold standard for diagnosing GORD, sensitivity of pH monitoring alone was 23% in infants, but increased with age, reaching 76% in children aged 9 years or older. The sensitivity of pH monitoring alone in children with oesophageal symptoms was 38%, and was 64% in children with gastrointestinal symptoms. Reflux oesophagitis was identified in 31 of 119 children (26%) who underwent endoscopy. Logistic regression analysis showed that the best predictors of endoscopic reflux esophagitis were the longest acid episode and DeMeester reflux composite. The optimum thresholds were DeMeester

reflux composite score of 29 of greater (AUC 79%) and duration of longest acid reflux of 18 minutes or more (AUC 78%).

A diagnostic study (6) assessed impedance monitoring plus pH monitoring compared with pH monitoring alone in infants with wheeze and suspected GORD (n=38). Impedance monitoring plus pH monitoring was also compared with the lipid-laden macrophage index. Overall, 61% of participants had abnormal impedance monitoring plus pH monitoring results, 8% of whom had abnormal pH monitoring results. Lipid-laden macrophage index was significantly higher in infants with abnormal compared with normal impedance monitoring plus pH monitoring results. The current definitions of abnormal impedance monitoring plus pH monitoring results – reflux index of 10% or more and more than 100 distal reflux episodes – had low sensitivity (23%) but high specificity (96–100%, respectively) in diagnosis of GORD-related aspiration.

Intelligence gathering

Topic expert feedback suggested that the guideline should include additional information on food allergy and that cow's milk exclusion in breastfeeding mothers may be warranted.

Impact statement

Investigations are recommended only for children with specific indications. The finding that treatment is the first action for GORD in neonatal units is consistent with this recommendation.

Ultrasound has low-to-moderate accuracy for diagnosing reflux. Multiple intraluminal impedance plus pH monitoring appears to have low sensitivity for diagnosing GORD-related aspiration, although this may increase with the child's age. The findings that investigations do not perform well supports the approach to only investigate when specific indications are suspected.

The guideline on GORD in children cross-refers to NICE's guideline on food allergy in several places, and no new evidence was identified to suggest any additional signs or symptoms of food allergy to consider in children with GORD. NICE's guideline on food allergy in children and young people covers cow's milk exclusion in breastfeeding mothers. Therefore, no update to the guideline in GORD in children is necessary at this time.

New evidence is unlikely to change guideline recommendations.

Testing for *Helicobacter pylori*

2018 surveillance summary

A diagnostic study (7) assessed carbon-13 urea breath testing for *H pylori* in children with dyspepsia (n=60). Biopsy samples were obtained from the antrum of the

stomach and the duodenum and used as the gold standard for diagnosis. Carbon-13 urea breath testing was positive in 47% of participants, of whom *H pylori* infection was confirmed by biopsy in 57%. The abstract did not report rates of *H pylori* infection in people who had a negative carbon-13 urea breath test. The carbon-13

urea breath test had sensitivity of 76% and specificity of 69%.

Intelligence gathering

No additional information related to this section was identified.

Impact statement

The guideline did not include recommendations on testing for *H pylori* in

children. *H pylori* breath testing has low-to-moderate ability to detect infection with this organism. The new evidence does not suggest a need to add recommendations in this area.

New evidence is unlikely to change guideline recommendations.

Initial management of GOR and GORD

- 1.2.1 Do not use positional management to treat GOR in sleeping infants. In line with [NHS advice](#), infants should be placed on their back when sleeping.
- 1.2.2 In breast-fed infants with frequent regurgitation associated with marked distress, ensure that a person with appropriate expertise and training carries out a breastfeeding assessment.
- 1.2.3 In formula-fed infants with frequent regurgitation associated with marked distress, use the following stepped-care approach:
- review the feeding history, **then**
 - reduce the feed volumes only if excessive for the infant's weight, **then**
 - offer a trial of smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk) unless the feeds are already small and frequent, **then**
 - offer a trial of thickened formula (for example, containing rice starch, cornstarch, locust bean gum or carob bean gum).
- 1.2.4 In breast-fed infants with frequent regurgitation associated with marked distress that continues despite a breastfeeding assessment and advice, consider alginate therapy for a trial period of 1–2 weeks. If the alginate therapy is successful continue with it, but try stopping it at intervals to see if the infant has recovered.
- 1.2.5 In formula-fed infants, if the stepped-care approach is unsuccessful (see recommendation 1.2.3), stop the thickened formula and offer alginate therapy for a trial period of 1–2 weeks. If the alginate therapy is successful continue with it, but try stopping it at intervals to see if the infant has recovered.

Surveillance decision

This section of the guideline should not be updated.

Positioning

2018 surveillance summary

A randomised crossover study (8) assessed positioning in premature infants (n=32). After feeding, the infant was placed in one of four positions for 12 hours: facilitated foetal tucking posture in lateral position, free body posture in lateral position, facilitated foetal tucking posture in supine position, and free body posture in supine position. The incidence of reflux was significantly lower with lateral position than for supine position. The difference between tucking and free postures was not significant.

A randomised controlled trial (9) assessed left lateral positioning in infants with GORD (n=51). Babies were assigned to one of four groups: left lateral positioning plus proton pump inhibitor (PPI); head of cot elevation plus PPI; left lateral positioning plus antacid; and head of cot elevation plus antacid. Head of cot elevation and antacids were considered control interventions. Left lateral positioning plus PPIs was most effective for reducing reflux episodes and oesophageal acid exposure. Left lateral positioning was associated with reduced reflux compared with head of cot elevation irrespective of acid suppression therapy.

PPIs reduced exposure to acid irrespective of positioning. No treatment improved crying or irritability.

Intelligence gathering

Topic expert feedback suggested a need to increase the focus on non-drug treatments such as positioning.

Impact statement

The guideline states: 'Do not use positional management to treat GOR in sleeping infants. In line with [NHS advice](#), infants should be placed on their back when sleeping.'

