National Collaborating Centre for Women's and Children's Health

Final version

Gastro-oesophageal reflux disease in children and young people

Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people

NICE Guideline 1

Methods, evidence and recommendations

January 2015

Final version

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Update information
October 2019: A footnote has been added to recommendations in section 1.3 on PPI and H_2RA licensing for use in children. Recommendation 1.3.7 has been amended to clarify when metoclopramide, domperidone or erythromycin can be offered.
Minor update
May 2021: Recommendation 1.3.7 has been amended to highlight the MHRA drug safety updates about the risk of infantile hypertrophic pyloric stenosis with erythromycin, cardiac risks with erythromycin and potential drug interaction of erythromycin with rivaroxaban.
These changes can be seen in the short version of the guideline at: www.nice.org.uk/guidance/NG1

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Contents

Guideline summary

Guideline development group membership, NCC-WCH staff and acknowledgements

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Table 2: Expert adviser to the group

Name	Role
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Table 3: National Collaborating Centre for Women's and Children's Health

Name	Role
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Shona Burman-Roy (from August 2014)	Team Leader
Jiri Chard (until August 2014)	Team Leader
Kate Coles (from January 2014)	Project Manager
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Maryam Gholitabar (from November 2014)	Research Associate
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Name	Role
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1 Introduction

Introduction

Gastro-oesophageal reflux (GOR) is a normal physiological process that usually happens after eating in healthy infants, children, young people and adults. In contrast, gastro-oesophageal reflux disease (GORD) occurs when the effect of GOR leads to symptoms severe enough to merit medical treatment. GOR is more common in infants than in older children and young people, as shown by by the effortless regurgitation of feeds in young babies.

In clinical practice, it is difficult to differentiate between GOR and GORD, and the terms are used interchangeably by health professionals and families. There is no simple, reliable and accurate diagnostic test to confirm whether the condition is GOR or GORD, and this, in turn, affects research and clinical decisions. Furthermore, the term GORD covers a number of specific conditions that have different effects and present in different ways. This makes it difficult to identify the person who genuinely has GORD and to estimate the real prevalence and burden of the problem. Nevertheless, regardless of the definition used, GORD affects many children and families in the UK who therefore commonly seek medical advice and, as a result, it constitutes a health burden for the NHS.

Generally, experts suggest that the groups of children most affected by GORD are infants who are otherwise normal, children with identifiable risk factors and pubescent young people who acquire the problem in a similar way to adult patients. The two other specific populations of children affected by GORD are premature infants and children with complex, severe neurodisabilities. In this last group, the diagnosis is complicated further by a tendency to confuse vomiting with or without gut dysmotility with severe GORD. In addition, for the child with neurodisabilities, a diagnosis of GORD often fails to recognise a number of distinct problems that may co-exist and combine to produce a very complicated feeding problem in an individual with already very complex health needs; for example a child with severe cerebral palsy may be dependent on enteral tube feeding, have severe chronic vomiting, be constipated, suffer marked kyphoscoliosis, possess a poor swallow mechanism and be unable to safely protect their airway, resulting in a risk of regular aspiration pneumonia.

This guideline focuses on symptoms of and interventions for GORD. Commonly observed events, such as infant regurgitation, are covered, as well as much rarer but potentially more serious problems, such as apnoea. Where appropriate, clear recommendations are given as to when and how reassurance should be offered. In contrast, advice is given to healthcare professionals regarding when investigations should be considered or treatments are indicated. Finally, it is emphasised that other, and on occasion more serious, conditions that need different management can be confused with some of the relatively common manifestations of GOR or GORD. These warning signs are defined under the headings of ‘red flags’, along with recommended initial actions.

The focus of this guideline is primary and secondary care while ‘dove-tailing’ with the likely investigation and management that could be expected when a referral to tertiary care is indicated. Where a particular area of specialist interest is not covered as expected, this is likely to be because of the very specific focus of the guideline or due to a lack of evidence or consensus. This guideline is specifically about GORD in children. It is not a detailed guideline on complex feeding issues, a protocol for an approach to ‘the vomiting child’ or a textbook for the tertiary specialist. In addition, where there is a perceived absence of evidence or a lack of consensus then other specific areas may appear neglected, but when this occurs an effort has been made to make detailed and prescriptive research recommendations.

1.1 Aim of the guideline

The guideline development group was asked to produce a clinical guideline on the investigation and management of gastro-oesophageal reflux disease in children.

1.2 Definitions used in this guideline

When developing this guideline the following definitions were used. For further information on terms please see glossary and abbreviations in Section 9.

1.2.1 Infants, children and young people

The age ranges are defined as follows:

- Infants: under 1 year
- Children: 1 to under 12 years
- Young people: 12 to under 18 years.

1.2.2 Gastro-oesophageal reflux (GOR)

Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus. It is a common physiological event that can happen at all ages from infancy to old age, and is often asymptomatic. It occurs more frequently after feeds/meals. In many infants, GOR is associated with a tendency to 'overt regurgitation' – the visible regurgitation of feeds.

1.2.3 Gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux disease (GORD) refers to gastro-oesophageal reflux that causes symptoms (for example, discomfort or pain) severe enough to merit medical treatment, or to gastro-oesophageal reflux-associated complications (such as oesophagitis or pulmonary aspiration). In adults, the term GORD is often used more narrowly, referring specifically to reflux oesophagitis.

1.2.4 Marked distress

There is very limited evidence, and no objective or widely accepted clinical definition, for what constitutes 'marked distress' in infants and children who are unable to adequately communicate (expressively) their sensory emotions. In this guideline, 'marked distress' refers to an outward demonstration of pain or unhappiness that is outside what is considered to be the normal range by an appropriately trained, competent healthcare professional, based on a thorough assessment. This assessment should include a careful analysis of the description offered by the parents or carers in the clinical context of the individual child.

1.2.5 Occult reflux

The movement of part or all of the stomach contents up the oesophagus, but not to the extent that it enters the mouth or is obvious to the child, parents or carers, or observing healthcare professional. There is no obvious, visible regurgitation or vomiting. It is sometimes referred to as silent reflux.

1.2.6 Overt regurgitation

The voluntary or involuntary movement of part or all of the stomach contents up the oesophagus at least as far as the mouth, and often emerging from the mouth. Regurgitation is in principle clinically observable, so is an overt phenomenon, although lesser degrees of regurgitation into the mouth might be overlooked.

1.2.7 Specialist

A paediatrician with the skills, experience and competency necessary to deal with the particular clinical concern that has been identified by the referring healthcare professional. In this guideline this is most likely to be a consultant general paediatrician. Depending on the clinical circumstances, 'specialist' may also refer to a paediatric surgeon, paediatric gastroenterologist or a doctor with the equivalent skills and competency.

1.3 Areas within the remit of the guideline

Based on the stated aim for the guideline, the population covered includes all people aged under 18 years. The guideline development group was aware that within this overall population there were age-specific sub-groups, such as infants aged under 1 year, that needed to be examined, and that special attention should be given to those with neurodisabilities.

The guideline had a remit to cover identification, diagnosis and management of GOR and GORD within the stated population, from transient reflux in infants up to severe life-long disease. This was broken down into the following areas:

- the natural history of overt GOR
- the distinction between physiological GOR and GORD
- risk factors associated with developing GORD
- indications for investigations
- indications for treatment
- effectiveness of treatments for GOR/GORD:
  - positional management
  - changes to feeds (including composition and regimens)
  - alginates and antacids
  - H2-receptor antagonists
  - proton pump inhibitors
  - prokinetic agents
  - jejunal feeding
  - fundoplication surgery.

1.4 Areas outside the remit of the guideline

The remit of this guideline is limited to children and young people aged under 18 years; therefore people aged 18 years and above are not covered in this guideline. However, separate guidance for management of reflux in adults is being produced concurrently with this guideline.

Within the population of those aged under 18 years, 2 specific groups were excluded from the guideline:

- Children and young people with Barrett's oesophagus – this group was excluded as this is a very rare condition in this age group and it requires specialist long-term management.
- Reflux associated with pregnancy – while this group may use some of the same treatments, the care pathway is separate from those covered in this guideline.

Furthermore, many of the areas covered by the guideline require a high degree of technical knowledge and specialist equipment; for example undertaking and assessing results of endoscopy. A decision was made not to cover these, as it was assumed that those providing

care would be competent to do so and the constant evolution of equipment made assessment impractical.

1.5 For whom is this guideline intended

This clinical guideline is intended for use by all healthcare professionals who are involved in the care or management of children and young people with GOR or GORD. The guideline is intended for use in the full range of healthcare settings, including community, primary, secondary and tertiary care.

1.6 Who has developed the guideline

The guideline was developed by a multi-professional and lay working group (the guideline development group) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included two consultant paediatric gastroenterologists, two consultant paediatricians, one consultant in paediatric neurodisability, one paediatric surgeon, two general practitioners, one advanced paediatric nurse practitioner, one paediatric dietician, one health visitor and two patient/carer/consumer representatives.

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval and appraisal of the evidence, and health economics modelling.

All guideline development group members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. For details of guideline development group members' declarations of interests see Appendix D.

1.7 Related NICE guidelines

Details are correct at time of writing (November 2014). Further information is available on the NICE website.

1.7.1 Published guidelines

1.7.1.1 General

- Medicines adherence (2009). NICE guidance 76.

1.7.1.2 Condition-specific

- Obesity (2014). NICE guideline CG189
- Dyspepsia and gastro-oesophageal reflux disease (2014). NICE guideline CG184
- Autism – management of autism in children and young people (2013). NICE guideline CG170
- Feverish illness in children (2013). NICE guideline CG160
- Postnatal care (2013) NICE guideline CG37
- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease (2013). NICE interventional procedure guidance 461
- Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease (2012). NICE interventional procedure guidance 431
- Spasticity in children and young people (2012). NICE guideline CG145

- Endoluminal gastroplication for gastro-oesophageal reflux disease (2011). NICE interventional procedure guidance 404
- Food allergy in children and young people (2011). NICE guideline CG116
- Barrett's oesophagus – ablative therapy (2010). NICE guideline CG106
- Constipation in children and young people (2010). NICE guideline CG99
- Diarrhoea and vomiting in children under 5 (2009). NICE guideline CG84
- Surgical management of otitis media with effusion in children (2008). NICE guideline CG60
- Maternal and child nutrition (2008) NICE guidance PH11
- Urinary tract infection in children (2007). NICE guideline CG54
- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatments of gastro-oesophageal reflux disease (2007). NICE interventional procedure guideline 222
- Catheterless oesophageal pH monitoring (2006). NICE interventional procedure guidance 187
- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease (2004). NICE interventional procedure guidance 55

2 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at www.nice.org.uk).

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the guideline development group throughout the development process and specifically addressed in individual recommendations where relevant. For further information, see the NICE Equality Scheme.

2.1 Developing review questions and protocols and identifying evidence

The scope for this guideline (see Appendix B) outlines the main areas where guidance is needed. The guideline development group formulated review questions based on the scope and prepared a protocol for each review question (see Appendix E). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix F) to the following databases: Medline (1948 onwards), Embase (1980 onwards) and 4 Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment [HTA] database). Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluation Database (NHS EED). Where possible, search strategies were restricted to English language. If this was not possible, studies in languages other than English were not reviewed. Search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no searching of grey literature, nor was hand searching of journals undertaken.

All the searches were updated and re-executed within 6 to 8 weeks of the start of the stakeholder consultation to ensure the reviews were up-to-date. This process was completed by April 2014.

2.2 Reviewing and synthesising evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating).
- Limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow up; these can reduce the quality rating).
- Inconsistency of effects across studies (this can reduce the quality rating).
- Indirectness (the extent to which the available evidence fails to address the specific review question; this can reduce the quality rating).
- Imprecision (reflects the confidence in the estimate of effect and this can reduce the quality rating). For continuous variables (such as change in temperature) the guideline development group was asked to predefine minimally important differences (the smallest difference between treatments that healthcare professionals or patients think is clinically beneficial). However, the guideline development group was unable to agree these, so

imprecision was graded based on the GRADE default for risk ratios and odds ratios of −0.75/1.25 and for continuous outcomes of SMD±0.5.

- Other considerations (including large magnitude of effect, evidence of a dose–response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

For each review question the highest available level of evidence was sought. The type of review question determines the highest level of evidence. For questions on therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low or very low if factors listed above are not addressed adequately. For questions on prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of high, which might be downgraded to moderate, low or very low, depending on the factors listed above. For diagnostic tests, studies examining the performance of the test started as high quality if information on accuracy was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was considered optimal.

Where appropriate, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled risk ratios (RRs), pooled odds ratios (ORs) or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used to investigate the impact of the heterogeneity. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies) the range of effect sizes reported in the included studies was presented. The GRADE profiles are not directly applicable to epidemiological studies or non-comparative cohort studies. Where these studies are presented, they are included in descriptive paragraphs and/or tables as appropriate.

For studies evaluating the accuracy of a diagnostic test, summary statistics (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and likelihood ratios for positive and negative test results [LR+ and LR−, respectively]) were calculated or quoted where possible (see Table 4). The following definitions were used when summarising the likelihood ratios for the guideline development group:

- Convincing: positive likelihood ratio (LR+) 10 or higher, negative likelihood ratio (LR−) 0.1 or lower
- Strong: LR+ 5 or higher (but less than 10), LR− 0.2 or lower (but higher than 0.1)
- Not strong: LR+ 4.9 or lower, LR− higher than 0.2

The following definitions were used when summarising the levels of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the guideline development group:

- High: 90% and above
- Moderate: 75% to 89%
- Low: 74% or below

Particular emphasis was placed on the positive likelihood ratio, with a ratio of 5 or higher being considered a good indicator that a symptom or sign should be used.

Some studies were excluded from the guideline reviews after obtaining copies of the publications because they did not meet inclusion criteria specified by the guideline development group (see Appendix H). The characteristics of each included study were

summarised in evidence tables for each review question (see Appendix I). Where possible, dichotomous outcomes were presented as relative risks (RRs) or ORs with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or standard deviations (SDs).

Table 4: '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d=N (total number of tests in study)

2.3 Outcome measures

For this guideline, the review questions were judged on a number of outcomes. The justification for using these outcomes was based on their relevance to the groups covered by the guideline and consensus among members of the guideline development group. The guideline development group selected 7 or 8 outcomes for each review when assessing the effectiveness of a particular treatment. No further distinction was made with regard to whether each was critical or important to the guideline development group's decision-making. Outcomes included those that were felt to be desirable (for example reduction in overt regurgitation) and unwanted effects of treatment that it would be important to reduce to a minimum.

2.4 Incorporating health economics

The aims of the health economic input to the guideline were to inform the guideline development group of new economic issues relating to reflux in children and young people, and to consider whether the recommendations continued to represent a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

Systematic searches for published economic evidence were undertaken for all clinical questions in the guideline. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature identified in the literature search are presented alongside the clinical effectiveness reviews.

The guideline development group prioritised a number of clinical questions where it was thought that economic considerations would be particularly important in formulating recommendations. For this guideline the areas prioritised for economic analysis were:

- antacids/alginates
- H2-receptor antagonists
- proton pump inhibitors
- prokinetic agents
- enteral tube feeding
- fundoplication surgery

A systematic search for published economic evidence was undertaken for these questions. Due to the limited evidence on the effectiveness of managing GORD in children, economic analysis was restricted to costs and resource use of each of the management approaches.

2.5 Evidence to recommendations

Recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the guideline development group to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. Statements summarising the guideline development group's interpretation of the evidence and any extrapolation from the evidence used when making recommendations were also written to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of clinical benefits and harms consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues).

The guideline development group also identified areas where evidence to answer its review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process, formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted. The guideline development group identified 9 'key priorities for implementation' (key recommendations) and 3 high priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the greatest impact on clinical care and outcomes in the NHS as a whole; they were selected using a variant of the nominal group technique (see the NICE guideline manual 2012). The priority research recommendations were selected in a similar way.

2.6 Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. The guideline development group carefully considered and responded to all comments received from stakeholder organisations. The comments and responses were reviewed by NICE in accordance with the NICE guideline development process (see the NICE guidelines manual 2012).

3 Recommendations and care pathway

3.1 Key priorities for implementation

The following recommendations have been identified as priorities for implementation. The full list of recommendations is in Section 3.2.

- Give advice about gastro-oesophageal reflux (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.
- In infants, children and young people with vomiting or regurgitation, look out for the 'red flags' in Table R1, which may suggest disorders other than GOR. Investigate or refer using clinical judgement.
- 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.
- Do not offer an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of gastrointestinal reflux disease (GORD) in infants, children and young people.
- 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 R1)
  - melaena (black, foul-smelling stool; assessment to take place on the same day if clinically indicated; also see Table R1)
  - 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.
- 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).
- In formula-fed infants, if the stepped-care approach is unsuccessful (see recommendation 26), 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.
- Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom.
- 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.

Table R1: 'Red flags' symptoms suggesting conditions 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

Symptoms and signs	Possible diagnostic implications	Suggested actions
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

3.2 Recommendations

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.
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).
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.

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.
5. In infants, children and young people with vomiting or regurgitation, look out for the 'red flags' in Table R1, which may suggest disorders other than GOR. Investigate or refer using clinical judgement.
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.
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.
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.
9. Recognise the following as possible symptoms of GOR in children and young people:
    - heartburn
    - retrosternal pain
    - epigastric pain.
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.

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.
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.
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.
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)
15. Do not offer an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of GORD in infants, children and young people.
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.
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.
18. Offer an upper GI contrast study for children and young people with a history of GORD presenting with dysphagia.
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.
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 R1)
    - melaena (black, foul-smelling stool; assessment to take place on the same day if clinically indicated; also see Table R1)
    - 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.

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 Chapter 9)
    - a suspected diagnosis of Sandifer’s syndrome.
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.
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.
24. 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.
25. 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.
26. 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).
27. 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.

28. In formula-fed infants, if the stepped-care approach is unsuccessful (see recommendation 26), 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.
29. Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom.
30. Consider a 4-week trial of a PPI or H_2RA 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.
31. Consider a 4-week trial of a PPI or H_2RA for children and young people with persistent heartburn, retrosternal or epigastric pain.
32. Assess the response to the 4-week trial of the PPI or H_2RA, and consider referral to a specialist for possible endoscopy if the symptoms:
    - do not resolve **or**
    - recur after stopping the treatment.
33. When choosing between PPIs and H_2RAs, 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.
34. Offer PPI or H_2RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis, and consider repeat endoscopic examinations as necessary to guide subsequent treatment.
35. 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.
36. 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.
37. 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.

38. 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.
39. 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.
40. Offer an upper GI endoscopy with oesophageal biopsies for infants, children and young people before deciding whether to offer fundoplication for presumed GORD.
41. 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.
42. 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.

Table R1: 'Red flags' symptoms suggesting conditions 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

Symptoms and signs	Possible diagnostic implications	Suggested actions
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

3.3 Research recommendations

1. What are the symptoms of GORD in infants, children and young people with a neurodisability?
2. What is the effectiveness and cost effectiveness of a trial of hydrolysed formula in formula-fed infants with frequent regurgitation associated with marked distress?
3. In infants, children and young people with overt or occult reflux, is fundoplication effective in reducing acid reflux as determined by oesophageal pH monitoring?

3.4 Care pathway

The terms GOR and GORD are used as convenient labels to describe a number of specific conditions and groups of symptoms. This makes diagnosing GOR or GORD difficult, and an individual may have symptoms that places them in several categories. GORD incorporates a disparate range of disorders – for example heartburn, erosive oesophagitis, pulmonary aspiration and others. It is therefore unfeasible to devise a simple flow diagram to deal with these very varied conditions, as infants, children and young people with GOR or GORD could be in more than one place at any time on such a care pathway.

The unlinked boxes below summarise the recommendations for ease of reference. The recommendations are grouped by:

- GORD – recognition and diagnosis
- investigation
- management of overt regurgitation in infants and children
- management of heartburn, retrosternal or epigastric pain
- management of endoscopically determined reflux oesophagitis
- enteral feeding
- fundoplication

Box A - Gastro-oesophageal reflux disease – recognition and diagnosis

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.

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).

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.

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.

In infants, children and young people with vomiting or regurgitation, look out for the 'red flags' in Table R1, which may suggest disorders other than GOR. Investigate or refer using clinical judgement.

Table R1: 'Red flags' symptoms suggesting conditions 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

Box A (continued) - Gastro-oesophageal reflux disease – recognition and diagnosis

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.

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.

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.