Evidence suggesting that lateral position is associated with lower incidence of GORD is consistent with the evidence considered when developing the guideline. However, the guideline committee 'felt strongly that they would be wrong to contradict in any way the Department of Health guidance on back (supine) sleeping for all infants at all times', because the campaign to promote supine sleeping has resulted in lower rates of sudden infant death syndrome. The new evidence from two small studies is therefore insufficient to change recommendations in this area.

New evidence is unlikely to change guideline recommendations.

Feed thickeners

2018 surveillance summary

A Cochrane review (10) of 8 studies assessed feed thickeners in infants with reflux (n=637). Most participants in the included studies were formula-fed term infants. Formula-fed term infants with reflux on feed thickeners had almost 2 fewer episodes of regurgitation per day and were more likely to have no symptoms of regurgitation at the end of the intervention period compared with unthickened feeds. Treating 5 infants with thickened feed would result in one infant being asymptomatic from regurgitation or vomiting. No studies reported failure to thrive as an outcome. In 2 studies (n=116), feed thickeners reduced the number of reflux episodes lasting longer than 5 minutes and duration of longest reflux episode. No major side effects of feed thickeners were reported. However, the authors noted that evidence was insufficient to conclude which type of feed thickener is most effective.

A randomised controlled trial (11) assessed magnesium alginate plus the anti-foaming agent simeticone compared with rice starch thickener, and with reassurance and lifestyle changes in infants with reflux (n=75). After 1 month, infants treated with alginate plus simeticone had greater reductions in symptoms than either rice starch or reassurance and lifestyle changes. Infants treated with rice starch had greater reductions in symptoms than reassurance and lifestyle changes.

A randomised controlled trial (12) assessed carob bean gum galactomannan thickened formula in infants with reflux (n=56). Two

concentrations of cold-soluble galactomannans and one concentration of hot-soluble galactomannans were compared. The lower concentration of cold-soluble carob bean gum galactomannans was associated with significantly greater reductions in reflux symptoms and 'percentage of all reflux'.

A randomised controlled trial (13) assessed low-lactose infant formula pre-thickened with rice starch compared with standard infant formula in term infants with frequent regurgitation who were otherwise healthy (n=132). Infants received formula from about 14 days after birth to 112 days of age. Weight gain and formula intake did not differ significantly between groups. Regurgitation was significantly lower with thickened formula.

Intelligence gathering

Topic expert feedback suggested that in infants, thickeners with calorific content should be avoided in preference of non-caloric thickening agents and that earlier introduction of solid foods would be a source of naturally thickened food.

Impact statement

A stepped-care approach to feeding interventions for frequent regurgitation with marked distress is recommended for formula-fed infants. Feed thickeners are the last step before medical therapy.

Evidence suggests that feed thickeners are more effective than reassurance and lifestyle changes. A Cochrane review on feed thickeners noted that evidence was insufficient to conclude which type of feed thickener is most effective. Other identified trials did not provide sufficient evidence to contradict that conclusion.

The Scientific Advisory Committee on Nutrition has published [Feeding in the first year of life](#), recommending solid foods from around 6 months of age. The rationale for this recommendation was: 'The available evidence indicates that the introduction of solid foods or infant formula before 6 months of age reduces the amount of breast milk consumed and is associated with greater risk of infectious illness in infants.'

No evidence was identified to suggest whether thickeners with calorific content adversely affects babies' weight.

New evidence is unlikely to change guideline recommendations.

Alginate and simeticone

2018 surveillance summary

A survey of 207 UK neonatal units (3) investigated current practice in investigation and management of GORD. Responses were obtained from 84% of neonatal units. Gaviscon (sodium alginate and magnesium alginate) was used as first line treatment in 60% of units. Thickening agents were used in 27% of units.

A Cochrane review (14) of 24 studies assessed drug treatments for GORD in children (n=1,201). Meta-analysis of data for individual drugs or drug classes was not possible. Evidence indicated that Gaviscon Infant improves symptoms in infants, including those with functional reflux.

A randomised controlled trial (11) assessed magnesium alginate plus the anti-foaming agent simeticone compared with rice starch thickener, and with reassurance and lifestyle changes in infants with reflux (n=75). After 1 month, infants treated with alginate plus simeticone had greater reductions in symptoms than either rice

starch or reassurance and lifestyle changes. Infants treated with rice starch had greater reductions in symptoms than reassurance and lifestyle changes.

Intelligence gathering

Topic expert feedback suggested that Infant Gaviscon has a high salt content and that care should be taken with dosing to avoid exceeding the recommended salt intake for an infant. Additionally, if frequent feeding is undertaken, Infant Gaviscon will not be able to be used with every feed.

Impact statement

The first interventions recommended differ for breastfed and formula-fed infants. For breastfed babies, a breastfeeding assessment should be conducted. If symptoms continue, a trial of alginate should be considered.

A stepped-care approach for formula-fed babies is recommended, first addressing mechanisms of feeding and ending with a trial of thickened formula. Alginate is the first medical therapy recommended for

bottle-fed babies for whom the stepped-care approach has failed.

Data from UK practice suggests that alginate therapy is the most common first therapy for GORD in infants, and under one third of infants receive thickening agents. These findings suggest that guidance on using thickeners before alginate may not be followed adequately.

In developing the guideline, there was a lack of evidence on thickeners compared with alginate. Therefore, the rationale for recommending feed thickeners in formula-fed babies was: 'where there is no evidence to support a cost effectiveness assessment, the cheaper option should be offered first'. Furthermore, the group decided that where there is no hierarchy of efficacy, the intervention that is least intrusive should be offered first, in this case feeding changes'. The evidence on feed thickeners identified in surveillance has no impact on these conclusions.

Alginate plus simethicone may be more effective than feed thickener or reassurance and lifestyle changes.

Simeticone is not recommended for the treatment of GORD, but is widely available in the UK in a formulation for the relief of wind (Infacol). The new evidence comes from a small, three-arm study, in which a maximum of 25 infants received alginate plus simeticone. It is unclear whether treatment effects would be attributable to alginate, or simeticone, or both. Therefore, it is unlikely that this evidence could change current recommendations.

For the issue raised by topic experts of high salt content of [Gaviscon Infant](#), the SPC notes: 'Follow dosage instructions exactly to avoid an excessive amount of product per feed and the possible risk of hypernatraemia.' NICE guidelines assume that prescribers will use a medicine's SPC to inform decisions made with individual patients.

Overall, the guideline does not need updating at this time.

New evidence is unlikely to change guideline recommendations.

Extensively hydrolysed formula

2018 surveillance summary

A crossover study (15) assessed extensively hydrolysed infant formula compared with standard formula in premature infants with reflux (n=23). All infants receiving tube feeding were fed with standard formula, expressed breast milk or a mix of these two feeds (based on the mother's preference) for 24 hours then

all crossed over to extensively hydrolysed formula for the subsequent 24 hours. The median total reflux episodes and median acidic reflux episodes were significantly lower with extensively hydrolysed formula. There was no difference in reflux index, bolus exposure indexes, and number of episodes lasting more than 5 minutes.

Intelligence gathering

No additional information related to this section was identified.

Impact statement

The guideline has no recommendations on extensively hydrolysed formula, but has a research recommendation – what is the effectiveness and cost effectiveness of a trial of hydrolysed formula in formula-fed infants with frequent regurgitation associated with marked distress?

Evidence from a small crossover study suggested that extensively hydrolysed formula may reduce the overall number of reflux episodes, but may not affect the severity or duration of reflux episodes.

The new evidence cannot be considered to answer the research recommendation because it does not address two aspects of interest noted in the rationale for making the research recommendation. The first is that it is unclear whether participating infants had a personal or family history of atopy. The second is that it is unclear whether participating infants had initial management up to and including alginates before trying hydrolysed formula.

New evidence is unlikely to change guideline recommendations.

Children with neurodisability

2018 surveillance summary

No evidence related to this section was identified.

Intelligence gathering

Topic expert feedback also highlighted that evidence remains lacking for appropriate treatments for children with neurodisability.

Impact statement

No new evidence for initial interventions children with neurodisability was identified. Therefore, there is no information to guide additional recommendations for this population.

New evidence is unlikely to change guideline recommendations.

Pharmacological treatment of GORD

- 1.3.1 Do not offer acid-suppressing drugs, such as PPIs or H₂RAs, to treat overt regurgitation in infants and children occurring as an isolated symptom.
- 1.3.2 Consider a 4-week trial of a PPI or H₂RA for those who are unable to tell you about their symptoms (for example, infants and young children, and those with a neurodisability associated with expressive communication difficulties) who have overt regurgitation with 1 or more of the following:
 - unexplained feeding difficulties (for example, refusing feeds, gagging or choking)

- distressed behaviour
 - faltering growth.
- 1.3.3 Consider a 4-week trial of a PPI or H₂RA for children and young people with persistent heartburn, retrosternal or epigastric pain.
- 1.3.4 Assess the response to the 4-week trial of the PPI or H₂RA, and consider referral to a specialist for possible endoscopy if the symptoms:
- do not resolve **or**
 - recur after stopping the treatment.
- 1.3.5 When choosing between PPIs and H₂RAs, take into account:
- the availability of age-appropriate preparations
 - the preference of the parent (or carer), child or young person (as appropriate)
 - local procurement costs.
- 1.3.6 Offer PPI or H₂RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis, and consider repeat endoscopic examinations as necessary to guide subsequent treatment.
- 1.3.7 Do not offer metoclopramide, domperidone or erythromycin to treat GOR or GORD without seeking specialist advice and taking into account their potential to cause adverse events.

Surveillance decision

This section of the guideline should not be updated.

Editorial amendments were identified:

- A footnote should be added to recommendations 1.3.1–1.3.6 to refer to MHRA drug safety updates for PPIs.
- Recommendation 1.3.7 should be amended to reflect the strength of MHRA advice restricting the use of domperidone and metoclopramide.

Drug treatments for GORD in children

2018 surveillance summary

A survey of 207 UK neonatal units (3) investigated current practice in

investigation and management of GORD. Responses were obtained from 84% of neonatal units. Gaviscon (sodium alginate and magnesium alginate) was used as first line treatment in 60% of units. Other treatments included ranitidine in 53% of units, thickening agents in 27%, PPIs in

23%, domperidone in 22% and erythromycin in 6%.

A Cochrane review (14) of 24 studies assessed drug treatments for GORD in children (n=1,201). Meta-analysis of data for individual drugs or drug classes was not possible because of heterogeneous study populations and variations in study design. Evidence suggested that PPIs reduce reflux symptoms in children with confirmed erosive oesophagitis. It was not possible to determine superiority of one PPI over another. Some evidence indicated that H₂RAs are effective in treating GORD in children. Evidence was insufficient for assessment of prokinetics. No randomised controlled trials on drug treatments for children with neurodisability were identified.

A systematic review (16) of 6 studies assessed drug treatments for GORD in preterm infants in neonatal care units. Meta-analysis was not possible because studies did not assess the same interventions or outcomes. The number of participants in studies was not reported in the abstract. Results of individual studies showed reduced oesophageal acid exposure (percentage of time with pH less than 4) with omeprazole and fewer reflux episodes with alginate, both compared with placebo. GORD symptoms were reduced with ranitidine and metoclopramide, but esomeprazole and lansoprazole showed no benefits over placebo. The authors concluded that the evidence was insufficient to conclude whether these drugs were effective or safe in preterm infants.