Recognise the following as possible symptoms of GOR in children and young people:

- heartburn
- retrosternal pain
- epigastric pain.

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.

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.

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.

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.

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.

Box B – Investigation

Do not offer an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of GORD in infants, children and young people.

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.

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.

Offer an upper GI contrast study for children and young people with a history of GORD presenting with dysphagia.

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 R1)
- melaena (black, foul-smelling stool; assessment to take place on the same day if clinically indicated; also see Table R1)
- 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.

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 epileptic seizure-like events
- unexplained upper airway inflammation
- dental erosion associated with a neurodisability
- frequent otitis media
- a possible need for fundoplication (see Chapter 9)
- a suspected diagnosis of Sandifer's syndrome

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.

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.

Box C - Management of overt regurgitation in infants and children

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.

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.
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.

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).

In formula-fed infants, if the stepped-care approach is unsuccessful (see recommendation 26), 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.

Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom.

Consider a 4-week trial of PPI or H_2RA 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.

When choosing between PPIs and H_2RAs,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.

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.

Box D - Management of heartburn, retrosternal or epigastric pain

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)

Consider a 4-week trial of a PPI or H_2RA for those 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.

Consider a 4-week trial of a PPI for children and young people with persistent heartburn, retrosternal or epigastric pain.

Assess the response to the 4-week trial of the PPI or H_2RA, and consider referral to a specialist for possible endoscopy if the symptoms:

- do not resolve **or**
- recur after stopping the treatment

When choosing between PPIs and H_2RAs, 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.

Offer PPI or H_2RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis, and consider repeat endoscopic examinations as necessary to guide subsequent treatment.

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.

Box E - Management of endoscopy-proven reflux oesophagitis

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.
When choosing between PPIs and H_2RAs, 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.

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.

Box F - Enteral feeding

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

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.

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.

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.

Box G - Fundoplication

Offer an upper GI endoscopy with oesophageal biopsies for infants, children and young people before deciding whether to offer fundoplication for presumed GORD.

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.

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.

4 Diagnosing and investigating GORD

4.1 Natural course of overt regurgitation

The divide between GOR and GORD is poorly defined, and this affects decisions about investigation and treatment. One aim of the guideline is to provide a working definition of what is 'normal' GOR that does not require management and what is 'abnormal' so may require management. The purpose of this review is to provide a description of the onset, progress and eventual recovery in children and young people with symptoms of overt reflux. GER and GERD are equivalent acronyms to GOR and GORD that reflect the American English spelling of oesophagus as esophagus. These terms were included in the search strategies (see Appendix F) and are used in the appendices where they have been used in the studies contributing to the evidence base for the guideline (Appendix I) or excluded from it (Appendix H).

4.1.1 Review questions

What is the clinical course of overt gastroesophageal reflux (GOR)?

- What is the usual age of overt gastroesophageal reflux onset?
- How does the frequency of overt gastroesophageal reflux change with age?
- At what age is the usual max frequency of overt gastroesophageal reflux?
- At what age does overt reflux resolve?
- Does overt gastroesophageal reflux follow an episodic pattern?

For full details see review protocol in Appendix E.

4.1.2 Description of included studies

The search strategy created for this review can be located in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profile below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Fifteen observational studies were identified for inclusion for this review question (Campanozzi et al., 2009; De et al., 2001; Gunasekaran et al., 2008; Hegar et al., 2004; Hegar et al., 2009; Hegar et al., 2013; Iacono et al., 2005; Martin et al., 2002; Miyazawa et al., 2002; Nelson et al., 1997; Nelson et al., 1998; Orenstein et al., 1996; Osatakul et al., 2002; Ruigomez et al., 2010; Van Howe et al., 2010). Seven were prospective cohort studies (Campanozzi et al., 2009; Hegar et al., 2009; Hegar et al., 2013; Iacono et al., 2005; Martin et al., 2002; Osatakul et al., 2002; Van Howe et al., 2010), 5 were cross-sectional studies (De et al., 2001; Hegar et al., 2004; Gunasekaran et al., 2008; Miyazawa et al., 2002; Nelson et al., 1997), 2 were case–control studies (Nelson et al., 1998; Orenstein et al., 1996) and 1 was a retrospective cohort study (Hegar et al., 2013). Five studies were undertaken in the USA (Gunasekaran et al., 2008; Nelson et al., 1997; Nelson et al., 1998; Orenstein et al., 1996; Van Howe et al., 2010), 3 in Indonesia (Hegar et al., 2004; Hegar et al., 2009; Hegar et al., 2013), 2 in Italy (Campanozzi et al., 2009; Iacono et al., 2005), 1 in Australia (Martin et al., 2002), 1 in Japan (Miyazawa et al., 2002), 1 in Thailand (Osatakul et al., 2002), 1 in India (De et al., 2001) and 1 in the UK (Ruigomez et al., 2010).

The smallest study included 128 children (Van Howe et al., 2010) and the largest study included 6677 children (Iacono et al., 2005). The age of the children ranged from 10 days to 24 months (Campanozzi et al., 2009; De et al., 2001; Hegar et al., 2004; Hegar et al., 2009; Hegar et al., 2013; Iacono et al., 2005; Martin et al., 2002; Miyazawa et al., 2002; Nelson et al., 1997; Nelson et al., 1998; Orenstein et al., 1996; Osatakul et al., 2002; Van Howe et al.,

2010). Two studies included older children: in 1 study (Ruigomez et al., 2010) they were aged 1 to 17 years and in the other (Gunasekaran et al., 2008) they had a mean age (with standard deviation [SD]) of 15.7±1.3 years. The settings of the studies varied, including paediatric practices, well-baby clinics, high schools, a rural referral hospital, a teaching maternity hospital, a private public hospital and an outpatient clinic.

The definition of regurgitation used was reported in 10 studies (Campanozzi et al., 2009; Gunasekaran et al., 2008; Hegar et al., 2004; Hegar et al., 2009; Hegar et al., 2013; Iacono et al., 2005; Martin et al., 2002; Miyazawa et al., 2002; Nelson et al., 1998; Ruigomez et al., 2010) and was varied (for example 'the effortless return of gastric contents at least into the mouth and the loss of a small part of the meal, without retching'). One study specifically examined GORD (as opposed to regurgitation) identified on the basis of Read codes (Ruigomez et al., 2010). Nine studies (Campanozzi et al., 2009; De et al., 2001; Gunasekaran et al., 2008; Hegar et al., 2004; Miyazawa et al., 2002; Nelson et al., 1997; Nelson et al., 1998; Orenstein et al., 1996; Van Howe et al., 2010) used a questionnaire to obtain data on regurgitation, 3 studies (Hegar et al., 2009; Martin et al., 2002; Osatakul et al., 2002) used a diary, 1 study (Iacono et al., 2005) used a standard clinical chart, and 1 study (Ruigomez et al., 2010) used computerised medical records.

No evidence was identified on premature babies or children with neurodisabilities. Two studies (Campanozzi et al., 2009; Orenstein et al., 1996) included a small proportion of preterm infants, but a subgroup analysis was not presented for this group.

Although the decision was taken to use observational studies, because of the differences in study population and study design (for example long-term follow-up), the results were reported individually as it was inappropriate to perform a meta-analysis on shared study outcomes. The guideline development group prioritised prospective longitudinal cohort studies, but downgraded cross-sectional or retrospective studies as they did not allow a suitable comparison by age.

4.1.3 Evidence profile

The overall quality of studies was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias. The epidemiological nature of the review question posed and complexity of the evidence identified meant that the data was better represented in graphical form rather than standard GRADE profiles. A narrative description of the evidence for each outcome is therefore provided below the GRADE profile. Outcomes are reported as described in the original studies.

Table 5: GRADE findings for natural history of GOR

Quality assessment							
Number. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Natural history of overt GOR							
1 (Campanozzi et al., 2009)	Prospective cohort	Serious[1]	None	None	None	Some[2]	Moderate
1 (De et al., 2001)	Cross-sectional	Serious[3]	None	None	None	None	Moderate
1 (Gunasekaran et al., 2008)	Cross-sectional	No serious	None	None	None	None	High
1 (Hegar et al., 2004)	Cross-sectional	No serious	None	None	None	None	High
1 (Hegar et al., 2009)	Prospective cohort	Serious[4]	None	None	None	None	Moderate

Quality assessment							
Number. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
1 (Hegar et al., 2013)	Prospective cohort	Serious[5]	None	None	None	None	Moderate
1 (Lacono et al., 2005)	Prospective cohort	No serious	None	None	None	None	High
1 (Martin et al., 2002)	Prospective cohort	Serious[1]	None	None	None	None	Moderate
1 (Miyazawa et al., 2002)	Cross-sectional	No serious	None	None	None	None	High
1 (Nelson et al., 1997)	Cross-sectional	Serious[3]	None	None	None	None	Moderate
1 (Nelson et al., 1998)	Case-control	Very serious[1,3]	None	None	None	None	Low
1 (Orenstein et al., 1996)	Case-control	Serious[3]	None	None	None	Some[6]	Moderate
1 (Osatakul et al., 2002)	Prospective cohort	Serious[3]	None	None	None	None	Moderate
1 (Ruigomez et al., 2010)	Retrospective cohort	Very serious[7]	None	Some[8]	None	None	Very low
1 (Van Howe et al., 2010)	Prospective cohort	Very serious[1,3]	None	None	None	None	Low

GOR gastro-oesophageal reflux
[1] Unclear whether loss to follow-up is unrelated to key characteristics
[2] Prematurity: 8.6% premature at entry to study
[3] Outcome is not clearly defined: definition of regurgitation not reported
[4] All dropouts because of excessive symptoms were in the partially breastfed group
[5] Presentation of results not particularly clear: it has been assumed that the infants for which data has not been presented are ones that did not regurgitate rather than being considered as missing data or infants lost to follow up (as authors state 4 subjects were lost to follow up). Also, unclear how many subjects were given conservative treatment.
[6] Prematurity: 26% of those attending well-baby clinic and 14% of those referred to gastroenterology department premature at entry to study
[7] Retrospective study design, based on electronic medical records across a number of GP practices, so variation in tests and treatments, only 15.3% of GORD cohort had a record of a formal diagnostic test being undertaken, none of the children in the control cohort had been tested for GOR.
[8] This study examines GORD not regurgitation.

4.1.4 Evidence statements

See Table 5.

4.1.4.1 Average age at which overt reflux was first reported

Two studies were identified for the age of onset of reflux. One study (Iacono et al., 2005) reported a mean (SD) age of 32±25 days for the diagnosis of regurgitation. The evidence for this finding was of high quality.

The second study (Campanozzi et al., 2009) reported a mean (SD) age of 3.8±2.7 months for infants affected with regurgitation. The evidence for this finding was of moderate quality.

4.1.4.2 Average age at which overt reflux was most frequent

No evidence was identified for this outcome.

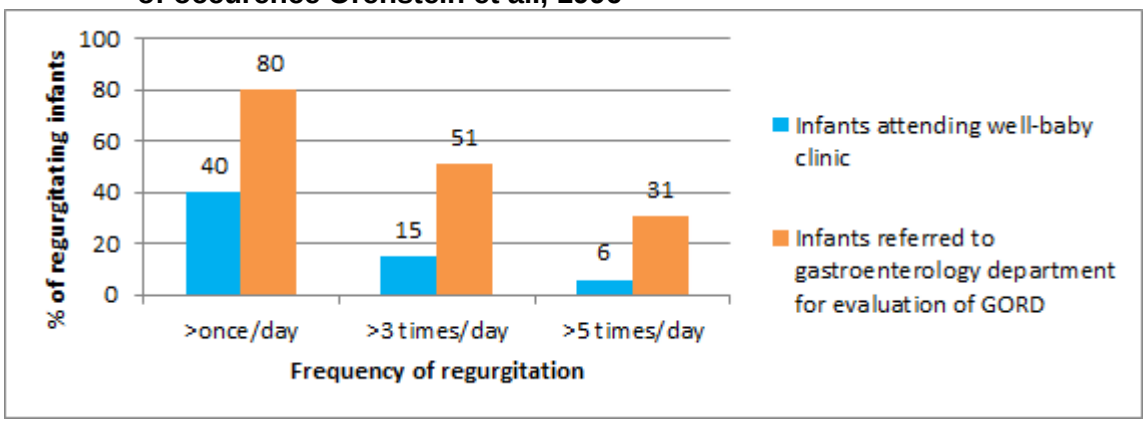
4.1.4.3 The reported maximum daily frequency of reflux

Four studies (Nelson et al., 1998; Orenstein et al., 1996; Gunasekaran et al., 2008; Hegar et al., 2013) reported evidence on the maximum daily frequency of reflux (number of episodes of regurgitation).

The first study (Nelson et al., 1998) reported the percentage of infants (mean age: 7.2 months, range: 6 to 12 months) spitting up at least once a day at the start of the study (94%) and at the 1 year follow up (0%). The evidence was of low quality.

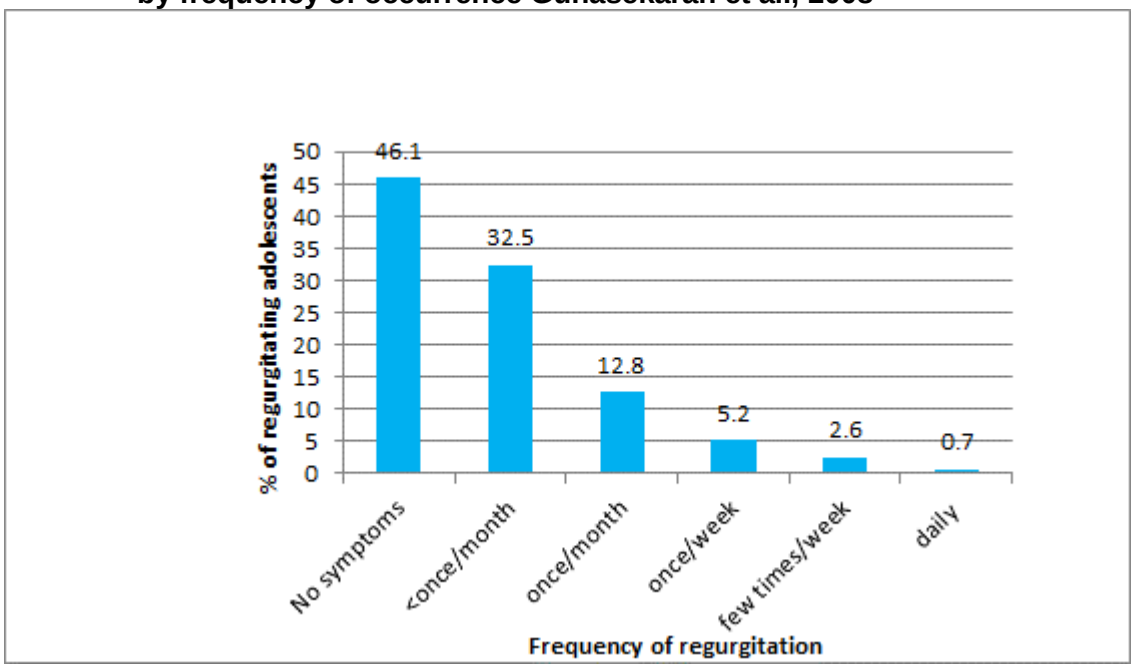
The second study (Orenstein et al., 1996) reported the percentage of infants with regurgitation more than once a day, more than 3 times a day and more than 5 times a day in infants attending a well-baby clinic (median age: 19 weeks, range: 3 to 60 weeks) compared with infants referred to the gastroenterology department (median age: 15 weeks, range: 4 to 56 weeks) for the evaluation of GORD (see Figure 1). GORD was defined as either testing positive on the 24-hour pH probe or evidence of oesophagitis on biopsy. The evidence was of moderate quality.

Figure 1: Reported percentage of infants with regurgitation categorised by frequency of occurence Orenstein et al., 1996



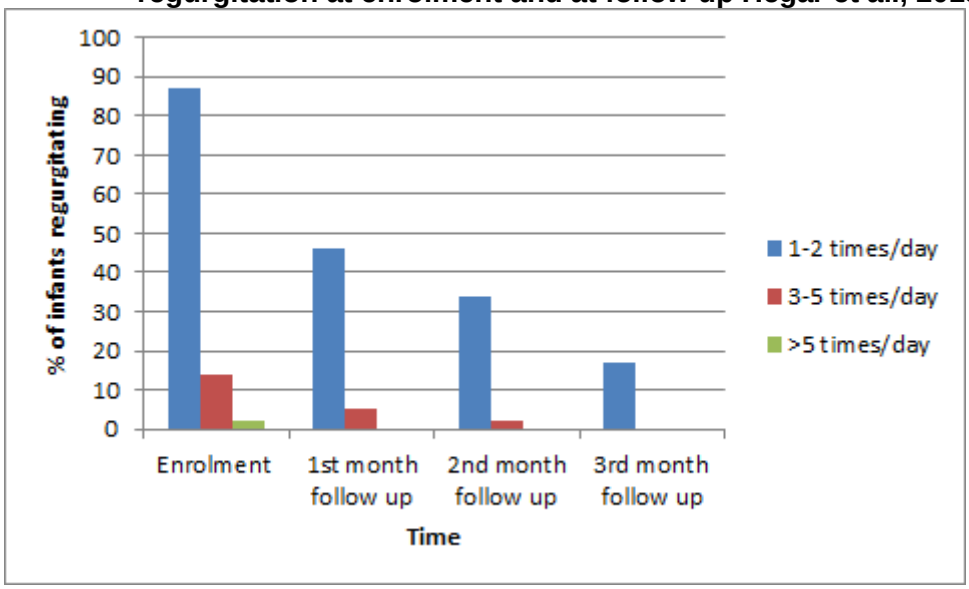
The third study (Gunasekaran et al., 2008) reported the percentage of adolescents (mean age: 15.7 years, range: 14 to 18 years) with no regurgitation, regurgitation less than once a month or regurgitation once a month, once a week, few times a week or daily (see Figure 2). The evidence was of high quality.

Figure 2: Reported percentage of adolescents experiencing regurgitation categorised by frequency of occurrence Gunasekaran et al., 2008



The fourth study (Hegar et al., 2013) reported the number of infants (aged 6 to 9 months) regurgitating 1–2 times a day, 3–5 times a day and more than 5 times a day at enrolment, first month of follow up, second month of follow up and third month of follow up (see Figure 3). The evidence was of moderate quality.

Figure 3: Reported percentage of infants categorised by different frequencies of regurgitation at enrolment and at follow up Hegar et al., 2013

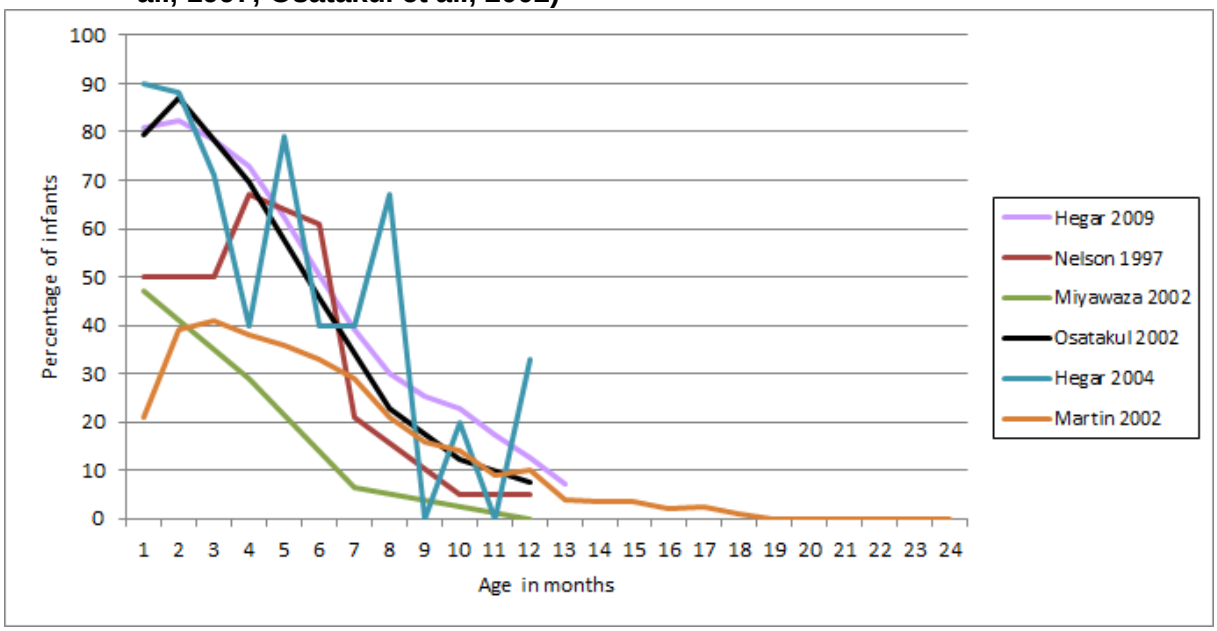


4.1.4.4 Average frequency of overt reflux at specific ages

4.1.4.4.1 Reported as percentage of infants with regurgitation at specific ages

Six studies (Hegar et al., 2004; Hegar et al., 2009; Martin et al., 2002; Miyawaza et al., 2002; Nelson et al., 1997; Osatakul et al., 2002) reported evidence on the percentage of infants with any regurgitation at specific ages (see figure 4). Five of these studies (Hegar et al., 2009; Martin et al., 2002; Miyawaza et al., 2002; Nelson et al., 1997; Osatakul et al., 2002) showed a decreasing incidence of regurgitation from the age of 4 months onwards. The evidence was of moderate to high quality.