Acid suppressing drugs

A randomised controlled trial (17) assessed omeprazole compared with ranitidine in

infants with GORD (n=60). After 2 weeks there was no difference between treatments on GORD symptoms.

A randomised controlled trial (18) assessed hypoallergenic diet compared with ranitidine in infants with GORD (n=50). After 2 weeks, frequency of vomiting was reduced in both groups, with no significant difference between groups. Respiratory symptoms were reported to have reduced in both groups, but the abstract did not report on the difference between the two groups. Irritability was not reduced in either group.

A randomised controlled trial (19) assessed weight-adjusted dosing of esomeprazole compared with placebo in infants with GORD (n=98). All participants had 2 weeks treatment with esomeprazole before random allocation to the study groups. There was no significant difference in the proportion of children stopping treatment because of worsening symptoms between esomeprazole and placebo. In post-hoc analysis, the time to stopping treatment was significantly longer with esomeprazole in infants who had symptomatic GORD (diagnosed without investigation).

Intelligence gathering

Topic experts highlighted the study showing an association between early use of H₂RAs and PPIs and subsequent diagnosis of allergic diseases, including food allergy.

Topic expert feedback suggested that guidance on whether to choose an H₂RA or a PPI as the first line drug treatment would be welcome.

Topic expert feedback suggested that drug treatments may be used more frequently

in general practice than might be expected if non-drug treatment recommendations were being followed.

Topic expert feedback indicated that the recommendation on use of domperidone and metoclopramide did not reflect the strength of MHRA advice restricting use of these drugs.

Impact statement

Evidence identified in surveillance suggests no difference in effectiveness between an H₂RA and a PPI. PPIs may have benefits over placebo but an H₂RA may have no benefit over a hypoallergenic diet. Children with signs and symptoms of food allergy should receive care in line with the guideline on [food allergy](#). Therefore, no update in this area is necessary.

The guideline has no recommendations specifically of premature babies. Evidence appears to be insufficient to guide new recommendations in this area.

Evidence suggests that more than half of infants with GORD receive H₂RAs and nearly a quarter receive PPIs. This may be expected in line with current recommendations to offer these drugs for signs and symptoms of GORD after trying alginate therapy.

The MHRA drug safety updates on domperidone and metoclopramide were issued before the guideline published and were considered during development of the guideline. After reviewing the guideline committee's reasons for the recommendation on use of domperidone and metoclopramide, we propose an editorial amendment of this recommendation to reflect the strength of MHRA advice restricting the use of domperidone and metoclopramide.

New evidence is unlikely to change guideline recommendations.

Adverse events associated with drug treatments for GORD

PPIs and H₂RAs

A cohort study (20) based on National data from the Netherlands assessed safety of omeprazole, other PPIs or H₂RAs in children. Overall, 2,820 children were prescribed esomeprazole, 13,818 children were prescribed other PPIs, and 6,832 were prescribed H₂RAs. In total, 504 children (2%) were admitted to hospital for 762 predefined events. For most adverse events, there was no significant difference in occurrence across the treatments.

Failure to thrive was significantly more likely with esomeprazole compared with other PPIs. No other adverse events showed significant associations with drug treatment.

An analysis of data from a randomised controlled trial (21) assessed the effect of exposure to gastric acid reducing drugs and incidence of late-onset sepsis in very low birth weight infants. The trial assessed bovine lactoferrin with or without *Lactobacillus rhamnosus* compared with placebo (n=743). Overall, 235 infants received inhibitors of gastric acidity and 86 had late-onset sepsis. Exposure to gastric

acid inhibitors was associated with a small but significant increase in the odds of developing late-onset sepsis. Each additional day of exposure to gastric acid inhibitors significantly increased risk of late-onset sepsis in infants who did not receive bovine lactoferrin but no significant association was seen in infants who received bovine lactoferrin.

A randomised controlled trial (22) assessed probiotics compared with placebo in children with GORD (n=128). Before the study, all participants had glucose hydrogen breath testing then took PPIs for 12 weeks before another glucose hydrogen breath test. A control group of healthy children also had glucose hydrogen breath testing (n=120). After 12 weeks of PPI treatment, the children with GORD were randomly assigned to *Lactobacillus reuteri* DSM 17938 or placebo for 12 weeks. All participants remained on PPIs. After 12 weeks of treatment, 'dysbiosis' was detected in significantly more children in the placebo group. There was no significant difference in detection of bacterial overgrowth in children who took probiotics and the control group.

A cohort study (23) assessed ranitidine in premature babies admitted to neonatal intensive care units. Of 300 newborn babies admitted to the neonatal intensive care unit, 115 received ranitidine. Significantly more infants exposed to ranitidine had infections or culture-positive late-onset infections. Mortality was significantly higher in infants receiving ranitidine. There was no significant association with incidence of necrotising enterocolitis.

A cohort study (24) assessed the risk of developing allergy in children exposed to

PPIs or H₂RAs in the first 6 months of life. Of 792,130 children, 7.6% were prescribed an H₂RA, and 1.7% were prescribed a PPI. After a median follow-up of 4.6 years, children exposed to either class of drugs had significantly greater likelihood of food allergy, drug allergy, anaphylaxis, allergic rhinitis and asthma, than those who were not exposed to these drugs.

Metoclopramide and domperidone

A systematic review (25) of 108 studies assessed metoclopramide in children for any indication (n=2,699). The most common adverse effects reported in prospective studies of metoclopramide in children were extrapyramidal symptoms (9% of children), diarrhoea (6% of children), and sedation (6% of children). Arrhythmia, respiratory distress or arrest, neuroleptic malignant syndrome, and tardive dyskinesia were reported to be rarely associated with metoclopramide use, although data were not reported in the abstract.

A systematic review (26) of 5 studies assessed adverse effects of domperidone in children (n=137). One study showed a significant effect on QTc interval. Most studies reported rare occurrences of pathological QTc intervals but did not consistently consider confounding factors such as abnormal electrolyte level or concurrent treatment.