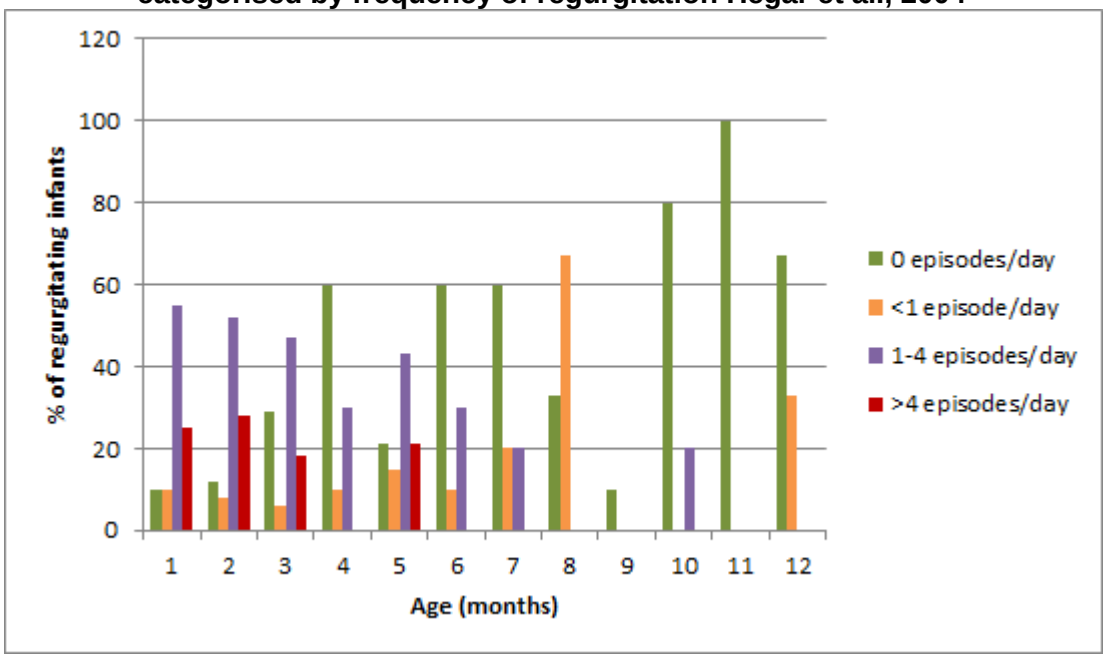
Figure 4: Percentage of infants with any regurgitation at specific ages Hegar et al., 2004; Hegar et al., 2009; Martin et al., 2002; Miyawaza et al., 2002; Nelson et al., 1997; Osatakul et al., 2002)



4.1.4.4.2 Reported as percentage of infants with regurgitation at specific ages categorised by frequency of regurgitation

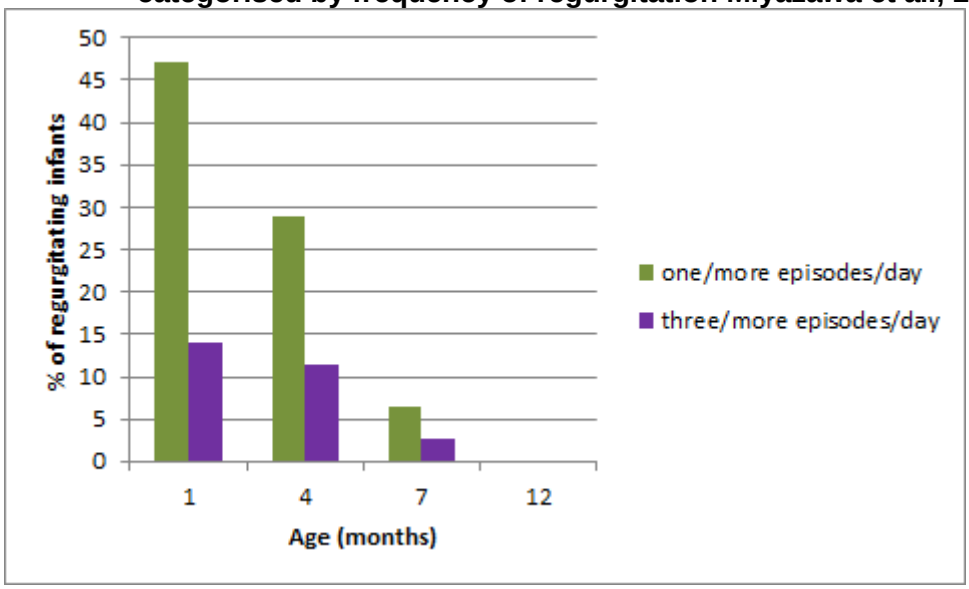
Four of the six studies (Hegar et al., 2004; Hegar et al., 2009; Miyawaza et al., 2002; Osatakul et al., 2002) also categorised the frequency of regurgitation at specific ages. The first 2 of these 4 studies (Hegar et al., 2004; Hegar et al., 2009) reported the proportion of infants with less than 1 episode per day, 1 to 4 episodes per day and more than 4 episodes per day in each age group (see figures 5a and 5b). The evidence was of high and moderate quality, respectively.

Figure 5: Reported percentage of infants with regurgitation at specific ages categorised by frequency of regurgitation Hegar et al., 2004



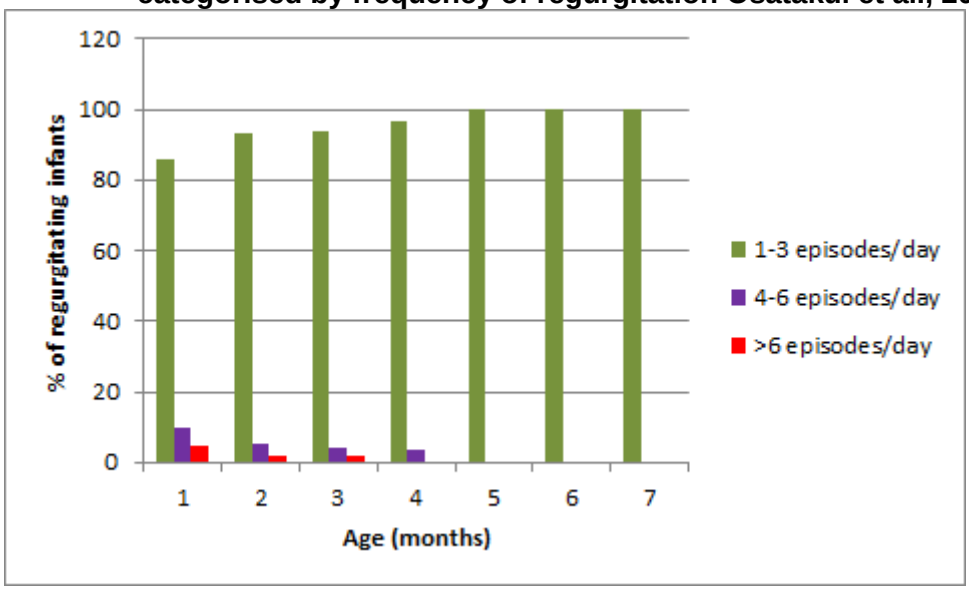
The third study (Miyawaza et al., 2002) reported the proportion of infants with 1 or more episodes per day and 3 or more episodes per day at specific ages (see Figure 6). The evidence was of high quality.

Figure 6: Reported percentage of infants with regurgitation at specific ages categorised by frequency of regurgitation Miyazawa et al., 2002



The fourth study (Osatakul et al., 2002) reported the proportion of infants with 1 to 3 episodes per day, 4 to 6 episodes per day and more than 6 episodes per day at specific ages (see Figure 7). The evidence was of moderate quality.

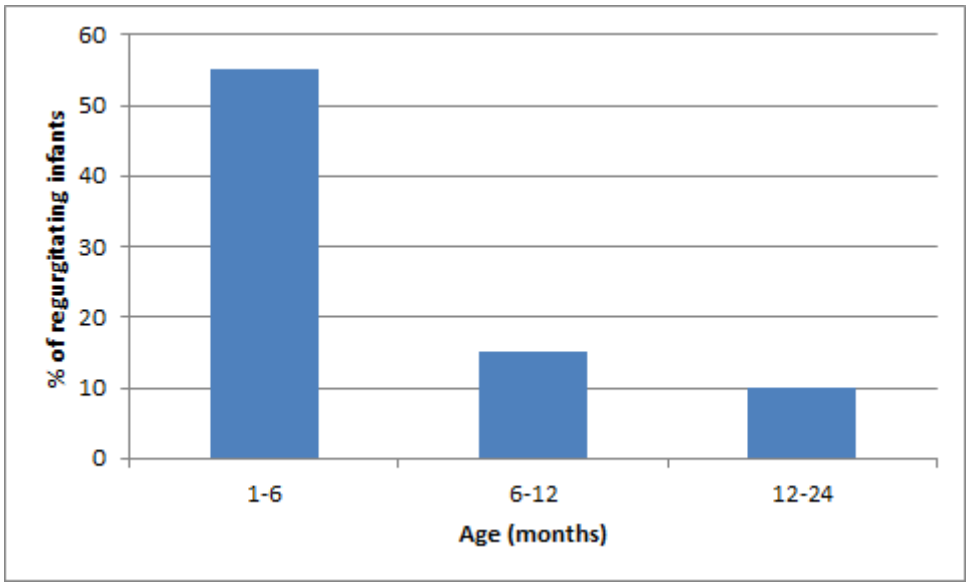
Figure 7: Reported percentage of infants with regurgitation at specific ages categorised by frequency of regurgitation Osatakul et al., 2002



4.1.4.4.3 *Reported as percentage of infants with regurgitation at specific ages not categorised by frequency of regurgitation*

One other study (De et al., 2001) reported the proportion of infants with regurgitation at specific ages but at overlapping time intervals (see Figure 8). The evidence was of moderate quality.

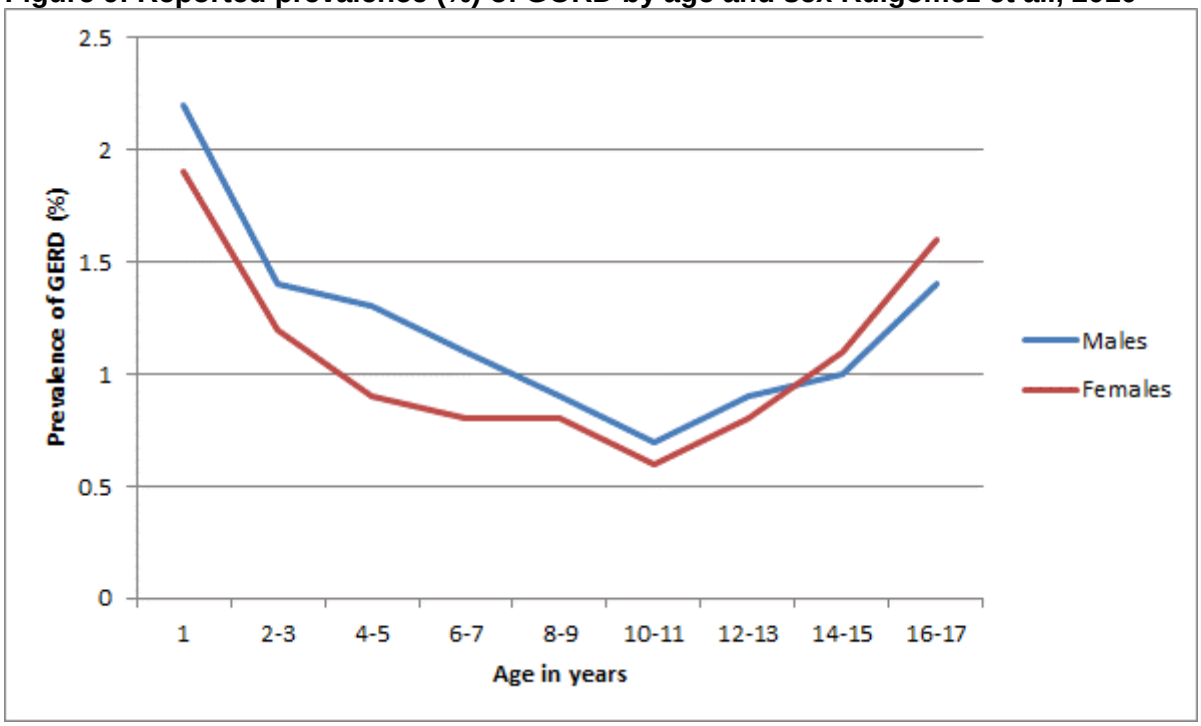
Figure 8: Reported percentage of infants with regurgitation at specific ages De et al., 2001



4.1.4.4.4 *Reported as the prevalence (%) of GORD during the study period (2000–2005) at specific ages*

One study (Ruigomez et al., 2010) reported the prevalence of GORD at specific ages during the study period (see Figure 9). The evidence was of very low quality.

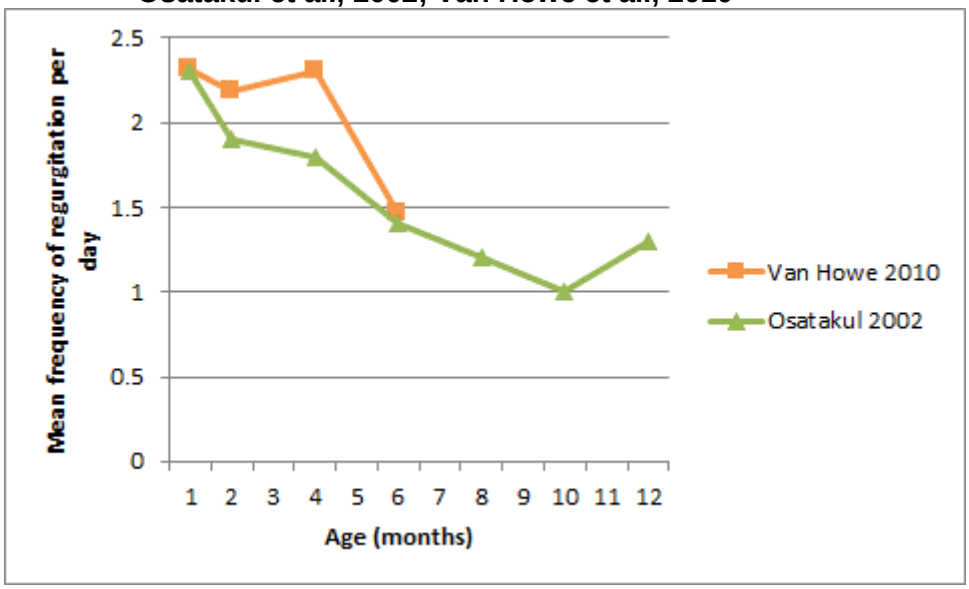
Figure 9: Reported prevalence (%) of GORD by age and sex Ruigomez et al., 2010



4.1.4.4.5 Reported as mean frequency of regurgitation per day at specific ages

Two studies (Osatakul et al., 2002; Van Howe et al., 2010) reported evidence on the mean frequency of regurgitation per day at specific ages (see Figure 10). The evidence was of moderate and low quality, respectively.

Figure 10: Reported mean frequency of regurgitation per day at specific ages Osatakul et al., 2002; Van Howe et al., 2010



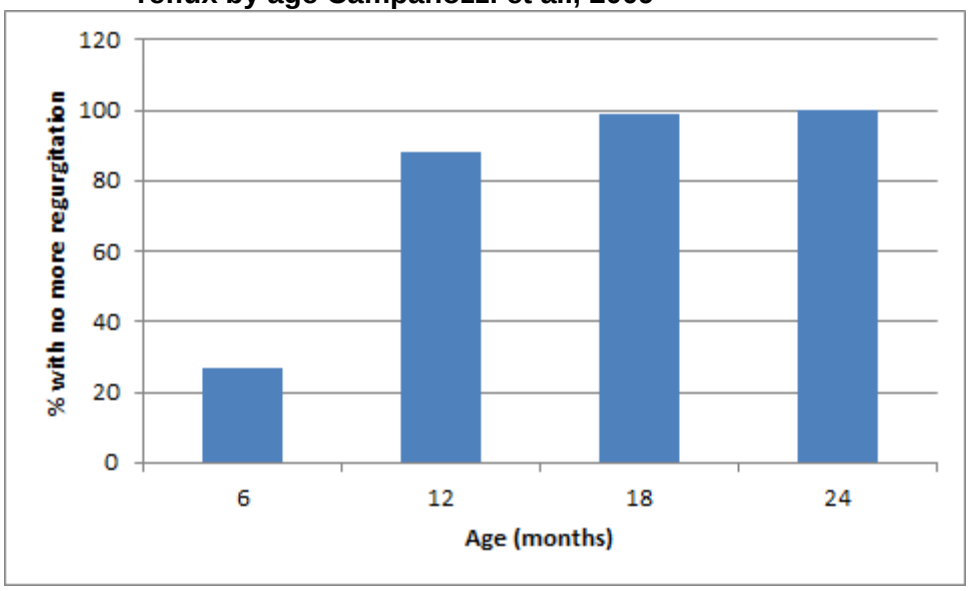
4.1.4.5 Age of cessation of overt reflux

Three studies (Campanozzi et al., 2009; Martin et al., 2002; Miyazawa et al., 2002) reported evidence on the age of cessation of overt reflux.

In the first study (Martin et al., 2002) reflux was negligible by age 19 months (see Figure 4). The evidence was of moderate quality.

In the second study (Campanozzi et al., 2009) reflux had ceased in all infants by age 24 months (see Figure 11). The evidence was of moderate quality.

Figure 11: Reported percentage of infants and young children with cessation of overt reflux by age Campanozzi et al., 2009



In the third study (Miyazawa et al., 2002), reflux had ceased in all infants by age 12 months (see Figure 6). The evidence was of high quality.

4.1.5 Health economics profile

No health economic studies were identified for this question and no analysis was undertaken.

4.1.6 Evidence to recommendations

4.1.6.1 Relative value placed on the outcomes considered

The guideline development group wished to identify evidence with regard to the natural course of gastro-oesophageal reflux with overt regurgitation in order to make recommendations that would help in the recognition and management of this condition. They considered the following outcomes to be important:

- age of onset of regurgitation
- frequency of regurgitation at different ages
- maximum frequency of regurgitation
- age at resolution of regurgitation
- the occurrence of episodic or intermittent regurgitation.

4.1.6.2 Consideration of clinical benefits and harms

Clinical experience shows that gastro-oesophageal reflux presenting as overt reflux is a common condition in infants, to the extent that it is considered a normal physiological phenomenon. It is acknowledged that in most infants this form of gastro-oesophageal reflux is managed in primary care. Active management is often used, for example the prescribing of anti-reflux medicine, though it has been debated whether this treatment is necessary as the reflux does not cause any harm. This evidence review was undertaken to define what normal physiological reflux is, to explore what patterns are expected when infants have normal physiological reflux and to identify when there are signs that the reflux is not this physiological condition but perhaps a more serious condition that may need to be referred for specialist management. The results of this review would be used in conjunction with results of a review on symptoms and signs, and the clinical knowledge of the guideline development group, to make recommendations on when GOR becomes problematic and requires investigation and treatment.

4.1.6.2.1 Age of onset

Two studies were found that explored the age of onset of physiological reflux. One study reported a mean age of study enrolment of 3.8 months but the actual age of onset was not reported. The second study reported a mean age of 32 days (SD±25 days) at first presentation with regurgitation. This more accurately reflected the age of onset, in that this was a prospective cohort study with follow up from birth to 6 months. From this study the guideline development group concluded that in most babies with regurgitation the onset is noticed within the first 8 weeks of life.

No studies were identified that clearly demonstrated the maximum age at which infant regurgitation may begin. However, based on their own experience, the group believed that it was very unusual for it to begin for the first time in later infancy and they concluded that the onset of vomiting or regurgitation in a baby of 6 months or older should be a cause for diagnostic uncertainty. They recommended that onset after 6 months should be considered as a possible red flag for other disorders. For example, they were aware of reports of infants in whom an incorrect diagnosis of regurgitation resulted in late diagnosis of a brain tumour.

4.1.6.2.2 Age of cessation of regurgitation

Six studies reported on the frequency of reflux at various ages in young children. One cross-sectional study showed that reflux was less frequent in older infants. Five prospective studies reported a progressive decline in reflux frequency from about 4 months. In these studies the proportion of infants with overt reflux during the first 6 months of life ranged from 20% to 80%, and based on these studies the guideline development group concluded that at least 40% are affected by this condition. Most studies reported that by age 12 months fewer than 10% of the infants had overt reflux. The group believed that healthcare professionals should be aware of this, because unusually persistent regurgitation might require careful consideration of the need for investigation.

4.1.6.2.3 Frequency of reflux

In 1 population based study, the frequency of regurgitation episodes was reported in a cohort of 100 infants. Based on this study the guideline development group included in its recommendations a statement that more than 5% of infants have 6 or more episodes of regurgitation each day. Recognising frequent regurgitation was considered important. Even simple physiological reflux may be associated with frequent regurgitation and does not in itself suggest the presence of gastro-oesophageal reflux disease.

While the frequency of regurgitation in all babies is greater in early infancy, the frequency of reflux episodes also declines over time in those infants where regurgitation is considered problematic.

4.1.6.3 Consideration of health benefits and resource uses

Pharmaceutical treatments are often offered as a way to manage reflux in young infants when the level of reported reflux is within normal physiological ranges. Although the treatments offered are relatively inexpensive and have a low rate of adverse events, the number of infants being prescribed these treatments means this has significant resource implications.

4.1.6.4 Quality of evidence

The evidence review included observational studies where the quality of the evidence ranged from low to high. Observational studies were chosen as the most appropriate source of data for this review question. Therefore the studies were not downgraded if they are not RCTs, as outlined in the GRADE methodology (see Chapter 3).

The guideline development group noted that although only 1 study was from the UK, the populations within the included studies were still relevant to the UK. Although the physiology of reflux would not be significantly varied in different countries, there may be differences that would need to be incorporated into recommendation considerations, the most pertinent of which was the diet of the mother. Furthermore, the care pathway for infants reported in the studies would not match with the existing newborn policy within the NHS. Important milestones that would aid diagnosis of reflux complications, like the 6–8 week check, would not be accounted for in the evidence reported.

The group noted that the definition of GOR and GORD varied between studies. While this is understandable, as there has been no universal definition of GORD, it did not allow for a suitable comparison of outcomes between studies as the populations selected as having 'GORD' would vary, depending on that study's definition. In addition to this, the way data was obtained varied. The group prioritised those studies that measured reflux using accredited diagnostic tools (for example 24-hour pH monitoring or an endoscopic investigation) over those that defined outcomes and populations using questionnaires.

Finally, the guideline development group had concerns about study populations being small and the study setting not being representative of the normal situation found in the UK. The group found most of the studies' cohorts were underpowered and therefore could not be used in isolation to support a recommendation. Furthermore, the group prioritised those studies that were undertaken in settings that mirrored the general population where uncomplicated physiological reflux would be found in the NHS (for example within a well-baby clinic).

4.1.6.5 Other considerations

4.1.6.5.1 Recognition of simple ('physiological') infant regurgitation

The evidence shows that in infancy episodic regurgitation of feeds is a very frequent occurrence. This is a normal phenomenon, with some infants regurgitating more than others. This is generally thought to occur because of a relative immaturity of the normal mechanisms that exist to limit gastro-oesophageal reflux – for example the lower oesophageal sphincter. Other contributing factors may include the infant's consumption of relatively large quantities of liquid feeds and the fact that young infants are generally recumbent. Although parents (and sometimes healthcare professionals) may be concerned that overt regurgitation might be due to an underlying disorder, the group was aware that this is rarely the case in reality when such regurgitation occurs in isolation. However, certain associated clinical manifestations might indicate the presence of an alternative condition to gastro-oesophageal reflux or a reflux associated condition.

4.1.6.5.2 Appearance of regurgitation associated GORD

The guideline development group recognised there are occasions where simple regurgitation may be considered as harmful or bothersome where the onset, cessation or frequency of otherwise seemingly simple infant regurgitation fall outside the expected parameters and therefore could merit further investigation or treatment.

The evidence from the current review was consistent with the group's clinical experience regarding the expected trend to resolution of regurgitation in simple gastro-oesophageal reflux. It is uncommon for regurgitation to persist after age 1 year and therefore the group advised that such persistence should be considered a red flag indicating a possible alternative diagnosis or unusually troublesome reflux, perhaps amounting to gastro-oesophageal reflux disease.

In the group's clinical opinion, the presence of blood or bile in vomit or regurgitated gastric contents would not be expected with simple GOR. It might suggest the presence of an alternative and more serious disorder.

4.1.6.5.3 Premature infants

The guideline development group discussed the course of overt regurgitation in premature infants. The guideline development group's experience was that regurgitation was frequent in such infants, but that it followed a similar pattern to other groups, and declined with age. However, no evidence was identified for this particular population. Therefore, the group made no specific recommendation describing the course of regurgitation in premature infants.

4.1.6.5.4 Neurodevelopment

The guideline development group was aware that both frequency and duration of regurgitation was an issue reported in children with neurodisabilities. However, no evidence was identified for this particular population. Therefore, the group made no specific recommendation describing the course of regurgitation in such children.

4.1.7 Recommendations

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.

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).**

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.

4.1.8 Research recommendations

No research recommendations in this area.

4.2 Signs and symptoms

Infants, children and young people present to health professionals with a whole variety of symptoms that may suggest or be interpreted as GORD. Conversely, other complaints, for example bile stained vomiting, are believed to indicate important alternative diagnoses that require very different investigation and management (red flags).

On occasion, symptoms and signs could indicate a clear need for investigation or treatment of possible GORD, but the reliability of these clinical manifestations is not always clear and consequently inappropriate interpretation of their significance can lead to unnecessary or even incorrect intervention with no obvious benefit to the child or family. The guideline development group considered that it was important to examine the relevant evidence with the aim of determining the validity of commonly used symptoms and signs in identifying GORD and, conversely, to clarify the 'red flags' that should alert professionals and parents to other problems. The value of disease severity scores was also briefly considered, but it was concluded that such tools are generally not validated and are of limited practical value in clinical practice and so they were excluded from a more detailed review.

A two-stage process was used for this review question. The first stage involved noting a comprehensive list of symptoms and signs that have been proposed previously as indicators of possible GORD: this list was generated by considering existing guidelines, systematic reviews, consensus documents and utilising the expert knowledge and experience of the guideline development group members. The group carefully prioritised important items for the evidence-based review based on group consensus, having agreed that a review of all possible symptoms and signs was not needed. The second stage involved undertaking a detailed systematic review of each of the symptoms and signs prioritised by the group and, where appropriate, making recommendations.

A general concern with the evidence was that it relied on surrogate markers of GORD (for example a pH study analysis of acid reflux) and these are not necessarily indicative of the full spectrum of complications recognised within GORD.

4.2.1 Identifying symptoms and signs of GORD

4.2.1.1 Description of included studies

The search strategy created for this review can be found in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profile below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Three systematic reviews were identified that outlined symptoms and signs of GORD (Sherman et al., 2009; Vandenplas et al., 2009; Tolia et al., 2009). The first review was undertaken with the intention of establishing a definition of GORD in children (Sherman et al., 2009), the second was part of comprehensive treatment guidance (Vandenplas et al., 2009) and the third was a review of extra-oesophageal presentations of GORD in children (Tolia et al., 2009).

In total 28 separate symptoms and signs were identified (see Table 7). The quality of these reviews is outlined in Table 6.

Table 6: GRADE profile of systematic reviews of symptoms and signs

Quality assessment							
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Identification of symptoms and signs of GORD							
1 Vandenplas et al., 2009	Systematic review & consensus	Very serious[1,2]	None	None	None	None	Low
1 Tolia et al., 2009	Systematic review	Serious[1]	None	None	None	None	Moderate
1 Sherman et al., 2009	Systematic review & consensus	Serious[1]	None	None	None	None	Moderate

GORD gastro-oesophageal reflux disease
[1] Search strategy not presented
[2] Inclusion and exclusion criteria not presented

Table 7: Results from systematic reviews of symptoms, signs and other associations of GOR

Study	Symptoms, signs and other associations identified by review
Vandenplas et al., 2009	Symptoms: • recurrent regurgitation with/without vomiting • weight loss or poor weight gain • irritability in infants • ruminative behaviour • heartburn or chest pain • hematemesis • dysphagia • odynophagia • wheezing • stridor • cough • hoarseness Signs: • reflux oesophagitis • oesophageal stricture • Barrett's oesophagus • laryngeal/pharyngeal inflammation • recurrent pneumonia • anaemia • dental erosion • feeding refusal • dystonic neck posturing/Sandifer syndrome • apnoea spells • ALTE (Apparent Life Threatening Event)
Tolia et al., 2009	• asthma • pneumonia • ALTE • bronchiectasis • ENT (ear, nose and throat) symptoms • dental erosion

Study	Symptoms, signs and other associations identified by review
Sherman et al., 2009	• excessive regurgitation • heartburn in retrosternal area • epigastric pain • sleep disturbance • reflux oesophagitis • haemorrhage • Barrett's oesophagus • stricture • Sandifer's syndrome • dental erosion • asthma • chronic cough • chronic laryngitis • hoarseness • feeding refusal/anorexia • unexplained crying • choking/gagging/coughing • sleep disturbance • abdominal pain • pulmonary fibrosis • bronchopulmonary dysplasia • pharyngitis • sinusitis • serious otitis media • apnoea • bradycardia

4.2.1.2 Prioritisation of symptoms and signs

The guideline development group discussed the list of symptoms and signs included in the reviews. Based on their knowledge and experience, they combined a number of symptoms and signs under more general headings, such as lower respiratory tract infection. They prioritised 11 symptoms and signs for detailed review based on the fact that these have been proposed as possible indicators of GORD. These were:

- distressed behaviour
  - infant colic/excessive crying
  - posturing
- apnoea
- epigastric or chest pain
- hoarseness
- feeding difficulties
- otitis media
- lower respiratory tract infection
- faltering growth
- chronic cough
- dental erosion
- asthma.

Where possible, diagnostic accuracy figures (positive and negative likelihood ratios, sensitivity, specificity, positive and negative predictive values) have been calculated and used to evaluate the usefulness of the symptoms and signs. However, the guideline development group prioritised likelihood ratios because this statistic is more robust than positive predictive value and negative predictive values as these are not influenced by disease prevalence. Likelihood ratios also give information on the usefulness of a test to greater extent than if sensitivity or specificity was used in isolation.

The following criteria were used when summarising the usefulness of positive and negative likelihood ratios, or sensitivity and specificity.

Positive likelihood ratio:

- Very useful – more than 10
- Moderately useful – from 5 up to 10
- Not useful – less than 5

Negative likelihood ratio:

- Very useful – 0 to 0.1
- Moderately useful – from more than 0.1 up to 0.5
- Not useful – more than 0.5

Sensitivity and specificity:

- High – 90% and above
- Moderate – 75% to 89%
- Low – 74% or below

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.The decision was taken to use observational studies, but because of the differences in study population and study design (for example long-term follow-up), the results were reported individually as it was inappropriate to perform a meta-analysis on shared study outcomes. The guideline development group prioritised prospective longitudinal cohort studies, but downgraded cross-sectional or retrospective studies as they did not allow a suitable comparison by age.

The results of individual reviews are reported below.

4.2.2 Distressed behaviour

4.2.2.1 Introduction

Infants and young children often display signs suggesting discomfort or distress which are not readily explained. Infants with recurring intense periods of crying can be labelled as suffering from ‘infant colic’, although the precise nature of this commonly described condition remains uncertain. Children and young people with a complex severe neurodisability may also have episodes of intense distress that are possibly due to discomfort or pain. Once again, the aetiology often remains unknown and, as with normal infants and some younger children, the history is often difficult to elicit because of potential communication problems. In all of these settings gastro-oesophageal reflux (with or without overt regurgitation) has been proposed as a possible explanation or contributing factor. For the purposes of this review the term ‘distress’ included ‘infant colic’, excessive crying, the adoption of unusual postures that to the observer suggested possible distress and the reporting of disturbed sleep in the infant.

4.2.2.2 Description of included studies

Seven observational studies were included in this review (Deal et al., 2005; Carr et al., 2000; Costa et al., 2004; Ghaem et al., 1998; Salvatore et al., 2005; Orenstein et al., 1996; Mathisen et al., 1999).

Three of the studies were undertaken in the USA (Deal et al., 2005; Carr et al., 2000; Orenstein et al., 1996), 2 in Australia (Ghaem et al., 1998; Mathisen et al., 1999), 1 in Brazil (Costa et al., 2004) and 1 in Belgium (Salvatore et al., 2005).

Two studies used a case–control design (Deal et al., 2005; Orenstein et al., 1996). Five studies used a cohort design (Carr et al., 2000; Costa et al., 2004; Ghaem et al., 1998; Salvatore et al., 2005; Mathisen et al., 1999). One of these was a retrospective review of records (Carr et al., 2000). Sample size ranged from 40 to 797.

4.2.2.3 Evidence profile

Study quality was assessed using the GRADE methodology. The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- distress in children and young adults for identifying the presence of GORD
  - ‘infant colic’/excessive crying
  - posturing
  - disturbed sleep.

Table 8: GRADE profile for evaluation of diagnostic value of symptoms of distress for identifying presence of GORD

Quality assessment							Number of	Measure of diagnostic accuracy*						Quality
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	
Cries more than normal in the opinion of the parent used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Prospective case-control	Serious[1]	None	None	Serious[2]	None	135	0.54 [0.37, 0.71]	0.86 [0.76, 0.92]	-[a]	-[a]	3.88 [2.19, 6.88]	0.53 [0.37, 0.77]	Low
1 (Salvatore et al., 2005)	Prospective cohort	None	None	None	Serious[2]	None	99	0.62 [0.38, 0.82]	0.52 [0.4, 0.63]	0.25 [0.14, 0.4]	0.84 [0.7, 0.93]	1.29 [0.86, 1.93]	0.73 [0.41, 1.32]	Moderate
Cries for more than 1 hour per day used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Prospective case-control	Serious[1]	None	None	Serious[2]	None	135	0.54 [0.37, 0.71]	0.83 [0.75, 0.9]	-[a]	-[a]	3.19 [1.88, 5.42]	0.55 [0.38, 0.8]	Low
1 (Salvatore et al., 2005)	Prospective Cohort	None	None	None	Serious[2]	None	99	0.33 [0.15, 0.57]	0.82 [0.72, 0.9]	0.33 [0.15, 0.57]	0.82 [0.72, 0.9]	1.88 [0.87, 4.06]	0.81 [0.59, 1.12]	Moderate
Cries for more than 3 hours per day used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Case-control	Serious[3]	None	None	Serious[2]	None	135	0.29 [0.15, 0.46]	0.97 [0.71, 0.99]	-[a]	-[a]	9.52 [2.78, 32.63]	0.74 [0.6, 0.91]	Low
1 (Salvatore et al., 2005)	Prospective cohort	None	None	None	Serious[2]	None	99	0.57 [0.34, 0.78]	0.61 [0.49, 0.72]	0.28 [0.15, 0.44]	0.84 [0.72, 0.93]	1.46 [0.92, 2.31]	0.71 [0.42, 1.19]	Moderate
Crying when feeding used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Prospective case-control	Serious[1]	None	None	Serious[2]	None	135	0.8 [0.63, 0.92]	0.86 [0.85, 0.92]	0.67 [0.5, 0.8]	0.92 [0.85, 0.97]	5.71 [3.42, 9.55]	0.23 [0.12, 0.45]	Low
1 (Salvatore et al., 2005)	Prospective Cohort	None	None	None	Serious[2]	None	99	0.57 [0.34, 0.78]	0.61 [0.72, 0.72]	0.28 [0.15, 0.44]	0.84 [0.72, 0.93]	1.46 [0.92, 2.31]	0.71 [0.42, 1.19]	Moderate
1 (Mathisen et al., 1999)	Prospective cohort	Serious[3]	None	None	Serious[2]	None	40	0.85 [0.62, 0.97]	0.8 [0.6, 0.94]	0.81 [0.58, 0.95]	0.84 [0.6, 0.97]	4.25 [1.74, 10.41]	0.19 [0.06, 0.54]	Low
Back arching or abnormal posturing used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Prospective case-control	Serious[1]	None	None	Serious[2]	None	135	0.6 [0.42, 0.76]	0.9 [0.78, 0.95]	-[a]	-[a]	6 [3.14, 11.46]	0.44 [0.29, 0.67]	Low
1 (Carr et al., 2000)	Retrospective cohort	Very serious[4]	None	None	None	None	295	0.03 [0.01, 0.06]	1 [0.96, 1]	1 [0.54, 1]	0.28 [0.23, 0.34]	∞	0.97 [0.95, 0.99]	Low

Quality assessment							Number of	Measure of diagnostic accuracy*						Quality
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	
1 (Deal et al., 2005) (1–11 months)	Prospective case-control	Serious[5]	None	None	Serious[2]	None	67	0.66 [0.49, 0.8]	0.78 [0.56, 0.93]	-[a]	-[a]	3.03 [1.35, 6.78]	0.44 [0.27, 0.7]	Low
1 (Costa et al., 2004)	Cross-sectional survey	Very serious[6]	None	None	None	None	797	0.45 [0.34, 0.56]	0.97 [0.95, 0.98]	0.63 [0.5, 0.74]	0.93 [0.91, 0.95]	13.26 [8.41, 20.91]	0.57 [0.47, 0.69]	Very low
Waking >3/night >2h/night used to identify presence of GOR/D														
1 (Ghaem et al., 1998)	Case-control	None	None	None	Serious[2]	None	102	0.55 [0.43, 0.67]	0.73 [0.52, 0.88]	-[a]	-[a]	2.05 [1.06, 3.99]	0.61 [0.43, 0.86]	Moderate

GOR/D gastro-oesophageal reflux/disease, h hour
** Calculated by the NCC technical team based on figures presented within the studies*
[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.
[1] Classification of control group was based on not being treated for GORD. The GORD group was based on pH monitoring
[2] Wide confidence intervals covering categories from low to high.
[3] Children in the control group were not tested for GOR. Small sample size
[4] Retrospective chart review based on diagnosis of GORD
[5] Presence of GORD was based on clinical judgement, which would include items contained in questionnaire
[6] Definition of GORD based on Rome II criteria, no objective measure undertaken

4.2.2.4 Evidence statements

See Table 8.

Seven studies evaluated the diagnostic accuracy of distress (as characterised by excessive crying, back arching, crying during or after feeding, or disturbed sleep) for identifying children and young adults with GORD.

The reported usefulness of 'crying' ranged from 'not useful' to 'moderately useful' for identifying infants with GORD, and was 'not useful' for identifying those without GORD. The studies were of moderate to low quality.

The reported usefulness of 'crying when feeding' ranged from 'not useful' to 'moderately useful' for identifying infants with GORD, and was 'not useful' to 'moderately useful' for identifying those without GORD. The studies were of moderate to low quality.

The reported usefulness of 'back arching or abnormal posturing' ranged from 'not useful' to 'very useful' for identifying children with GORD, and 'not usefu' to 'moderately useful' for identifying those without GORD. The studies were of moderate to low quality.

One study reported that 'waking at night' was not a useful marker of the presence of GORD in young children. This study was of moderate quality.