Overdose with GORD treatments in children

A cohort study (27) assessed the association with formulation and dose of drug treatments for GORD in children younger than 5 years reported to the UK National Poisons Information Service between July 2007 and June 2015. There were 517 single-agent ranitidine

overdoses in children under 5 years; 145 domperidone overdoses, and 135 omeprazole overdoses. Most ranitidine overdose enquiries (79%) in children younger than 5 years were in infants under 6 months of age. This age group also accounted for 47% of domperidone and 6% of omeprazole enquiries. In children younger than 6 months, 101 cases were 10-fold overdoses, 86 of which occurred with ranitidine. The authors suggested that this could be due to a syrup formulation with a high concentration of ranitidine.

Intelligence gathering

Topic expert feedback noted that in children, the dosage of ranitidine is based on the child's weight, and that if the dose is not adjusted upwards as the child gains weight, the treatment may become ineffective.

Impact statement

Several studies have identified adverse events associated with drug treatments for GORD; however, it is difficult to confirm whether the adverse events are related to the drugs or to the condition being treated. For example, GORD due to food allergy may be treated with acid suppressing drugs before an accurate diagnosis is made. The allergy and any associated allergies could subsequently be incorrectly attributed to the drug treatment.

Current recommendations on drug treatments for children with GORD are restricted in terms of the populations in which these drugs should be offered. PPIs and H₂RAs should be offered for only 4 weeks. If symptoms do not respond or recur after stopping treatment, referral to a specialist for possible endoscopy should

be considered. In developing the recommendations, the guideline committee balanced the known risks of gastric acid inhibitors with their potential benefits, specifically in healing erosive oesophagitis.

The adverse events suggested to be associated with gastric acid inhibitors, particularly infections, are similar to those identified while developing the guideline.

There appears to be a substantially higher number of incidents of ranitidine overdose in children in the UK relative to the levels of overdose of domperidone and omeprazole. Ranitidine was involved in 85% of reported 10-fold overdoses in children younger than 6 months. The guideline committee noted that the liquid formulation of ranitidine was preferable in children who were unable to swallow pills or capsules. Therefore, there are practical reasons for choosing this formulation in children. NICE guidelines assume that prescribers will use a medicine's SPC to inform decisions made with individual patients. This includes adjusting weight-based dosages according to the child's current weight.

The adverse events associated with metoclopramide and domperidone were recognised when developing the guideline and led to these drugs being recommended only with specialist advice. The MHRA drug safety updates on domperidone and metoclopramide were issued before the guideline published and were considered during development of the guideline. After reviewing the guideline committee's reasons for the recommendation on use of domperidone and metoclopramide, we propose an editorial amendment to reflect the

strength of MHRA advice restricting the use of domperidone and metoclopramide. Overall, the new evidence is unlikely to affect current recommendations because the new evidence has not changed the

balance of the recognised risks and benefits of drug treatments for GORD.

New evidence is unlikely to change guideline recommendations.

Enteral tube feeding for GORD

- 1.4.1 Only consider enteral tube feeding to promote weight gain in infants and children with overt regurgitation and faltering growth if:
- other explanations for poor weight gain have been explored **and/or**
 - recommended feeding and medical management of overt regurgitation is unsuccessful.
- 1.4.2 Before starting enteral tube feeding for infants and children with faltering growth associated with overt regurgitation, agree in advance:
- a specific, individualised nutrition plan
 - a strategy to reduce it as soon as possible
 - an exit strategy, if appropriate, to stop it as soon as possible.
- 1.4.3 In infants and children receiving enteral tube feeding for faltering growth associated with overt regurgitation:
- provide oral stimulation, continuing oral feeding as tolerated
 - follow the nutrition plan, ensuring that the intended target weight is achieved and that appropriate weight gain is sustained
 - reduce and stop enteral tube feeding as soon as possible.
- 1.4.4 Consider jejunal feeding for infants, children and young people:
- who need enteral tube feeding but who cannot tolerate intragastric feeds because of regurgitation **or**
 - if reflux-related pulmonary aspiration is a concern.

Surveillance decision

This section of the guideline should not be updated.

A systematic review (28) of 3 studies (n=556) assessed fundoplication plus gastrostomy compared with jejunal feeding in children with neurodisability. No significant differences were seen in pneumonia, mortality, major complications, or minor complications. No studies reported on quality of life.

An observational study (29) assessed jejunal feeding (n=163) compared with fundoplication (n=1,178) in children with neurodisability. A matched sample of 114 children in each group was analysed. There was no significant difference between the procedures for reflux-related admission to hospital in the first year after the procedure. Failure to thrive, repeat of initial intervention and crossover to other intervention were reported to be more common with jejunal feeding, although data were not reported in the abstract. Odds of death were similar with both interventions.

Intelligence gathering

Topic expert feedback suggested that additional recommendations on treatments for children with neurodisability would be useful.

Impact statement

The guideline noted that ‘many of the children classed as having severe neurodisabilities may have swallowing difficulties and poorly functioning airway protective reflexes. This means they may be dependent on enteral feeding and at risk of aspiration and pneumonia.’

Evidence suggests that jejunal feeding may be as effective as fundoplication in children with neurodisability. This supports the recommendations to consider enteral or jejunal feeding for children with overt regurgitation and faltering growth if other explanations for poor weight gain have been explored or recommended feeding and medical management of overt regurgitation is unsuccessful.

The evidence does not suggest a need for specific recommendations on enteral feeding or fundoplication for children with neurodisability.

New evidence is unlikely to change guideline recommendations.