4.2.2.5 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.2.6 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.3 Apnoea

It has been postulated that some cardio-respiratory events in infants, especially those in the pre-term category, have been caused in part by reflux. The fact that infants have apnoea due to many other causes, often unidentified, is therefore an important consideration in evaluating the pathological role of reflux. For instance it is known that an immature respiratory control centre is often implicated, as are sepsis, neurological disease and potentially immature swallowing with aspiration during feeding. The importance of confirming an aetiological role for reflux in the genesis of apnoea is underlined by the high rate of prescription of anti-reflux medications in infants, especially in neonatal units, when apnoea is encountered.

4.2.3.1 Description of included studies

Thirteen studies were included in this review (Sacre et al., 1989; Tolia et al., 2003; Mazliah et al., 2000; Orenstein et al., 1996; Salvatore et al., 2005; Koda et al., 2010; Costa et al., 2004; Carr et al., 2000; Assadamongkol et al., 1993; Mezzacappa et al., 2008; Mousa et al., 2005; Peters et al., 2002; Yuksel et al., 2013).

Four studies were undertaken in the USA (Carr et al., 2000; Tolia et al , 2003; Orenstein et al., 1996; Mousa et al., 2005), 1 in Thailand (Assadamongkol et al., 1993), 3 in Brazil (Costa et al., 2004; Koda et al., 2010; Mezzacappa et al., 2008), 1 in Malaysia (Mazliah et al., 2000), 2 in Belgium (Sacre et al., 1989; Salvatore et al., 2005), 1 in Turkey (Yuksel et al., 2013) and 1 in Germany (Peters et al., 2002).

Two studies examined the temporal relationship between apnoea and GOR (Mousa et al., 2005; Peters et al., 2002). Eleven studies examined the relationship between reported presence of apnoea and GORD (Sacre et al., 1989; Tolia et al., 2003; Mazliah et al., 2000; Orenstein et al., 1996; Salvatore et al., 2005; Koda et al., 2010; Costa et al., 2004; Carr et al., 2000; Assadamongkol et al., 1993; Mezzacappa et al., 2008; Yuksel et al., 2013). Sample sizes ranged from 19 to 798.

4.2.3.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- apnoea in children and young adults for identifying the presence of GORD.

Table 9: GRADE profile for evaluation of the temporal association between apnoea for GOR

Quality assessment								
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Temporal association	Quality
Temporal link between apnoea and reflux in infants									
1 (Mousa et al., 2005)	Cohort	Serious[1]	None	Serious[2]	None	Yes	25	6173 5-minute time events were recorded across the 25 children. 4706 (76.2%) of the time events had no GOR or apnoea. 89 had apnoea with GOR. 439 apnoea events alone. 939 reflux alone. In 2 of 25 children apnoea and GOR events was statistically associated. Across the whole group the association was not statistically significant (p=0.214).	Low
Temporal link between apnoea and reflux in premature infants									
1 (Petersen et al., 2002)	Cohort	Serious[3]	None	Serious[4]	None	No	19	A total of 524 reflux events and 2039 apnoea events were recorded. Apnoea during reflux free periods no different from apnoea during reflux periods (0.19/min [0.00 to 0.85] vs 0.25/min [0.00 to 1.15]); p>0.05 in 19 infants.	Low

GOR gastro-oesophageal reflux, min minutes, p probability
[1] Small sample size
[2] 11 of 25 children were premature
[3] Small sample size
[4] Included a specific group of children attending an asthma outreach program

Table 10: GRADE profile for evaluation of apnoea for identifying GORD

Quality assessment								Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Apparent life threatening event used to identify presence of GOR/D														
1 (Sacre et al., 1989)	Case-control study	None	None	None	None	None	449	0.42 [0.3, 0.55]	0.91 [0.88, 0.94]	-[a]	-[a]	4.92 [3.17, 7.62]	0.63 [0.51, 0.79]	High
1 (Tolia et al., 2003)	Retrospective chart review	Very serious[1]	None	None	Serious[2]	Yes[3]	342	0.31 [0.24, 0.38]	0.8 [0.74, 0.86]	0.6 [0.49, 0.71]	0.54 [0.48, 0.61]	1.57 [1.07, 2.28]	0.86 [0.76, 0.98]	Very low
Recurrent apnoea used to identify presence of GOR/D														
1 (Mazliah et al., 2000)	Cross-sectional survey	Serious[4]	None	None	Serious[2]	None	44	0.06 [0.01, 0.21]	1 [0.75, 1]	1 [0.16, 1]	0.31 [0.18, 0.47]	∞	0.94 [0.85, 1.03]	Low
Apnoea ever used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Case-control	Serious[5]	None	None	Serious[2]	None	135	0.43 [0.26, 0.61]	0.98 [0.93, 1]	-[a]	-[a]	21.43 [5.16, 89.04]	0.58 [0.44, 0.78]	Low

Quality assessment								Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Apnoea with cyanosis used to identify presence of GOR/D														
1 (Orenstein et al., 1996)	Case-control	Serious[5]	None	None	Serious[2]	None	135	0.17 [0.07, 0.34]	1 [0.96, 1]	-[a]	-[a]	∞	0.83 [0.71, 0.96]	Low
1 (Salvatore et al., 2005)	Cohort	None	None	None	Serious[2]	None	99	0.11 [0.01, 0.35]	0.85 [0.75, 0.92]	0.15 [0.02, 0.45]	0.8 [0.69, 0.88]	0.75 [0.18, 3.08]	1.04 [0.86, 1.26]	Moderate
Apnoea (not specified) used to identify presence of GOR/D														
1 (Koda et al., 2010)	Retrospective cohort	Very serious[6]	None	None	None	None	307	0.18 [0.09, 0.3]	0.87 [0.82, 0.91]	0.24 [0.12, 0.39]	0.83 [0.78, 0.87]	1.4 [0.73, 2.68]	0.94 [0.83, 1.07]	Low
1 (Costa et al., 2004)	Cross-sectional	Very serious[7]	None	None	None	None	798	0.35 [0.25, 0.46]	0.97 [0.95, 0.98]	0.58 [0.44, 0.72]	0.92 [0.9, 0.94]	11.21 [6.8, 18.48]	0.67 [0.58, 0.78]	Low
1 (Carr et al., 2000)	Retrospective cohort	Very serious[8]	None	None	None	None	295	0.03 [0.01, 0.06]	0.93 [0.85, 0.97]	0.5 [0.21, 0.79]	0.27 [0.21, 0.32]	0.38 [0.13, 1.14]	1.05 [0.98, 1.12]	Low
1 (Assadamongkol et al., 1993)	Retrospective cohort	Very serious[9, 11]	None	None	Very serious[2]	None	55	0.12 [0.02, 0.3]	0.97 [0.82, 1]	0.75 [0.19, 0.99]	0.55 [0.4, 0.69]	3.35 [0.37, 30.21]	0.92 [0.78, 1.07]	Very low
1 (Yuksel et al., 2013)	Case-control	Serious[11]	None	Serious[12]	None	None	71	0.05 [0.01, 0.17]	1 [0.89, 1]	-[a]	-[a]	∞	0.95 [0.88, 1.02]	Low
Apnoea in preterm infants only used to identify presence of GOR/D														
1 (Mezzacappa et al., 2008)	Retropsective case-control	Very serious[10]	None	None	None	None	194	0.94 [0.87, 0.98]	0.13 [0.06, 0.21]	-[a]	-[a]	1.08 [0.98, 1.19]	0.45 [0.16, 1.25]	Low

GOR/D gastro-oesophageal reflux/disease
** Calculated by the NCC technical team based on figures presented within the studies*
[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.
[1] Retrospective chart review based on diagnosis of GORD
[2] Wide confidence intervals covering categories from low to high.
[3] ALTE as a presenting symptom. ALTE not defined
[4] Method of confirming GORD varied between children.
[5] Classification of control group was based on not being treated for GORD.
[6] Retrospective chart review
[7] Definition of GORD included having apnoea
[8] Retrospective chart review
[9] Retrospective chart review
[10] Retrospective chart review
[11] Small sample size
[12] All children had otitis media

4.2.3.3 Evidence statement

See Error! Reference source not found. **and Table 9: GRADE profile for evaluation of the temporal association between apnoea for GOR**

Quality assessment								
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Temporal association
Temporal link between apnoea and reflux in infants								
1 (Mousa et al., 2005)	Cohort	Serious[1]	None	Serious[2]	None	Yes	25	6173 5-minute time events 4706 (76.2%) of the time e apnoea with GOR. 439 apr In 2 of 25 children apnoea associated. Across the who statistically significant (p=0
Temporal link between apnoea and reflux in premature infants								
1 (Petersen et al., 2002)	Cohort	Serious[3]	None	Serious[4]	None	No	19	A total of 524 reflux events Apnoea during reflux free p reflux periods (0.19/min [0. p>0.05 in 19 infants.

GOR gastro-oesophageal reflux, min minutes, p probability
[1] Small sample size
[2] 11 of 25 children were premature
[3] Small sample size
[4] Included a specific group of children attending an asthma outreach program

Table 10.

Evidence from 2 studies showed there was no temporal association between apnoea events and GOR. The evidence was of low quality.

Nine studies found that apnoea was not a useful marker for the presence of GOR/GORD, but 2 studies showed it was a moderately or very useful marker. All 11 studies found that absence of apnoea was not useful for identifying the absence of GOR/GORD. The quality of evidence ranged from high to very low quality.

4.2.3.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.3.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.4 Epigastric or chest pain

The context of pain due to reflux is one that is well established in the adult gastroenterological literature. This pertains to the young adult also. Chest pain can be caused by many different pathologies and diseases emanating from outside the gastrointestinal tract. However, epigastric pain may equally be due to multiple aetiologies such as peptic ulcer disease, cholecystitis, pancreatitis and gastritis. Therefore, although it is assumed that pain is a manifestation of reflux, reflux may be responsible only in a proportion of situations and children.

4.2.4.1 Description of included studies

Four studies on abdominal or chest pain were included in the review (Carr et al., 2000; Deal et al., 2005; Stordal et al, 2005; Uzun et al., 2012).

Two studies were undertaken in the USA (Carr et al., 2000; Deal et al., 2005), 1 in Norway (Stordal et al., 2005) and 1 in Turkey (Uzun et al, 2012). Samples sizes ranged from 67 to

321 children. Prevalence of GORD ranged from 12% to 73%. One study (Stordal et al., 2005) undertook a cohort and case–control comparisons within the same study.

Two studies reported on chest pain or heartburn (Stordal et al., 2005; Carr et al., 2000). Three studies reported on abdominal pain or 'stomach ache' (Stordal et al., 2005; Deal et al., 2005; Uzun et al., 2012). One study reported specifically on epigastric abdominal pain (Stordal et al., 2005).

4.2.4.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- Abdominal and chest pain in children and young adults for identifying the presence of GORD.

Table 11: GRADE profile for evaluation of abdominal and chest pain in children and young adults for identifying presence of GORD

Quality assessment								Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Chest pain (including heartburn) used to identify presence of GOR/D														
1 (Stordal et al, 2005)	Cohort	None	None	None	Serious[1]	Some[2]	99	0.27 [0.14, 0.44]	0.81 [0.69, 0.9]	0.45 [0.24, 0.68]	0.65 [0.53, 0.75]	1.4 [0.67, 2.91]	0.9 [0.72, 1.14]	Moderate
1 (Stordal et al, 2005)	Case-control	Serious[3]	None	None	Serious[1]	Some[2]	321	0.27 [0.14, 0.44]	0.96 [0.93, 0.98]	- [a]	- [a]	6.98 [3.18, 15.3]	0.76 [0.62, 0.92]	Low
1 Carr et al, 2000	Retrospective case-control	Very serious[4]	None	None	Very serious[1]	Some[5]	295	0.12 [0.08, 0.17]	0.79 [0.69, 0.87]	- [a]	- [a]	0.58 [0.33, 1.01]	1.11 [0.98, 1.26]	Very low
Abdominal pain or "stomach ache" used to identify presence of GOR/D														
1 (Stordal et al, 2005)	Cohort	None	None	None	Very serious[1]	Some[2]	99	0.62 [0.45, 0.78]	0.16 [0.08, 0.28]	0.31 [0.21, 0.42]	0.42 [0.22, 0.63]	0.74 [0.56, 0.97]	2.35 [1.16, 4.73]	Low
1 (Stordal et al, 2005)	Case-control	Serious[3]	None	None	Very serious[1]	Some[2]	321	0.62 [0.45, 0.78]	0.67 [0.61, 0.72]	0.2 [0.13, 0.28]	0.93 [0.89, 0.96]	1.88 [1.39, 2.54]	0.57 [0.37, 0.86]	Very low
1 (Carr et al, 2000)	Retrospective cohort	Very serious[4]	None	None	Very serious[1]	Some[5]	295	0.18 [0.13, 0.24]	0.63 [0.52, 0.73]	0.56 [0.43, 0.68]	0.22 [0.17, 0.28]	0.48 [0.32, 0.72]	1.31 [1.09, 1.56]	Very low
1 (Deal et al, 2005)	Case-control	Serious[6]	None	None	Very serious[1]	None	67	0.43 [0.27, 0.59]	0.96 [0.81, 1]	- [a]	- [a]	11.48 [1.62, 81.21]	0.6 [0.45, 0.79]	Very low
1 (Uzun et al, 2012)	Retrospective cohort	Very serious[4]	None	None	Very serious[1]	Some[7]	70	0.23 [0.11, 0.39]	0.87 [0.7, 0.96]	0.69 [0.39, 0.91]	0.47 [0.34, 0.61]	1.79 [0.61, 5.26]	0.88 [0.71, 1.1]	Very low
Epigastric pain used to identify presence of GOR/D														
1 (Stordal et al, 2005)	Cohort	None	None	None	Serious[1]	Some[2]	99	0.27 [0.14, 0.44]	0.56 [0.43, 0.69]	0.27 [0.14, 0.44]	0.56 [0.43, 0.69]	0.62 [0.34, 1.13]	1.29 [0.96, 1.73]	Moderate
1 (Stordal et al, 2005)	Case-control	Serious[3]	None	None	Serious[1]	Some[2]	321	0.27 [0.14, 0.44]	0.93 [0.89, 0.96]	- [a]	- [a]	3.84 [1.95, 7.56]	0.79 [0.64, 0.96]	Low

GOR/D gastro-oesophageal reflux/disease

[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.

[1] Wide confidence intervals covering categories from low to high.

[2] Based on children referred for pH assessment
[3] Unknown if control group had abnormal pH as not tested.
[4] Based on retrospective review of medical notes. Based on recorded symptoms rather than questionnaire.
[5] Mean average age was 4.4 years so accuracy of symptoms reporting is unclear.
[6] Presence of GORD was based on clinical judgement rather than a diagnostic test.
[7] Children aged 2 to 17 years – so reliability of reporting across the group is unclear

4.2.4.3 Evidence statement

See Table 11.

This review assessed the accuracy of abdominal or chest pain in identifying individuals who had gastro-oesophageal reflux – mainly based on oesophageal pH monitoring. The guideline development group outlined 3 specific types of pain based on location within the body: chest (heartburn), abdominal (including stomach ache) and epigastric.

4.2.4.3.1 Chest pain (including heartburn)

Two studies evaluated the diagnostic accuracy of chest pain for GORD. One study reported a moderate useful positive likelihood ratio, while the other did not. One study found a moderately useful negative likelihood ratio the other 2 did not. Sensitivity was low across all studies, and specificity ranged from high to moderate. The evidence for this finding ranged from moderate to very low quality.

4.2.4.3.2 Abdominal pain (including 'stomach ache') and epigastric pain

Four studies evaluated the diagnostic accuracy of abdominal pain generally for GORD and a fifth looked specifically at epigastric abdominal pain.

One study on abdominal pain generally found a very useful positive likelihood ratio, while the other 3 found it was not useful. One study of abdominal pain generally found a moderately useful negative likelihood ratio, but the other 3 did not. Sensitivity was low across all studies, and specificity ranged from high to low. The evidence for this finding range from low to very low quality.

One study evaluated the diagnostic accuracy of epigastric abdominal pain for GORD. The study found that epigastric pain was not a useful outcome on any diagnostic measure except specificity, which was high. The evidence for this finding ranged from moderate to low quality.

4.2.4.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.4.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.5 Hoarseness

Dysphonia, hoarseness, voice abnormalities and loss of speech have traditionally been attributed in some cases to reflux (GOR or GORD) and otolaryngologists and ENT surgeons have suggested that GOR or GORD may play a part in the genesis of these symptoms. Hence the evidence for this assertion required objective assessment.

4.2.5.1 Description of included studies

Two studies were included in this review (Carr et al., 2000; Yuksel et al., 2013). One study was undertaken in the USA and had a sample size of 295. The other study was undertaken in the Turkey and included 71 children.

4.2.5.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- association between hoarseness (and associated conditions) and GORD in children.

Table 12: GRADE profile for evaluation of hoarseness to identify GORD

Quality assessment							Number of children	Measure of diagnostic accuracy*						Quality
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	
Hoarseness														
1 (Carr et al., 2000)	Retrospective cohort	Very serious[1]	None	None	None	None	295	0.34 [0.28, 0.41]	0.54 [0.43, 0.65]	0.66 [0.57, 0.75]	0.24 [0.18, 0.31]	0.75 [0.55, 1.01]	1.21 [0.97, 1.51]	Low
1 (Yuksel et al., 2013)	Case-control	Serious[2]	None	Serious[3]	Very serious[4]	None	71	0.08 [0.02, 0.21]	0.97 [0.84, 1]	0.75 [0.19, 0.99]	0.46 [0.34, 0.59]	2.46 [0.27, 22.54]	0.95 [0.85, 1.06]	Very low

** Calculated by the NCC technical team based on figures presented within the studies*
[1] Retrospective chart review
[2] Retrospective chart review
[3] All children had otitis media
[4] Confidence intervals cover several categories of usefulness

4.2.5.3 Evidence statements

See Table 12.

Two studies suggest that hoarseness is not useful for identifying GORD. The evidence ranged from low to very low quality.

4.2.5.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.5.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15 .

4.2.6 Feeding difficulties

Whether or not the infant is still refluxing, feed refusal, pulling away from the breast or bottle, subsequent feeding aversion with gagging, pouching food in the cheeks and even precipitation of vomiting are often assumed to have a basis in GORD. The assumption is that the infant had refluxed at some point and had then physiologically associated the feeding experience with pain. Some observers have even postulated that a pain pathway is 'hard-wired' into such infants at an early age, preventing a subsequent enjoyable feeding experience. Studies looking at this association may be hampered by the longitudinal timeline of such a process; that is, looking for GOR or GORD in an infant who is manifesting feeding problems may have 'missed the boat' as the reflux may have been instrumental in the evolution of the problem but may no longer be present. This is the challenge to objectivity in this area.

4.2.6.1 Description of included studies

Eight studies were included in this review (Deal et al., 2005; Heine et al., 2006; Orenstein et al., 1996; Salvatore et al., 2005; Carr et al., 2000; Mazliah et al., 2000; Mezzacappa et al., 2008; Yuksel et al., 2013). Four studies were undertaken in the USA (Deal et al., 2005; Orenstein et al., 1996; Salvatore et al., 2005; Carr et al., 2000), 1 in Australia (Heine et al., 2006), 1 in Malaysia (Mazliah et al., 2000), 1 in Turkey (Yuksel et al., 2013) and 1 in Brazil (Mezzacappa et al., 2008). One study (Deal et al., 2005) divided the patient population by age (1 to 11 months, and 12 months or more).

Five studies reported on feeding refusal (Deal et al., 2005; Heine et al., 2006; Orenstein et al., 1996; Salvatore et al., 2005; Carr et al., 2000). One study reported on feeding difficulties (Heine et al., 2006). One reported on choking/gagging (Carr et al., 2000). Two studies reported on crying when feeding (Salvatore et al., 2005; Mathisen, 1999). One study reported on feeding problems (Mazliah et al., 2000). One reported on feeding intolerance (Mezzacappa et al., 2008). One study reported reported on head aversion, facial grimaces, or body withdrawal when feeding (Mathisen, 1999). One study reported on feeding complex (Yuksel et al., 2013), which was defined as a symptom group consisting of irritability, pyrosis and failure to thrive

4.2.6.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- feeding difficulties in children and young adults for identifying the presence of GORD.

Table 13: GRADE profile for evaluation of feeding difficulties to identify GORD

Quality assessment							Number of patients	Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Feeding refusal used to identify presence of GOR/D														
1 (Deal et al., 2005) (1 - 11 months	Case-control	Serious[1]	None	None	Very serious[2]	None	67	0.41 [0.26, 0.58]	0.83 [0.61, 0.95]	-[a]	-[a]	2.38 [0.91, 6.24]	0.71 [0.52, 0.97]	Very low
1 (Deal et al., 2005) (12 or older months)	Case-control	Serious[3]	None	None	Very serious[2]	None	67	0.65 [0.48, 0.79]	0.76 [0.56, 0.9]	-[a]	-[a]	2.69 [1.36, 5.34]	0.46 [0.29, 0.74]	Very low
1 (Heine et al., 2006)	Cohort	None	None	Serious[3]	None	None	151	0.46 [0.26, 0.67]	0.58 [0.48, 0.66]	0.18 [0.09, 0.3]	0.84 [0.74, 0.91]	1.08 [0.67, 1.75]	0.94 [0.63, 1.4]	Moderate
1 (Orenstein et al., 1996)	Case-control	Serious[3]	None	None	Serious[2]	None	135	0.31 [0.17, 0.49]	0.96 [0.9, 0.99]	-[a]	-[a]	7.86 [2.67, 23.08]	0.71 [0.57, 0.9]	Low
1 (Salvatore et al., 2005)	Cohort	None	None	None	Serious[2]	None	99	0.52 [0.3, 0.74]	0.4 [0.29, 0.52]	0.19 [0.1, 0.32]	0.76 [0.6, 0.88]	0.88 [0.56, 1.37]	1.18 [0.7, 2]	Moderate
1 (Carr et al., 2000)	Retrospective cohort	Very serious[4]	None	None	Very serious[2]	None	295	0.22 [0.17, 0.28]	0.79 [0.69, 0.87]	0.73 [0.61, 0.84]	0.28 [0.22, 0.34]	1.05 [0.64, 1.71]	0.99 [0.86, 1.13]	Very low
Feeding difficulties used to identify presence of GOR/D														
1 (Heine et al., 2006)	Cohort	None	None	Serious[3]	None	None	151	0.46 [0.26, 0.67]	0.58 [0.48, 0.66]	0.18 [0.09, 0.3]	0.84 [0.74, 0.91]	1.08 [0.67, 1.75]	0.94 [0.63, 1.4]	Moderate
Choking/gagging used to identify presence of GOR/D														
1 (Carr et al., 2000)	Retrospective cohort	Very serious[4]	None	None	Very serious[2]	None	295	0.24 [0.18, 0.3]	0.86 [0.77, 0.93]	0.82 [0.7, 0.91]	0.3 [0.24, 0.36]	1.75 [0.96, 3.2]	0.88 [0.79, 0.99]	Very low
Crying when feeding used to identify presence of GOR/D														
1 (Salvatore et al., 2005)	Cohort	None	None	None	Serious[2]	None	99	0.57 [0.34, 0.78]	0.61 [0.49, 0.72]	0.28 [0.15, 0.44]	0.84 [0.72, 0.93]	1.46 [0.92, 2.31]	0.71 [0.42, 1.19]	Moderate
Mathisen et al., 1999	Case-control	Serious	None	None	Serious[2]	None	40	0.85 [0.62, 0.97]	0.8 [0.56, 0.94]	-[a]	-[a]	4.25 [1.74, 10.41]	0.19 [0.06, 0.54]	Low
Feeding problems used to identify presence of GOR/D														
1 (Mazliah et al., 2000)	Cross-sectional survey	None	None	None	Very serious[2]	None	44	0.06 [0.01, 0.21]	0.92 [0.64, 1]	0.67 [0.09, 0.99]	0.29 [0.16, 0.46]	0.84 [0.08, 8.46]	1.01 [0.84, 1.22]	Very low

Quality assessment							Number of patients	Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Feeding intolerance used to identify presence of GOR/D														
1 (Mezzacappa et al., 2008)	Retrospective Case-control	Very serious[4]	None	None	Serious[2]	None	174	0.71 [0.61, 0.8]	0.4 [0.3, 0.51]	-[a]	-[a]	1.19 [0.96, 1.48]	0.71 [0.47, 1.09]	Very low
Head aversion when feeding used to identify presence of GOR/D														
1 (Mathisen et al., 1999)	Case-control	Serious	None	None	Serious[2]	None	40	0.2 [0.06, 0.44]	0.9 [0.68, 0.99]	-[a]	-[a]	2 [0.41, 9.71]	0.89 [0.68, 1.16]	Low
Facial grimaces when feeding used to identify presence of GOR/D														
1 (Mathisen et al., 1999)	Case-control	Serious	None	None	Serious[2]	None	40	0.35 [0.15, 0.59]	0.8 [0.56, 0.94]	-[a]	-[a]	1.75 [0.61, 5.05]	0.81 [0.55, 1.2]	Low
Body withdrawal when feeding used to identify presence of GOR/D														
1 (Mathisen et al., 1999)	Case-control	Serious	None	None	Serious[2]	None	40	0.2 [0.06, 0.44]	0.95 [0.75, 1]	-[a]	-[a]	4 [0.49, 32.73]	0.84 [0.66, 1.07]	Low
Feeding complex														
1 (Yuksel et al., 2013)	Case-control	Serious[5]	None	Serious6	Serious[2]	None	71	0.44 [0.28, 0.6]	0.66 [0.47, 0.81]	-[a]	-[a]	1.27 [0.7, 2.3]	0.86 [0.59, 1.25]	Very low

GOR/D gastro-oesophageal reflux/disease
[*] Calculated by the NCC technical team based on figures presented within the studies
[1] Presence of GORD based on clinical judgement
[2] Wide confidence intervals covering categories from low to high.
[3] It is unknown if all participants received a reference standard
[4] Based on retrospective review of medical notes. Based on recorded symptoms rather than all symptoms that were present.
[5] Retrospective chart review
[6] All children had otitis media
[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated

4.2.6.3 Evidence statements

See Table 13.

4.2.6.3.1 Feeding refusal

Five studies evaluated the diagnostic accuracy of feeding refusal for identifying GORD. One study reported 'moderately useful' positive likelihood ratios; the rest found it was 'not useful'. One study reported moderately useful negative likelihood ratios; the rest found it was not useful. The evidence for these findings ranged from moderate to very low quality.

4.2.6.3.2 Feeding difficulties

One study evaluated the diagnostic accuracy of feeding difficulties for identifying GORD. The study reported that it was 'not useful' for identifying children with or without GORD. The evidence for this finding was of moderate quality.

4.2.6.3.3 Choking or gagging

One study evaluated the diagnostic accuracy of choking or gagging for identifying GORD. The study reported that it was 'not useful' for identifying children with GORD. The evidence for this finding was of very low quality.

4.2.6.3.4 Crying when feeding

Two studies evaluated the diagnostic accuracy of crying when feeding for identifying GORD. One study reported that it was 'not useful' for identifying those with or without GORD. The evidence for this finding was of moderate quality. The second study reported that no crying when feeding was a moderately useful sign to identify those without GORD. The evidence was of low quality.

4.2.6.3.5 Feeding problems

One study evaluated the diagnostic accuracy of feeding problems for identifying GORD. The study reported that it was 'not useful' for identifying those with or without GORD. The evidence for this finding was of very low quality

4.2.6.3.6 Feeding intolerance

One study evaluated the diagnostic accuracy of feeding refusal for identifying GORD. The study reported that it was 'not useful' for identifying those with or without GORD. The evidence for this finding was of very low quality.

4.2.6.3.7 Head aversion, facial grimaces or body withdrawal when feeding

One study evaluated the diagnostic accuracy of head aversion, facial grimaces or body withdrawal when feeding for identifying the presence of GORD. The study reported that each of these signs was 'not useful' for identifying those with or without GORD. The evidence was of low quality.

4.2.6.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.6.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.7 Otitis media

At first assessment it is not intuitive to invoke reflux as a cause of otitis media. Alternatively, there could be a common cause for both pathologies, but to examine the question of whether GOR or GORD causes otitis media is important. Both conditions are very common and therefore this was examined with the available evidence in the literature. Episodes of acute otitis media were looked at and serious otitis media ('glue ear') was also the subject of this particular review area.

4.2.7.1 Description of included studies

Four observational studies were included in this review (El-Serag et al., 2001; Kotsis et al., 2009; Aydin et al., 2011; O'Reilly et al., 2008). Two studies examined otitis media as a risk factor for presence of GORD (El-Serag et al., 2001; Kotsis et al., 2009). Two studies examined GORD as a risk factor for otitis media (Aydin et al., 2011; O'Reilly et al., 2008). Sample sizes ranged from 40 to 9900.

4.2.7.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- association between otitis media and GOR or GORD in children.

Table 14: GRADE profile for evaluation of otitis media for identifying GORD

Quality assessment								Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Presence of otitis media for identifying GORD														
1 (El-Serag et al., 2001)	Retrospective case-control	Very serious[1]	None	None	None	None	9900	0.1 [0.07, 0.13]	0.8 [0.79, 0.8]	-[a]	-[a]	0.49 [0.37, 0.66]	1.13 [1.09, 1.17]	Low
1 (Kotsis et al., 2009) – (Serious OM vs none)	Prospective cohort	None	None	None	Serious[2]	None[3]	109	0.32 [0.2, 0.45]	0.88 [0.75, 0.95]	0.76 [0.55, 0.91]	0.51 [0.4, 0.62]	2.59 [1.12, 5.97]	0.78 [0.64, 0.95]	Moderate
1 (Kotsis et al., 2009) – (Any OM vs none)	Prospective cohort	None	None	None	Serious[2]	None[4]	187	0.22 [0.15, 0.3]	0.88 [0.75, 0.95]	0.83 [0.67, 0.94]	0.28 [0.21, 0.36]	1.78 [0.79, 4.01]	0.89 [0.78, 1.02]	Very low
GOR for identifying OM														
1 (Aydin et al., 2011)	Case-control	Serious[5]	None	Serious[6]	Very serious[2]	None	40	0.3 [0.12, 0.54]	0.85 [0.62, 0.97]	-[a]	-[a]	2 [0.58, 6.91]	0.82 [0.59, 1.16]	Very low
1 (O'Reilly et al., 2008)	Case-control	Very serious[7]	None	None	None	None	509	0.2 [0.17, 0.24]	0.98 [0.92, 1]	-[a]	-[a]	12.95 [1.84, 91.23]	0.81 [0.77, 0.85]	Low

GORD gastro-oesophageal disease, OM otitis media
** Calculated by the NCC technical team based on figures presented within the studies*
[1] Retrospective and based on computer records
[2] Outcome cover several categories for several items
[3] Serious OM vs none
[4] Any OM vs none
[5] Small sample size
[6] Adenoid hypertrophy
[7] Identification of GORD based on medical records
[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.

4.2.7.3 Evidence statements

See Table 14.

Two studies (3 comparisons) found evidence that the presence of otitis media to identify GORD was not useful. The evidence for this finding was of moderate to very low quality. Evidence from 1 study showed the presence of GOR (the definition was not explicitly stated, but based on reading the medical records) was a very useful (positive likelihood ratio) symptom for identifying the presence of chronic or recurrent otitis media. The evidence was of low quality. Another study did not find the presence of GOR to be useful for identifying otitis media. The evidence was of very low quality.

4.2.7.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.7.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.8 Lower respiratory tract infection

GOR/GORD and respiratory infections are relatively common in infants, children and young people so it is desirable to know whether an association or causal link exists between them. It has been postulated that when a person has to make more effort to breathe during a lower respiratory infection, the increased negative pressure generated in the thorax may make them more predisposed to GOR: however, this is countered by the argument that reflux may cause micro-aspiration and therefore respiratory vulnerability to infection. Reflux in the neurologically compromised child can lead to aspiration and chest problems where airway protective mechanisms are absent or compromised, but this is different to concluding that reflux intrinsically leads to lower respiratory chest infection. The area is poorly understood and often confused because many of the children with severe, complex neurology have both problems. For these reasons the guideline development group decided that this area required examination.

4.2.8.1 Description of included studies

Five studies were included in this review (El-Serag et al., 2001; Mazliah et al., 2000; Assadamongkol et al., 1993; Salvatore et al., 2005; Orenstein et al., 1996).

One study was undertaken in the USA (Orenstein et al., 1996), 1 in Thailand (Assadamongkol et al., 1993), 1 in Malaysia (Mazliah et al., 2000), 1 in Belgium (Salvatore et al., 2005) and 1 in Australia (El-Serag et al., 2001). All 5 studies (El-Serag et al., 2001; Mazliah et al., 2000; Assadamongkol et al., 1993; Salvatore et al., 2005; Orenstein et al., 1996) examined the association between pneumonia and GORD. One of these studies also examined bronchiectasis and GORD (El-Serag et al., 2001). Sample sizes ranged from 44 to 9900.

4.2.8.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group.

- association between pneumonia and GOR in children.

Table 15: GRADE profile for evaluation of pneumonia

Quality assessment								Measure of diagnostic accuracy						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Ever had pneumonia used to identify presence of GOR/D														
1 (El-Serag et al., 2001)	Retrospective cohort	Very serious[1]	None	None	None	None	9900	0.06 [0.05, 0.07]	0.98 [0.97, 0.98]	0.41 [0.35, 0.47]	0.81 [0.8, 0.81]	2.76 [2.2, 3.45]	0.96 [0.95, 0.97]	Low
1 (Orenstein et al., 1996)	Case-control	Serious[2]	None	None	None	None	135	0.09 [0.02, 0.23]	1 [0.96, 1]	-[a]	-[a]	-[b]	0.91 [0.83, 1.01]	Moderate
1 (Salvatore et al., 2005)	Cohort	None	None	None	Serious[3]	None	99	0.2 [0.06, 0.44]	0.96 [0.89, 0.99]	0.57 [0.18, 0.9]	0.82 [0.73, 0.89]	5.13 [1.25, 21.11]	0.83 [0.67, 1.04]	Moderate
Aspiration pneumonia used to identify presence of GOR/D														
1 (Assadamongkol et al., 1993)	Retrospective cohort	Very serious[4]	None	None	None	None	55	0.5 [0.3, 0.7]	0.31 [0.15, 0.51]	0.39 [0.23, 0.58]	0.41 [0.21, 0.64]	0.73 [0.46, 1.14]	1.61 [0.83, 3.13]	Low
Recurrent pneumonia used to identify presence of GOR/D														
1 (Assadamongkol et al., 1993)	Retrospective cohort	Very serious[4]	None	None	None	None	55	0.08 [0.01, 0.25]	0.97 [0.82, 1]	0.67 [0.09, 0.99]	0.54 [0.39, 0.68]	2.23 [0.21, 23.19]	0.96 [0.84, 1.09]	Low
1 (Mazliah et al., 2000)	Cross-sectional survey	Serious[5]	None	None	Serious[3]	None	44	0.19 [0.07, 0.37]	0.62 [0.32, 0.86]	0.55 [0.23, 0.83]	0.24 [0.11, 0.42]	0.5 [0.19, 1.36]	1.31 [0.82, 2.08]	Low
Bronchiectasis with or without collapse used to identify presence of GOR/D														
1 (El-Serag et al., 2001)	Retrospective cohort	Very serious[1]	None	None	None	None	9900	0.24 [0.08, 0.47]	0.67 [0.56, 0.77]	0.16 [0.05, 0.34]	0.77 [0.65, 0.86]	0.72 [0.32, 1.65]	1.14 [0.85, 1.51]	Low

GOR/D gastro-oesophageal reflux/disease

[a] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated·*

[b] *Positive likelihood ratio could not be calculated because the number of controls with 'ever had pneumonia' was zero*

[1] *Retrospective and based on computer records..*

[2] *Classification of control group was based on not being treated for GORD.*

[3] *Wide confidence intervals covering categories from low to high.*

[4] *Retrospective chart review*

[5] *Method of confirming GORD varied between children*

4.2.8.3 Evidence statements

See Table 15.

4.2.8.3.1 Pneumonia

Three studies reported results ranging from not useful to moderately useful for the use of 'ever had pneumonia' as a diagnostic marker for GORD. One study showed that aspiration pneumonia was not a useful marker for GORD. Two studies found that recurrent pneumonia was not a useful marker for GORD. Quality of evidence ranged from medium to low quality.

4.2.8.3.2 Bronchiectasis

One study found that bronchiectasis was not a useful marker for identifying GORD. The study was of low quality.

4.2.8.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.8.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.9 Faltering growth

It has long been considered that an infant or young child who is experiencing reflux may have consequent growth compromise. The possible reasons put forward for this include:

- vomiting thereby diminishing nutritional intake
- associated feeding problems due to reflux-induced pain and irritability
- associated cows' milk protein allergy, small bowel enteropathy and absorption issues
- the increased energy required to feed frequently.

The guideline development group felt this area required objective interrogation of the literature.

4.2.9.1 Description of included studies

Six observational studies were included in this review (Orenstein et al., 1996; Salvatore et al., 2005; Costa et al., 2005; Carr et al., 2000; Tolia et al., 2003; Yuksel, 2013). One study was from Belgium (Orenstein et al., 1996), 1 from Brazil (Costa et al., 2004), 3 from the USA (Orenstein et al., 1996; Carr et al., 200; Tolia et al., 2003) and 1 from Turkey (Yuksel, 2013). Sample sizes ranged from 71 to 797 children.

Two studies reported on problems with weight gain (Orenstein et al., 1996; Salvatore et al., 2005). Three studies reported on failure to thrive (Costa et al., 2005; Carr et al., 2000; Tolia et al., 2003).

4.2.9.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- faltering growth in children and young adults for identifying the presence of GORD.

Table 16: GRADE profile for evaluation of faltering growth

Quality assessment								Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Weight gain problems														
1 (Orenstein et al., 1996)	Case-control	Serious[1]	None	None	Serious[2]	None	135	0.26 [0.12, 0.43]	1 [0.96, 1]	-[a]	-[a]	∞	0.74 [0.61, 0.9]	Low
1 (Salvatore et al., 2005)	Cohort	None	None	None	Serious[2]	None	99	0.19 [0.05, 0.42]	0.83 [0.73, 0.91]	0.24 [0.07, 0.5]	0.79 [0.69, 0.87]	1.14 [0.42, 3.14]	0.97 [0.77, 1.22]	Moderate
Failure to thrive														
1 (Carr et al., 2000)	Retrospective cohort	Very serious[3]	None	None	Very serious[2]	None	295	0.09 [0.05, 0.14]	1 [0.96, 1]	1 [0.82, 1]	0.29 [0.24, 0.35]	∞	0.91 [0.87, 0.95]	Very low
1 (Tolia et al., 2003)	Retrospective cohort	Very serious[3]	None	None	None	None	342	0.16 [0.11, 0.23]	0.9 [0.84, 0.94]	0.62 [0.47, 0.76]	0.51 [0.45, 0.57]	1.61 [0.92, 2.83]	0.93 [0.86, 1.01]	Low
1 (Costa et al., 2005)	Cross-sectional survey	Very serious[4]	None	None	None	None	797	0.3 [0.21, 0.41]	0.96 [0.94, 0.97]	0.49 [0.35, 0.63]	0.92 [0.89, 0.94]	7.67 [4.74, 12.4]	0.73 [0.63, 0.83]	Low
1 (Yuksel et al., 2013)	Case-control	Serious[5]	None	Serious[6]	Serious[7]	None	71	0.18 [0.06, 0.3]	0.78 [0.64, 0.92]	-[a]	-[a]	0.82 [0.32, 2.10]	1.05 [0.83, 1.34]	Very low

[*] *Calculated by the NCC technical team based on figures presented within the studies*
[a] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[1] *Control group not tested for reflux symptoms.*
[2] *Wide confidence intervals covering categories from low to high.*
[3] *Based on retrospective review of medical notes.*
[4] *Classification of cases and controls based on Rome II criteria for adults and not diagnostic tests.*
[5] *Retrospective chart review*
[6] *All children had otitis media*
[7] *Wide confidence intervals covering categories from low to moderate.*

4.2.9.3 Evidence statements

See Table 16.

4.2.9.3.1 Faltering growth

Two studies evaluated the diagnostic accuracy of weight gain problems for identifying GORD. Reported results ranged from 'not useful' to 'moderately useful' for identifying GORD and 'not useful' for identifying those without GORD. The evidence for this finding was of moderate to low quality.

Four studies evaluated the diagnostic accuracy of failure to thrive for identifying GORD. Reported results ranged from 'not useful' to 'very useful' for identifying GORD and 'not useful' for identifying those without GORD. The evidence for this finding was of low to very low quality.