Surgery for GORD

- 1.5.1 Offer an upper GI endoscopy with oesophageal biopsies for infants, children and young people before deciding whether to offer fundoplication for presumed GORD.
- 1.5.2 Consider performing other investigations such as an oesophageal pH study (or combined oesophageal pH and impedance monitoring if available) and an upper GI contrast study for infants, children and young people before deciding whether to offer fundoplication.
- 1.5.3 Consider fundoplication in infants, children and young people with severe, intractable GORD if:

- appropriate medical treatment has been unsuccessful **or**
- feeding regimens to manage GORD prove impractical, for example, in the case of long-term, continuous, thickened enteral tube feeding.

Surveillance decision

This section of the guideline should not be updated.

Laparoscopic or open fundoplication

A systematic review (30) of 9 studies (n=916) assessing laparoscopic compared with open Nissen fundoplication in children with GORD found longer duration of surgery with laparoscopic surgery. This review found laparoscopic surgery to be associated with fewer complications, but no differences were seen in time to full feeding, wound infection, or reoperation rates.

An earlier systematic review (31) compared laparoscopic fundoplication compared with open Nissen fundoplication. The findings were similar to those seen in the other review (30) with no significant differences in mortality, reoperation, or complications, and laparoscopic surgery was again noted to be longer in duration. However, this systematic review also noted a higher recurrence of GORD in children who had laparoscopic fundoplication compared with open fundoplication. The abstract did not report the number of included studies or participants.

A systematic review (32) of 3 studies (n=171) found similar results – that laparoscopic fundoplication in children was associated with increased recurrence of GORD and longer duration of surgery than open surgery. There was no significant

difference in mortality, postoperative complications, readmission, or hospital stay.

A randomised controlled trial (33) assessed laparoscopic fundoplication compared with open fundoplication in children with GORD aged 2 years and younger (n=39). Laparoscopic fundoplication had significantly longer operating times and higher cost. No significant differences were seen in length of stay in hospital, time to full feeding, or analgesic needs.

A randomised controlled trial (34) assessed laparoscopic and open fundoplication in children with GORD (n=87). The median age of children was 4.7 years in the laparoscopic surgery group and 3.7 years in the open surgery group. Just over half of the participants in both groups had neurodisability. GORD recurred in significantly more children after laparoscopic surgery than after open surgery.

Long-term results from a randomised controlled trial (35) assessed laparoscopic fundoplication compared with open fundoplication in children with GORD (n=39). Most participants (n=31) had neurodisability, seven of whom died before 4-year follow-up. After 4 years, there was no significant difference in recurrent GORD. Further fundoplication

was performed in one patient in each group. Weight Z scores increased in both groups, which the authors noted indicated improved nutritional status. Gas bloating, dumping syndrome and quality of life were similar in both groups. Children in the laparoscopic fundoplication group had less retching.

Robot-assisted or open fundoplication

One systematic review (36) of 6 studies (n=297) assessed robot-assisted fundoplication compared with laparoscopic fundoplication in children with GORD. Operating time, length of stay in hospital, and postoperative complications did not differ significantly between the surgical methods.

Partial or complete fundoplication

One systematic review (37) of 14 studies assessed partial fundoplication compared with complete fundoplication in children with GORD. The number of participants was not reported in the abstract. There was no significant difference in surgical success between the two methods.

Oesophagocrural stitching during fundoplication

A randomised controlled trial (38) assessed placing 4 oesophagocrural stitches during laparoscopic fundoplication compared with not placing these stitches in children with GORD aged younger than 7 years undergoing fundoplication with minimal oesophageal dissection (n=120). Operative time was significantly longer with sutures. No wrap herniation occurred in either group, but one reoperation for wrap loosening was performed in the no suture group. Reflux symptoms and medications were not different at one month, one year, and final follow-up at a median of 4 years.

A systematic review (39) of 6 studies assessed fundoplication plus gastrostomy compared with gastrostomy in children (n=2,730). Fundoplication plus gastrostomy was associated with more minor complications and overall complications. Major complications and reflux-related complications were not significantly different between groups. About 9% of children who had gastrostomy alone subsequently had fundoplication.

Children with tracheoesophageal fistula or oesophageal atresia repair

A prospective study (1) surveyed parents of children who had repair of tracheoesophageal fistula or oesophageal atresia to determine the prevalence of GORD after these operations. Surgery for GORD was performed in 22%, and 27% of those patients had more than one procedure. The most common type of surgery was Nissen fundoplication (73%), followed by partial wrap (14%). Reflux recurred in 32% of patients after surgery.

Intelligence gathering

Topic expert feedback suggested that additional recommendations for children with neurodisability would be useful.

Impact statement

Gastrostomy plus fundoplication may be associated with more complications than gastrostomy alone, but a small proportion of children with gastrostomy may still need fundoplication. In the [previous section](#) on enteral feeding, fundoplication appeared to be as effective for GORD as jejunal feeding and gastrostomy. Evidence suggests some children who have

gastrostomy subsequently also need fundoplication.

Several studies of fundoplication suggest that laparoscopic fundoplication may take longer to perform and may result in a higher rate of recurrence of GORD. For most other outcomes, particularly complications, laparoscopic fundoplication appears to be similar to open fundoplication.

Partial fundoplication may have similar outcomes to complete fundoplication, and oesophagocrural stitches may lengthen operating time. Finally, fundoplication may be necessary in a proportion of children who had congenital oesophageal abnormalities repaired after birth.

None of these findings impact on current recommendations on fundoplication, which do not specify the type of fundoplication that should be considered. The evidence also cannot inform decisions about when to consider fundoplication. Current recommendations note that fundoplication should be considered in infants, children and young people with severe, intractable GORD if appropriate medical treatment has been unsuccessful or feeding regimens to manage GORD prove impractical, for example, in the case of long term, continuous, thickened enteral tube feeding.

New evidence is unlikely to change guideline recommendations.

Research recommendations

What are the symptoms of GORD in infants, children and young people with a neurodisability?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

What is the effectiveness and cost effectiveness of a trial of hydrolysed formula in formula-fed infants with frequent regurgitation associated with marked distress?