4.2.9.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.9.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.10 Asthma

As for lower respiratory infections, the increased effort to breathe induced by asthma has been assumed to increase reflux but, conversely, GOR/GORD has been thought to play a role in the genesis and exacerbation of asthma, perhaps by stimulation of vagal nerve afferents in the distal inflamed oesophagus with reflex bronchoconstriction, or by a route such as micro-aspiration. An association is well described but causality is not established in either direction. The guideline development group therefore believed this was an important area which needed to be assessed.

4.2.10.1 Description of included studies

Seven studies were included in this review (El-Serag et al., 2001; Ruigomez et al., 2010; Petersen et al., 1989; Debley et al., 2006; Stordal et al., 2006; Chopra et al., 1995; Gustafsson et al., 1990). Two of the studies examined presence of asthma to identify GORD (El-Serag et al., 2001; Ruigomez et al., 2010) and the other 5 examined whether the presence of GORD was a risk factor for asthma (Petersen et al., 1989; Debley et al., 2006; Stordal et al., 2006; Chopra et al., 1995; Gustafsson et al., 1990). In all these studies asthma was being examined as a risk factor rather than a symptom.

One study was undertaken in Sweden (Gustafsson et al., 1990), 1 in Norway (Stordal et al., 2006), 1 in the USA (Debley et al., 2006), 1 in India (Chorpa et al., 1995), 1 in Denmark (Petersen et al., 1989), 1 in the UK (Ruigomez et al., 2010) and 1 in Australia (El-Serag et al., 2001). Sample sizes ranged from 39 to 9900.

4.2.10.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- association between asthma and GOR or GORD in children.

Table 17: GRADE profile for evaluation of diagnostic value of asthma for identifying children with GORD

Quality assessment								Measure of diagnostic accuracy**						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Using presence of asthma to identify GORD														
1 (El-Serag et al., 2001)	Retrospective cohort	Very serious[1]	None	None	None	None	9900	0.13 [0.12, 0.15]	0.93 [0.93, 0.94]	-[a]	-[a]	1.95 [1.7, 2.24]	0.93 [0.91, 0.95]	Low
1 (Ruigomez et al., 2010)	Retrospective cohort	Very serious[2]	None	None	None	None	6677	0.25 [0.23, 0.27]	0.81 [0.8, 0.82]	-[a]	-[a]	1.31 [1.19, 1.45]	0.93 [0.9, 0.95]	Low
Using presence of GORD to identify asthma														
1 (Petersen et al., 1989)	Case-control	Serious[3]	None	None	Very serious[4]	None	39	0.33 [0.16, 0.55]	0.93 [0.68, 1]	-[a]	-[a]	5 [0.69, 36.08]	0.71 [0.52, 0.98]	VerylLow
1 (Debley et al., 2006)	Case-control	Serious[5]	None	None	None	None	2397	0.19 [0.15, 0.24]	0.97 [0.97, 0.98]	-[a]	-[a]	7.65 [5.18, 11.31]	0.83 [0.78, 0.88]	Moderate
1 (Stordal et al., 2006)	Case-control	Serious[6]	None	None	None	None	1136	0.2 [0.17, 0.23]	0.92 [0.88, 0.95]	-[a]	-[a]	2.37 [1.55, 3.61]	0.88 [0.83, 0.92]	Moderate
1 (Chopra et al., 1995)	Case-control	Serious[7]	None	None	Very serious[4]	None	90	0.39 [0.28, 0.5]	1 [0.69, 1]	-[a]	-[a]	∞	0.61 [0.51, 0.73]	Very low
1 (Gustafsson et al., 1990)	Case-control	Very serious[8]	None	None	Serious[4]	None	69	0.5 [0.34, 0.66]	0.85 [0.66, 0.96]	-[a]	-[a]	3.38 [1.3, 8.76]	0.59 [0.42, 0.83]	Very low

GORD gastro-oesophageal disease
[*] Calculated by the NCC technical team based on figures presented within the studies
[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated
[1] Retrospective and based on computer records
[2] Retrospective and based on computer records. On 15.7% of GORD group had formal test
[3] Definition of GORD was based on barium meal only
[4] Wide confidence intervals means results cover several categories
[5] Definition of GORD was based on a questionnaire
[6] Definition of GORD was based on a questionnaire
[7] GORD based on scintiscan. Control group was very small sample size
[8] Results are based on two separate studies using the same methodology. Cases include people age 18 and over

4.2.10.3 Evidence statements

See Table 17.

4.2.10.3.1 Asthma

Evidence from 2 studies found that asthma is not a useful diagnostic marker for identifying GORD, with both positive and negative likelihood ratios being low. The evidence was of low quality. Evidence from 2 of 5 studies suggests that the presence of GOR is a moderately useful diagnostic marker for children having asthma. The other 3 studies could not find a definitive effect. The evidence ranged from moderate to very low quality.

4.2.10.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.10.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.11 Chronic cough

The issues arising are the same as in the asthma section above, although laryngeal irritation by the refluxate is a possible cause of cough because the larynx is much more sensitive to acid and pepsin which are the major noxious substances in the refluxed stomach contents. Even small amounts of refluxate, and even when the refluxate is only weakly acidic, are thought to have an effect on the cough reflex. This was therefore examined by the guideline development group.

4.2.11.1 Description of included studies

Five observational studies were included in this review (Carr et al., 2000; Chang et al., 2006; Salvatore et al., 2005; Uzun et al., 2012; Yuksel et al., 2013). One study was undertaken in Australia (Chang et al., 2006), 1 in the USA (Carr et al., 2000), 1 in Belgium (Salvatore et al., 2005) and 2 in Turkey (Uzun et al., 2012; Yuksel et al., 2013). Sample sizes ranged from 70 to 214.

4.2.11.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- chronic cough in children and young adults for identifying the presence of GORD.

Table 18: GRADE profile for evaluation of diagnostic value of chronic cough for identifying children with GORD

Quality assessment							Number of children	Measure of diagnostic accuracy**						Quality
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	
Chronic cough used to identify presence of GOR/D														
1 (Uzun et al., 2012)	Retrospective cohort	Very serious[1]	None	None	None	None	70	0.67 [0.5, 0.81]	0.32 [0.17, 0.51]	0.55 [0.4, 0.7]	0.43 [0.23, 0.66]	0.98 [0.71, 1.37]	1.03 [0.53, 2.03]	Low
1 (Carr et al., 2000)	Retrospective cohort	Very serious[2]	None	None	None	None	214	0.51 [0.44, 0.58]	0.59 [0.48, 0.7]	0.77 [0.69, 0.83]	0.31 [0.24, 0.39]	1.25 [0.93, 1.68]	0.83 [0.66, 1.04]	Low
1 (Chang et al., 2006)	Prospective cohort	None	None	None	None	None	150	0.43 [0.32, 0.55]	0.51 [0.39, 0.63]	0.48 [0.36, 0.6]	0.46 [0.35, 0.57]	0.87 [0.61, 1.23]	1.13 [0.84, 1.52]	High
1 (Salvatore et al., 2005)	Prospective cohort	Serious[3]	None	None	None	None	99	0.24 [0.08, 0.47]	0.62 [0.51, 0.73]	0.15 [0.05, 0.31]	0.75 [0.63, 0.85]	0.63 [0.28, 1.43]	1.22 [0.91, 1.64]	Moderate
1 (Yuksel et al., 2013)	Case-control	Serious[4]	None	Serious[5]	None	None	71	0.54 [0.37, 0.7]	0.47 [0.29, 0.65]	0.55 [0.38, 0.71]	0.45 [0.28, 0.64]	1.01 [0.66, 1.57]	0.98 [0.6, 1.62]	Low

GOR/D gastro-oesophageal reflux/disease
** Calculated by the NCC technical team based on figures presented within the studies*
[1] Based on presenting symptoms rather than questionnaire, so not all children will have been asked about same symptoms
[2] Retrospective chart review
[3] Chronic cough based on a single question involving parental assessment
[4] Retrospective chart review
[5] All children had otitis media

4.2.11.3 Evidence statements

See Table 18.

4.2.11.3.1 Chronic cough

Evidence from 5 studies showed that presence of chronic cough was not a useful marker for the presence of GORD (positive or negative likelihood ratios). The evidence for this finding was of high to low quality.

4.2.11.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.11.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.12 Dental erosion

It was the experience of several expert members of the guideline development group that certain groups of children (especially those with complex neurodisabilities) can be referred to secondary and tertiary care for an opinion in respect of possible GORD based on abnormal dental findings. It is not clear whether dental enamel erosion (classically posterior molar) is caused by GOR/GORD and hence this was a condition that the guideline development group thought should be examined.

4.2.12.1 Description of included studies

Eight studies were included in this review (Guare et al., 2012; Linnett et al., 2002; Ersin et al., 2006; Polat et al., 2013; Shaw et al., 1998; Wild et al., 2011; Gonda-Domin et al., 2013; Farahmand et al., 2013). Seven studies used the presence of dental erosion in children with and without GORD and 1 examined the presence of GORD in children as a risk factor for dental erosion.

One study was undertaken in Brazil (Guare et al., 2012), 1 in Australia (Linnett et al., 2002), 2 in Turkey (Ersin et al., 2006; Polat et al., 2013), 1 in the UK (Shaw et al., 1998), 1 in the USA (Wild et al., 2011), 1 in Poland (Gonda-Domin et al., 2013) and 1 in Iran (Farahmand et al., 2013). Three of the studies examined only children with cerebral palsy (Guare et al., 2012; Polat et al., 2013; Wild et al., 2011). Sample sizes ranged from 21 to 114 children.

4.2.12.2 Evidence profile

The GRADE profiles that follow show results of included studies for the following symptoms and signs selected for review by the guideline development group:

- association between dental erosion and GOR or GORD in children.

Table 19: GRADE profile for evaluation of dental erosion to identify GORD

Quality assessment								Measure of diagnostic accuracy*						
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of children	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Quality
Presence of any type of dental erosion compared to no dental erosion used to identify presence of GOR/D														
1 (Linnett et al., 2002)	Case-control	Serious[1]	None	None	None	None	104	0.46 [0.32, 0.61]	0.6 [0.39, 0.73]	-[a]	-[a]	1.14 [0.73, 1.78]	0.9 [0.65, 1.26]	Moderate
1 (Ersin et al., 2006)	Case-control	Serious[2]	None	None	Serious[3]	None	80	0.76 [0.6, 0.89]	0.76 [0.62, 0.88]	-[a]	-[a]	3.21 [1.81, 5.66]	0.31 [0.17, 0.56]	Low
1 (Shaw et al., 1998)	Case-control	Serious[4]	None	None	Very serious[5]	None	41	0.81 [0.58, 0.95]	0.85 [0.58, 0.97]	-[a]	-[a]	5.4 [1.86, 15.64]	0.22 [0.09, 0.55]	Very low
1 (Wild et al., 2011)	Case-control	Serious[6]	None	None	None	None	72	0.76 [0.63, 0.86]	0.43 [0.12, 0.71]	-[a]	-[a]	1.33 [0.82, 2.14]	0.56 [0.26, 1.2]	Moderate
1 (Gonda-Domin et al., 2013)	Case-contorl	None	None	None	None	None	114	0.67 [0.53, 0.79]	0.74 [0.6, 0.84]	-[a]	-[a]	2.53 [1.58, 4.06]	0.45 [0.3, 0.67]	High
1 (Farahmand et al., 2013	Case-control	Very serious[7]	None	None	Serious[3]	None	64	0.98 [0.9, 1]	0.81 [0.69, 0.9]	-[a]	-[a]	5.18 [3.04, 8.82]	0.02 [0, 0.16]	Very low
Presence of any type of dental erosion compared to no dental erosion in children with cerebral palsy used to identify presence of GOR/D														
1 (Guare et al., 2012)	Case-control	Serious[8]	None	None	Very serious[9]	None	46	0.9 [0.68, 0.99]	0.81 [0.72, 0.93]	-[a]	-[a]	4.68 [2.1, 10.43]	0.12 [0.03, 0.47]	Very low
1 (Shaw et al., 1998)	Case-control	Very serious[10]	None	None	Serious[3]	None	21	0.75 [0.43, 0.95]	0.67 [0.3, 0.93]	-[a]	-[a]	2.25 [0.84, 6]	0.38 [0.13, 1.11]	Very low
Presence of GORD compared to no GORD as a cause of dental problems in children with cerebral palsy														
1 (Polat et al., 2013)	Case-control	Very serious[11]	None	None	Very serious[9]	None	37	0.84 [0.6, 0.97]	0.72 [0.54, 0.9]	-[a]	-[a]	3.03 [1.4, 6.55]	0.22 [0.07, 0.64]	Very low
Localised vs generalised erosions														
1 (Farahmand et al., 2013	Case-control	Very serious[7]	None	None	Very serious[3]	None	64	0.34 [0.22, 0.48]	0.55 [0.23, 0.83]	-[a]	-[a]	0.75 [0.35, 1.58]	1.21 [0.68, 2.15]	Very low

GOR/D gastro-oesophageal reflux/disease, GORD gastro-oesophageal disease, vs versus
[*] Calculated by the NCC technical team based on figures presented within the studies
[1] Control group were not assessed for GORD
[2] Unclear how presence of GOR was determined in case and control groups
[3] Confidence intervals are wide for both positive and negative likelihood rtios
[4] Unclear how GOR was determined in all children. Children referred to a tertiary dental unit.
[5] Confidence intervals are very wide for both positive and negative likelihood ratios
[6] Unclear if analysis was undertaken on all children or only those who had pH monitoring
[7] Excluded children where other sources of dental erosion were identified
[8] Small sample size
[9] Confidence intervals are wide or very wide for positive and negative likelihood ratios
[10] Unclear how GOR was determined in all children. Small sample size.
[11] Analysis relates to GORD as a risk factor for dental erosion rather than dental erosion as a marker of GORD
[a] Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated

4.2.12.3 Evidence statements

See Table 19.

4.2.12.3.1 Dental erosion

The results were moderately useful for 2 case–control studies that compared the presence of dental erosion in children with and without GOR/GORD, for distinguishing between children with and without GOR/GORD. Four studies showed that the presence of dental erosion was, however, not useful for identifying children with GOR/GORD. Four studies showed that the absence of dental erosion is moderately to very useful for identifying those without GOR/GORD. The quality of the evidence ranged from high to very low.

Results from 2 studies involving children with cerebral palsy showed that presence of dental erosion is not useful for identifying GORD, but absence of dental erosion was moderately useful for identifying those without GORD. However, wide confidence intervals mean that this finding is sensitive to change. Another study in children with cerebral palsy showed the presence of GORD compared with no GORD was not useful for identifying dental problems. The quality of the evidence for this was very low.

4.2.12.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.2.14.

4.2.12.5 Recommendations

The recommendations covering risk factors can be found in Section 4.2.15.

4.2.13 Health economics profile

No health economic data on symptoms and signs was identified, and no health economic evaluation was undertaken.

4.2.14 Evidence to recommendations

The aims of these questions were to determine the usefulness of individual symptoms and signs (observed distress, epigastric or chest pain, hoarseness) as pointers to a diagnosis of GORD and to examine the possible association between certain clinical conditions (namely apnoeic episodes, feeding difficulties, asthma, and recurrent otitis media and pneumonia) and gastro-oesophageal reflux.

4.2.14.1 Consideration of clinical benefits and harms

The clinical benefits and harms of each symptom and sign were discussed by the guideline development group with reference to the results of the systematic reviews and their own clinical experience. The group used the summary diagnostic criteria in its discussions, but noted that these criteria are usually applied to diagnostic tests rather than symptoms, and it was unlikely a symptom would meet the criteria for being ‘very useful’. Furthermore, the group was concerned that the ‘gold’ standard used to diagnose the presence of GOR or GORD only reflected surrogate markers, such as pH monitoring, or was based on questionnaires that included the symptom being tested as one of the items.

A false positive diagnosis of GORD could potentially have adverse consequences, including unnecessary investigations, such as endoscopy, or the use of unnecessary treatments. Endoscopy is usually performed under sedation or more frequently under general anethesia in children and there are small associated risks. Oesophageal pH monitoring can be a

somewhat distressing investigation, requiring placement of a naso-oesophogeal probe. Unnecessary treatment with drugs such as acid supressing agents (such as proton pump inhibitors [PPIs] or H2-receptor antagonists [H_2RAs]) is not high risk but nevertheless undesirable. Conversely, false negative clinical evaluation could result in delayed investigation or treatment.

4.2.14.1.1 Distress

This review identified studies in which a number of factors were examined that could be included under the general heading of distressed behaviour. These included excessive crying, crying while feeding and the adopting of unusual neck postures which were judged to indicate that the infant or child was likely to be experiencing some discomfort.

The guideline development group noted that 1 observational study of moderate quality showed that excessive crying alone was of no diagnostic use, but a second low quality study found that prolonged crying was associated with an increased likelihood of the child having gastro-oesophageal reflux. The group noted that in this study the presence of GORD (that is, reflux causing significant effects) used a definition of GORD that included 'excessive crying' as a component, so increasing the likelihood of GORD being diagnosed. One observational study did not find 'waking at night' to be a useful marker for the presence of GORD. The group agreed that that this symptom was actually common and had many potential explanations.

The group was therefore more convinced by the findings of the first study and did not consider that there was persuasive evidence that distressed behaviour (including excessive crying) is in itself a reason to suspects or investigate for gastro-oesophageal reflux.

Results from 4 low or very low quality observational studies showed that abnormal posturing was a potentially useful sign of GORD. The group considered that this was rather uncommon, and probably different to the more commonly observed signs of distress in an infant or young child. A particular rare posturing behaviour occasionally observed in children with neurodisabilities which is caused by gastro-oesophageal reflux known as Sandifer's syndrome. However, this has also been observed in neurologically normal children. This is characterised by episodic torticollis with neck extension and/or rotation. The group concluded that consideration should be given to referring any infant or child with persistent back arching or with features of Sandifer's syndrome for specialist assessment and that consideration should be given to performing an upper gastrointestinal examination and, if appropriate, oesophageal pH and impedance monitoring. The group made a specific recommendation to this effect.

4.2.14.1.2 Apnoea

Evidence from 13 observational studies was examined by the guideline development group. The group focused on the results of 2 studies that examined the temporal link between apnoea and reflux. The group believed these were the best designed studies for confirming a link between apnoea and reflux, noting that the other 11 studies reported variable diagnostic usefulness of apnoea for identifying GOR or GORD.

The group accepted that the evidence showed that apnoea and reflux were rarely associated, and therefore not diagnostically useful. Therefore, in the absence of other indicators that gastro-oesophageal reflux was present – such as clinical observation of overt regurgitation in association with the episodes – it would be important to consider other possible causes of apnoea before contemplating investigation for occult reflux. The group therefore made a recommendation that clinicians should be aware that apnoea and apparent life-threatening events are rarely due to gastro-oesophageal reflux, but that if, following an evaluation for other possible causes, reflux was thought to be a possible explanation, consideration should be given to doing a combined intraluminal oesophageal pH and impedance study.

4.2.14.1.3 Epigastric or chest pain

Evidence from 4 observational studies reported varying levels of usefulness of chest or epigastric pain as a pointer to GORD, with no consistent pattern being identified. The evidence in the included studies was from younger children and the inconsistent findings might be explained by their limited ability to describe and locate their symptoms. The guideline development group members believe, based on their clinical knowledge and experience, that retrosternal pain including 'heartburn' and epigastric pain were common symptoms associated with troublesome gastro-oesophageal reflux and that if they were persistent they might well indicate the presence of GORD. The group was aware of published studies in adults showing that epigastric pain and heartburn are reduced by the use of acid suppressing drugs. Therefore, the group concluded that in children who are able to express their symptoms, heartburn was a useful indicator of GORD. The group was sufficiently convinced of the importance of these symptoms that it recommended that if there was persistent heartburn, retrosternal or epigastric pain then a 4 week trial of treatment with a PPI be considered. It further recommended that if this was ineffective or if the symptom returned on discontinuing the treatment, consideration be given to referring the patient for an upper gastrointestinal endoscopy as it would be important to rule out other explanations for the symptom and to look for evidence of gastro-oesophageal reflux oesophagitis.

4.2.14.1.4 Hoarseness

Evidence from 2 observational studies did not finding diagnostic value for hoarseness as a pointer to GORD. While the guideline development group was aware that there is speculation that occult reflux may lead to inflammation of the vocal cords, and hence to various symptoms such as hoarseness, there was no evidence that this was a common presentation in children and young people. Therefore, the group recommended that in the absence of overt regurgitation, hoarseness occurring as the sole symptom did not indicate a need to either investigate or treat for GORD.