Summary of findings

One small study (15) assessed extensively hydrolysed infant formula compared with standard formula in premature infants with reflux (n=23). The median total reflux episodes and median acidic reflux episodes were significantly lower with extensively hydrolysed formula. There was no difference in reflux index, bolus exposure indexes, and number of episodes lasting more than 5 minutes.

The new evidence cannot be considered to answer the research recommendation because it does not address two aspects of interest noted in the rationale for making the research recommendation. The first is it is unclear whether participating infants had a personal or family history of atopy. The second is that it is unclear whether participating infants had initial management up to and including alginates before trying hydrolysed formula.

Surveillance decision

Overall, this evidence shows inconsistent effects on parameters associated with reflux – reducing the overall number of reflux episodes, but not affecting the severity or duration of reflux episodes. Therefore, no impact on the guideline is expected. This research recommendation will be considered again at the next surveillance point.

In infants, children and young people with overt or occult reflux, is fundoplication effective in reducing acid reflux as determined by oesophageal pH monitoring?

Summary of findings

New evidence on fundoplication was identified. Fundoplication appears to be effective when [compared with enteral feeding](#). Other studies compared [fundoplication interventions in both arms](#).

In two studies, one of which measured oesophageal pH, laparoscopic fundoplication was associated with higher recurrence of GORD. However, no information was identified to judge the effects of open fundoplication on GORD as measured by oesophageal pH.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

References

1. Acher, CW, Ostlie, DJ, Leys, CM, Struckmeyer, S, Parker, M, Nichol, PF (2016) Long-Term Outcomes of Patients with Tracheoesophageal Fistula/Esophageal Atresia: Survey Results from Tracheoesophageal Fistula/Esophageal Atresia Online Communities. *European Journal of Pediatric Surgery* 26(6):476–80
2. Smits, MJ, van WMP, Langendam, MW, Benninga, MA, Tabbers, MM (2014) Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review. *Neurogastroenterology & Motility* 26(11):1527–38
3. Rossor, T, Andradi, G, Bhat, R, Greenough, A (2018) Investigation and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units. *Acta Paediatrica* 107(1):48–51
4. Khatami, A, Allameh, MM, Shahnazi, M, Kiumarsi, A, Tajik, A (2015) A comparison between gastroesophageal ultrasonography vs. barium swallow in determining the pattern of gastroesophageal reflux in a pediatric population. *Medical Ultrasonography* 17(1):22–7
5. Ristic, N, Milovanovic, I, Radusinovic, M, Stevic, M, Ristic, M, Ristic, M, et al. (2017) The comparative analyses of different diagnostic approaches in detection of gastroesophageal reflux disease in children. *PLoS ONE [Electronic Resource]* 12(11):e0187081
6. Abdallah, A, El-Desoky, T, Fathi, K, Fawzi EW, Zaki, A (2017) Evaluation of gastro-oesophageal reflux disease in wheezy infants using 24-h oesophageal combined impedance and pH monitoring. *Arab Journal of Gastroenterology* 18(2):68–73
7. Honar, N, Minazadeh, A, Shakibzad, N, Haghghat, M, Saki, F, Javaherizadeh, H (2016) Diagnostic accuracy of urea breath test for helicobacter pylori infection in children with dyspepsia in comparison to histopathology. *Arquivos de Gastroenterologia* 53(2):108–12
8. Valizadeh, L, Ghahremani, G, Gharehbaghi, M, Jafarabadi, M (2017) The effect of body status on gastroesophageal reflux after feeding among hospitalized premature infants: a randomized crossover clinical trial. *Tehran university medical journal* 75(8):577–84
9. Loots, C, Kritas, S, van WM, McCall, L, Peeters, L, Lewindon, P, et al. (2014) Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. *Journal of Pediatric Gastroenterology & Nutrition* 59(2):237–43
10. Kwok, TC, Ojha, S, Dorling, J (2017) Feed thickener for infants up to six months of age with gastro-oesophageal reflux. *Cochrane Database of Systematic Reviews* (12)
11. Ummarino, D, Miele, E, Martinelli, M, Scarpato, E, Crocetto, F, Sciorio, E, et al. (2015) Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. *Journal of Pediatric Gastroenterology & Nutrition* 60(2):230–5
12. Georgieva, M, Manios, Y, Rasheva, N, Pancheva, R, Dimitrova, E, Schaafsma, A (2016) Effects of carob-bean gum thickened formulas on infants' reflux and tolerance indices. *World Journal of Clinical Pediatrics* 5(1):118–27
13. Lasekan, JB, Linke, HK, Oliver, JS, Carver, JD, Blatter, MM, Kuchan, MJ, et al. (2014) Milk protein-based infant formula containing rice starch and low lactose reduces common regurgitation in healthy term infants: a randomized, blinded, and prospective

- trial. *Journal of the American College of Nutrition* 33(2):136–46
14. Tighe, M, Afzal, NA, Bevan, A, Hayen, A, Munro, A, Beattie, RM (2014) Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database of Systematic Reviews* (11)
 15. Logarajaha, V, Onga, C, Jayagobib, PA, Khoob, PC, Heina, M, Fanga, H, et al. (2015) Pp-15 the Effect of Extensively Hydrolyzed Protein Formula in Preterm Infants with Symptomatic Gastro-Oesophageal Reflux. *Journal of Pediatric Gastroenterology & Nutrition* 61(4):526
 16. Dermyshe E, Mackie C, Kigozi P, Schoonakker B, Dorling J (2018) Antacid therapy for gastroesophageal reflux in preterm infants: a systematic review. *BMJ Paediatrics Open* 2(1):e000287
 17. Azizollahi, HR, Rafeey, M (2016) Efficacy of proton pump inhibitors and H2 blocker in the treatment of symptomatic gastroesophageal reflux disease in infants. *Korean Journal of Pediatrics* 59(5):226–30
 18. Famouri, F, Zibanejad, N, Kabiri, P, Kelishadi, R (2017) Comparison of hypoallergenic diet vs. ranitidine in treatment of gastroesophageal reflux disease of infants: A randomized clinical trial. *Iranian Journal of Pediatrics* 27(4)
 19. Winter, H, Gunasekaran, T, Tolia, V, Gottrand, F, Barker, PN, Illueca, M (2015) Esomeprazole for the Treatment of GERD in Infants Ages 1-11 Months. *Journal of Pediatric Gastroenterology & Nutrition* 60suppl1:S9-15
 20. Houben, E, Johansson, S, Nagy, P, Penning-van BFJA, Kuipers, EJ, Herings, RMC (2018) Observational cohort study: safety outcomes in children using proton pump inhibitors or histamine-2 receptor antagonists. *Current Medical Research & Opinion* 34(4):577–83
 21. Manzoni, P, Garcia SR, Meyer, M, Stolfi, I, Pagni, L, Messner, H, et al. (2018) Exposure to Gastric Acid Inhibitors Increases the Risk of Infection in Preterm Very Low Birth Weight Infants but Concomitant Administration of Lactoferrin Counteracts This Effect. *Journal of Pediatrics* 193:62–67.e1
 22. Belei, O, Olariu, L, Dobrescu, A, Marcovici, T, Marginean, O (2018) Is It Useful to Administer Probiotics Together With Proton Pump Inhibitors in Children With Gastroesophageal Reflux? *Journal of neurogastroenterology and motility* 24(1):51–7
 23. Santana, RNS, Santos, VS, Ribeiro-Junior, RF, Freire, MS, Menezes, MAS, Cipolotti, R, et al. (2017) Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. *BMC Infectious Diseases* 17(1):375
 24. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM (2018 [cited 2018 Sep 13]) Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. *JAMA Pediatrics* 172(6):e180315
 25. Lau MLM, Robinson, PD, Flank, J, Sung, L, Dupuis, LL (2016) The Safety of Metoclopramide in Children: A Systematic Review and Meta-Analysis. *Drug Safety* 39(7):675–87
 26. Morris, AD, Chen, J, Lau, E, Poh, J (2016) Domperidone-Associated QT Interval Prolongation in Non-oncologic Pediatric Patients: A Review of the Literature. *Canadian Journal of Hospital Pharmacy* 69(3):224–30

27. Crawford, C, Anderson, M, Cooper, G, Jackson, G, Thompson, J, Vale, A, et al. (2018) Overdose in young children treated with anti-reflux medications: Poisons enquiry evidence of excess 10-fold dosing errors with ranitidine. *Human & Experimental Toxicology* 37(4):343–9
28. Livingston, MH, Shawyer, AC, Rosenbaum, PL, Jones, SA, Walton, JM (2015) Fundoplication and gastrostomy versus percutaneous gastrojejunostomy for gastroesophageal reflux in children with neurologic impairment: A systematic review and meta-analysis. *Journal of Pediatric Surgery* 50(5):707–14
29. Stone, B, Hester, G, Jackson, D, Richardson, T, Hall, M, Gouripeddi, R, et al. (2017) Effectiveness of Fundoplication or Gastrojejunal Feeding in Children With Neurologic Impairment. *Hospital Pediatrics* 7(3):140–8
30. Ru, W, Wu, P, Feng, S, Lai, XH, Chen, G (2016) Laparoscopic versus open Nissen fundoplication in children: A systematic review and meta-analysis. *Journal of Pediatric Surgery* 51(10):1731–6
31. Lei, X, Ren, Q, Yang, Y, Bai, T (2017) Outcome Evaluation of Laparoscopic and Open Nissen Fundoplication in Children-A Systematic Review and Meta-Analysis. *American Surgeon* 83(1):90–7
32. Zhang, P, Tian, J, Jing, L, Wang, Q, Tian, J, Lun, L (2016) Laparoscopic vs. open Nissen's fundoplication for gastro-oesophageal reflux disease in children: A meta-analysis. *International Journal Of Surgery* 34:10–6
33. Papandria, D, Goldstein, SD, Salazar, JH, Cox, JT, McIltrout, K, Stewart, FD, et al. (2015) A randomized trial of laparoscopic versus open Nissen fundoplication in children under two years of age. *Journal of Pediatric Surgery* 50(2):267–71
34. Fyhn, TJ, Knatten, CK, Edwin, B, Schistad, O, Aabakken, L, Kjosbakken, H, et al. (2015) Randomized Controlled Trial of Laparoscopic and Open Nissen Fundoplication in Children. *Annals of Surgery* 261(6):1061–7
35. Pacilli, M, Eaton, S, McHoney, M, Kiely, EM, Drake, DP, Curry, JI, et al. (2014) Four year follow-up of a randomised controlled trial comparing open and laparoscopic Nissen fundoplication in children. *Archives of Disease in Childhood* 99(6):516–21
36. Cundy, TP, Harling, L, Marcus, HJ, Athanasiou, T, Darzi, AW (2014) Meta analysis of robot-assisted versus conventional laparoscopic fundoplication in children. *Journal of Pediatric Surgery* 49(4):646–52
37. Glen, P, Chasse, M, Doyle, MA, Nasr, A, Fergusson, DA (2014) Partial versus complete fundoplication for the correction of pediatric GERD: a systematic review and meta-analysis. *PLoS ONE [Electronic Resource]* 9(11):e112417
38. St. PSD, Poola, A, Adibe, O, Juang, D, Fraser, JD, Aguayo, P, et al. (2017) Are esophagocrural sutures needed during laparoscopic fundoplication: A prospective randomized trial. *Journal of Pediatric Surgery*.
39. Yap, BK, Nah, SA, Chen, Y, Low, Y (2017) Fundoplication with gastrostomy vs gastrostomy alone: a systematic review and meta-analysis of outcomes and complications. *Pediatric Surgery International* 33(2):217–28

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