4.2.14.1.5 Feeding difficulties

Eight observational studies found limited diagnostic value in using feeding difficulties to identify GORD. The guideline development group noted the variation in reported results and therefore focused on the highest quality studies.

The group reflected on the fact that feeding difficulties were a very common concern in infants and that although occult reflux might be considered a plausible contributor, there was little evidence to support this as a factor and probably many other factors might be more important. The group concluded that in the absence of overt regurgitation, unexplained feeding difficulties (for example feed refusal, gagging or choking) occurring as the sole symptom were not an indication to investigate or treat for GORD.

4.2.14.1.6 Otitis media

The results of 4 observational studies showed varying degrees of usefulness for otitis media being a marker for GORD. The guideline development group debated the plausibility of a physiological link between otitis media and reflux, as its occurrence would require entry of refluxate into the Eustacian canal. However, studies had demonstrated the presence of pepsin (a gastric digestive enzyme) in the middle ear. The group focused on the moderate quality evidence, and based on this it concluded that in situations where an infant presented with recurrent otitis media, reflux could be a potential cause, and therefore that healthcare professionals should be aware that frequently recurring otitis media is a potential complication of gastro-oesophageal reflux.

4.2.14.1.7 Lower respiratory tract infection

Evidence from 7 observational studies showed that previous episodes of pneumonia were a potentially useful marker for GORD. The guideline development group discussed the

mechanism whereby refluxate might be aspirated into the lungs in some susceptible children, especially those with neurodisabilities and premature infants, resulting in recurrent pneumonia.

The group believed that a single episode of pneumonia was a common phenomenon, but if repeated, reflux aspiration should be considered as a possible explanation.

4.2.14.1.8 Faltering growth

Evidence from 5 observational studies showed varied results on the usefulness in terms of likelihood ratios of faltering growth to identify GOR or GORD. The guideline development group concluded that presence of faltering growth could be a marker of GORD, but was concerned that using faltering growth in this way could lead both to inappropriate treatment and to other potential serious causes remaining uninvestigated. The group concluded that, in isolation, faltering growth should not be considered as a likely indicator of GORD.

4.2.14.1.9 Asthma

Evidence from 6 observational studies showed an association between presence of asthma and GORD. The guideline development group acknowledged the association between asthma and GORD but highlighted that the evidence did not demonstrate any causation. The group also highlighted evidence from RCTs that showed that pharmaceutical management of reflux had no effect on refractory asthma.

The group concluded that although the evidence consistently shows an association between asthma and the presence of occult gastro-oesophageal reflux, the clinical significance of this is uncertain. It could be that people with reflux are at greater risk of having asthma as a consequence, but it is just as plausible that asthma itself increases the propensity for gastric contents to enter the oesophagus. If the former was true, then, in principle, effective treatment of the reflux might benefit a patient's asthma and asthma could, in such individuals, be considered a complication of the reflux and hence a form of GORD. However, if the reflux is caused by the asthma, then the reflux tendency might not be of any clinical consequence. The group was aware that some studies had been performed to see if reflux treatment improved asthma control but the results were inconclusive. The group recommended that healthcare professionals should be aware of the association between reflux and asthma but that reflux had not been shown to cause or worsen asthma.

4.2.14.1.10 Chronic cough

Evidence from 5 observational studies showed that chronic cough was of no diagnostic value in identifying GORD. The guideline development group argued that, as with pneumonia and otitis media, reflux could, in principle, cause inflammation in the larynx as discussed in relation to hoarseness and that might lead to a chronic cough. However, it was highlighted that there were a number of potential causes of chronic cough in infants and children and the group concluded that if there was no history of overt regurgitation, the presence of chronic cough alone was not a pointer to the need to investigate or treat for gastro-oesophageal reflux.

4.2.14.1.11 Dental

The evidence from 8 observational studies showed mixed results for the association between dental erosion and reflux. The guidelines development group noted that much of the evidence showing an association was based on children with neurodisabilities. It was also highlighted that many children with neurodisabilities had extensive dental erosion caused by factors other than reflux, such as teeth grinding. However, it was suggested that the pattern of erosion would be different depending on the cause. The group concluded that the evidence was convincing enough to recommend that dental erosion could be due to gastro-oesophageal reflux in children with neurodisabilities.

4.2.14.1.12 Appearance of regurgitation associated with conditions other than GORD

Based on their clinical knowledge, the guideline development group members highlighted a number of clinical manifestations and features, including gastrointestinal and systemic manifestations, which they considered should be recognised as 'red flags' that suggested possible disorders other than gastro-oesophageal reflux in infants presenting with vomiting or regurgitation (see Table R1).

Although clinical experience shows that infants with simple reflux often have effortless regurgitation of feeds, many parents do report episodic forceful regurgitation and this may even be described as 'projectile'. The group considered frequent forceful or projectile regurgitation would be unusual and might indicate an alternative condition such as hypertrophic pyloric stenosis or some other objective disorder. The group recommended that frequent forceful (projectile) vomits should be considered as a possible 'red flag'. Likewise, bile-stained (green) vomits strongly suggest possible intestinal obstruction and this also would be a red flag suggesting a disorder other than GOR. Haematemesis is an important sign. It might be caused by severe erosive oesophagitis due to oesophageal reflux. However, it might also be due to other potentially serious upper gastrointestinal disorders such as gastric or duodenal ulceration or portal hypertension. An exception was in the breastfed infant when haematemesis can be explained by maternal nipple cracking and bleeding with swallowing of blood. In older children swallowed blood, for example from having had a significant nosebleed, might also provide a benign explanation.

Given that in most infants overt regurgitation will be noticed within the first 8 weeks of life and first presentation after 6 months of age was very unusual, the group considered that late presentation (after 6 months of age) should be a red flag for possible alternative diagnosis. It is known that other disorders in infancy might also present in the latter months of the first year with vomiting, for example urinary tract infections.

In addition infants, children and young people who present with regurgitation/vomiting associated with other symptoms may have conditions other than GOR. A wider differential diagnosis requires consideration. When an infant or young child is vomiting in addition to symptoms associated with fever (for example the infant is lethargic and/or irritable), the NICE clinical guideline on feverish illness in children should be referred to. Finally, although relatively rare, when vomiting occurs in relation or combination with symptoms that could also be associated with meningitis, refer to NICE clinical guideline on bacterial meningitis and meningococcal septicaemia.

Those who present with acute onset diarrhoea in addition to vomiting may have gastroenteritis. Those with regurgitation/vomiting associated with chronic diarrhoea or with blood in the stool may have various non-reflux explanations for their condition, for example food allergy (see NICE clinical guideline on food allergy in children and young people). It is suggested that those with an atopic condition (for example infant eczema) or with a close family history of atopic illness might also be at increased risk of food allergy (see NICE clinical guideline on food allergy in children and young people).The guideline development group recognised that some symptoms of a non IgE mediated cows' milk protein allergy can be similar to the symptoms of GORD. They further highlighted that non IgE mediated cows' milk protein allergy might particularly be suspected in infants with atopic symptoms, signs and/or a family history (see NICE clinical guideline on food allergy in children and young people).

4.2.14.2 Consideration of health benefits and resource uses

People seek medical advice due to the presence of symptoms and signs, and health professionals need to be able to use these symptoms and signs in order to identify the condition and differentiate serious from non-serious cases.

The guideline development group stated that having evidence based lists of symptoms and signs available would improve the initial management of examinations and reduce variation in practice. This would ensure that resources are focused on those who need further investigations and treatment, and avoid misdiagnosis and potentially unnecessary tests and treatment.

The group highlighted the fact that a list of symptoms and signs is potentially a rapid and non-invasive approach to identifying children and young people with GOR or GORD. Identifying such clinical manifestations would be considered routine in a standard consultation and there would be no associated additional costs.

4.2.14.3 Quality of evidence

These reviews were based on observational studies. The quality of the evidence ranged from high to very low quality.

Several limitations were identified with the evidence reviewed. The data reported in the studies often did not differentiate between infants that had occult gastro-oesophageal reflux or overt reflux and those where there was no clear indication of reflux of any form. This prevented the guideline development group from making recommendations for those children individually and, instead the group would only recommend if specific signs and symptoms were observed, investigation/treatment be carried out irrespective of the type (or lack of) concurrent gastro-oesophageal reflux.

The second important limitation was the varied and sometimes uncertain definitions used to encompass GORD in the literature. Most of the studies reported an association between a sign or symptom (or a facet of that symptom) and the prevalence of GORD, but the definition of GORD between papers varied to the extent that it would not be appropriate to group outcomes between different papers. The guideline development group therefore examined the definition of GORD, the validity of that definition and made its decision accordingly. For example, those studies where children underwent endoscopic investigation to ascertain if they had erosive esophagitis were looked on more favourably than ones where children were shown to have GORD through a questionnaire that had not been validated. Some authors considered that the term GORD encompassed those found to have an increased reflux index on oesophageal pH monitoring irrespective of whether there was a clinically important consequence arising from it. This clearly differs from the definition used in this guideline which restricts the term to those patients in whom gastro-oesophageal reflux is causing clinically important effects such as symptoms requiring treatment or significant complications such as reflux oesophagitis or aspiration pneumonia.

The third source of bias was heterogeneity between the results of studies. The group noted that there was rarely a consistent pattern in results for any symptom or sign. This could be caused by variation in study designs, included populations, and definition of GORD and outcomes being measured; however, it made it difficult for the group to reach clear conclusions on the use of the results.

The fourth source of bias was imprecision in the results within individual studies which often ranged ‘very useful’ to ‘not useful’. This variance meant that the group was often unable to interpret the results.

4.2.14.4 Other considerations

All recommendations were discussed in relation to possible equality issues, with specific attention being paid to children with neurodisabilities who are known to be at greater risk of developing GORD than the general population.

4.2.15 Recommendations

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.

5. **In infants, children and young people with vomiting or regurgitation, look out for the 'red flags' in Table R1, which may suggest disorders other than GOR. Investigate or refer using clinical judgement.**

Table R1: 'Red flags' symptoms suggesting conditions 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	May suggest infection (also see	Clinical assessment and urine

Symptoms and signs	Possible diagnostic implications	Suggested actions
Fever	the NICE guideline on feverish illness in children)	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

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.

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.**

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.

9. **Recognise the following as possible symptoms of GOR in children and young people:**
    - heartburn
    - retrosternal pain
    - epigastric pain.

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.**

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.**

4.2.16 Research recommendations

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

Why this is important

The evidence reviewed on the symptoms associated with GORD in infants, children and young people with a neurodisability was limited to 3 studies and graded as low- to very low-quality. The lack of a set of clearly defined features makes GORD difficult to recognise and differentiate from other vomiting problems. The proposed study would use objective measures of reflux (such as oesophageal pH monitoring) to assess GORD symptoms in children and young people with neurodisability.

4.3 Risk factors

A number of conditions and factors are commonly believed to be associated with an increased risk of developing GORD. The aim of this review was to identify potentially useful risk factors to aid health professionals with the diagnosis and possibly target investigation.

4.3.1 Review question

What are the risk factors associated with developing GOR/D?

4.3.2 Introduction

It was not practical or useful to assess all possible risk factors, so the guideline development group selected those that were most commonly used in clinical practice:

- chronic lung disease, excluding asthma
- congenital heart disease
- neurodisabilities
- prematurity
- congenital conditions requiring surgical repair
    - hiatal hernia
    - diaphragmatic hernia
    - oesophageal atresia
- a family history of GORD

- obesity.

Individual systematic reviews were undertaken for each of these and the results are reported below. For full details see the review protocol in Appendix E.

Risk factors can be assessed using case–control studies or cohort studies, with the information provided differing depending on the study design used. A retrospective case–control study will provide information on the prevalence of a factor between those who do or do not have a particular outcome, such as oesophagitis. A cohort study will provide information on factors that increase the future risk of developing an outcome.

Study quality was assessed using the GRADE methodology. Cohort or case–control studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias. Outcomes are reported as described in the original papers, so reflect the variation in reporting. Although the decision was taken to use observational studies, because of the differences in study population (such as age), risk factor definition and study design (for example long-term follow-up), the results were reported individually as it was inappropriate to perform a meta-analysis on shared study outcomes.

If reported in the studies, adjusted odds ratios have been extracted. Where odds ratios were not presented in the studies they have been calculated by the NCC Technical Team based on data reported in the studies.

4.3.3 Chronic lung disease

The term ‘Chronic lung disease’ covers a large number of conditions, but the convention for definitions and even the agreed names have changed over recent years, for example bronchopulmonary dysplasia and chronic lung disease of prematurity.

The main two areas identified for further scrutiny were the chronic suppurative lung conditions – that is, bronchiectasis or cystic fibrosis – and chronic lung disease (of prematurity) which can be defined according to dependence on additional oxygen at a particular corrected gestational age for premature infants or at a particular postnatal chronological age. In both cases a potential mechanism for increasing tendency to GOR or GORD could be the increased abdominal pressure created by the difficulty in effective ventilation together with a tendency to cough in the suppurative conditions. However, there are also likely to be confounding factors; for example most babies with chronic lung disease have been or still are premature. Finally, although strictly speaking asthma is also a chronic lung disease, it was not investigated as part of this review, but was investigated separately (see Section 5.2.14.1.9).

4.3.3.1 Description of included studies

The search strategy created for this review can be located in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profiles below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Five observational studies were identified for this review (Akinola et al., 2004; Mezzacappa et al., 2008; El-Serag et al., 2001; Ruigomez et al., 2010; Fuloria et al., 2000). Two were retrospective cohort studies (Akinola et al., 2004; Ruigomez et al., 2010) and 3 were case–control studies (Mezzacappa et al., 2008; El-Serag et al., 2001; Fuloria et al., 2000). Three studies were undertaken in the USA (Akinola et al., 2004; El-Serag et al., 2001; Fuloria et al., 2000), 1 in the UK (Ruigomez et al., 2010) and 1 in Brazil (Mezzacappa et al., 2008). Sample sizes ranged from 136 to 9900 children. The age of the subjects varied from those born prematurely in 3 studies (Akinola et al., 2004; Mezzacappa et al., 2008; Fuloria et al., 2000)

to children aged 1 to 17 years in 1 study (Ruigomez et al., 2010) and children aged 2 to 18 years in another study (El-Serag et al., 2001).

Four studies examined specific chronic lung disorders, including bronchopulmonary dysplasia in 2 studies (Akinola et al., 2004; Mezzacappa et al., 2008), cystic fibrosis in 1 study (Ruigomez et al., 2010) and both cystic fibrosis and bronchiectasis (as separate analyses) in another study (El-Serag et al., 2001). One of these 4 studies (Akinola et al., 2004) also examined severe chronic lung disease defined as oxygen requirement at 36 weeks postmenstrual age. One other study (Fuloria et al., 2000) examined chronic lung disease in general defined as the need for supplemental oxygen at 36 weeks post-conception age. The studies reported different outcomes including GOR in 2 studies (Akinola et al., 2004; Fuloria et al., 2000) and GORD in 3 studies (Mezzacappa et al., 2008; El-Serag et al., 2001; Ruigomez et al., 2010). The settings of the studies included neonatal intensive care units, hospitals and primary care practices.

4.3.3.2 Evidence profile

Table 20: GRADE profile for the association between chronic lung disease and risk of developing GORD

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Bronchopulmonary Dysplasia											
Prevalence and odds ratio for bronchopulmonary dysplasia in children with and without GOR[a]/GORD[b]											
1 (Akinola, 2004)	Retrospective cohort	Very serious[1,2]	None	Serious[3]	Very serious[4]	None	64/87 (74%)	38/50 (76%)	OR: 0.88 (0.39 to 1.97)*	-	Very low
1 (Mezzacappa, 2008)	Retrospective case-control	Very serious[1,5,6]	None	Serious[7]	Very serious[4]	None	33/87 (38%)	44/87 (51%)	Adjusted OR: 0.89 (0.46 to 1.75)[c]	-	Very low
Cystic fibrosis											
Prevalence and odds ratio for cystic fibrosis in children with and without GORD[d,e]											
1 (El-Serag, 2001)	Retrospective case-control	Very serious[7,8]	None	No serious	No serious	None	NR/1980	NR/7920	Adjusted OR: 2.89 (1.97 to 4.25)[f]	-	Low
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[1,9]	None	No serious	Very serious[4]	None	5/1700 (0.3%)	2/4977 (0.04%)	Adjusted OR: 3.3 (0.6 to 18.1)[g]	-	Very low
Bronchiectasis											
Prevalence and odds ratio for bronchiectasis (with or without collapse) in children with and without GORD[d]											
1 (El-Serag, 2001)	Retrospective case-control	Very serious[1,8]	None	No serious	Serious[4]	None	NR/1980	NR/7920	Adjusted OR: 2.28 (1.14 to 4.57)[f]	-	Very low
Chronic lung disease											
Prevalence and odds ratio for chronic lung disease of prematurity in children with and without GOR[h]											
1 (Fuloria, 2000)	Retrospective case-control	Serious[1]	None	Serious[10]	Serious[4]	None	NR	NR	Adjusted OR: 2.1 (1.1 to 3.5)[i]	-	Very low
Severe chronic lung disease											
Prevalence and odds ratio for severe chronic lung disease in children with and without GORa											
1 (Akinola, 2004)	Retrospective cohort	Very serious[1,2]	None	Serious[3]	Very serious[4]	None	46/87 (53%)	30/49 (61%)	OR: 0.71 (0.35 to 1.45)*	-	Very low

CI confidence interval, GOR/D gastro-oesophageal reflux/disease, GORD gastro-oesophageal disease, NR not reported, OR odds ratio

* *Calculated by the NCC technical team based on figures presented within the studies*

[a] *Akinola 2004: diagnostic criteria for GOR - 18 to 24 hour esophageal pH monitoring, infants were identified as positive for GOR if there was ≥10% acid reflux with the glucose water feed or ≥5% acid reflux with formula or breast milk*

[b] *Mezzacappa 2008: diagnostic criteria for GORD - prolonged distal intra-esophageal pH monitoring, reflux index ≥10%*

[c] *OR adjusted for birthweight and postconceptional age at time of pH study*

[d] *El-Serag 2001: diagnostic criteria for GORD – subjects identified from electronic medical records, based on ICD-9 coding of GORD (530.81, 530.10, 530.11, 530.19, 530.3)*

[e] *Ruigomez 2010: diagnostic criteria for GORD – identified by Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Non-specific symptoms such as epigastric pain to idenify cases was not used unless they were recorded alongside reflux symptoms.*

[f] *OR adjusted for age, gender and ethnicity*

[g] *OR adjusted for age, sex, year of diagnosis, visits to primary care physician in the previous year*

[h] Fuloria 2000: diagnostic criteria for GOR - defined as either treatment with anti-reflux medications (metaclopramide, bethanecol, cisparide, cimetidine or ranitidine) or a positive test for GOR. Tests for GOR included esophageal pH probe, upper gastrointestinal contrast studies and microscopic examination of tracheal aspirates for lipid laden macrophages. Tests for GOR were performed and treatment was initiated at the discretion of the attending neonatologist.
[i] OR adjusted for gestational age, gender, race, days on assisted ventilation and days of hospitalisation
[1] Retrospective study design
[2] Unadjusted ORs
[3] Infants less than 32 weeks gestational age admitted to the neonatal intensive care unit
[4] Confidence interval spans multiple interpretations
[5] No details of how bronchopulmonary dysplasia was defined/diagnosed
[6] Not explained which pH test was selected for inclusion as there seems to be more than one per child (235 pH studies in 193 infants)
[7] Birthweight <2000g and gestational age ≤37 weeks
[8] Both the risk factor and outcome based on reliability of coding in medical records
[9] Only 15.3% of GORD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control cohort had been tested for GOR
[10] Very low birth weight premature infants

4.3.3.3 Evidence statements

See Table 20.

4.3.3.3.1 Bronchopulmonary dysplasia

Two studies evaluated the odds of developing GOR or GORD in infants with bronchopulmonary dysplasia, but neither study found an association. The evidence was of very low quality.

4.3.3.3.2 Cystic fibrosis

Two studies evaluated the odds of developing GORD in children and young people with cystic fibrosis. One study reported a statistically significant association, the other did not. The evidence was of low and very low quality respectively.

4.3.3.3.3 Bronchiectasis (with or without collapse)

One study evaluated the odds of developing GORD in infants with bronchiectasis (with or without collapse). The study reported a statistically significant association. The evidence was of very low quality.

4.3.3.3.4 Chronic lung disease

One study evaluated the odds of developing GOR in infants with chronic lung disease. The study found an association between chronic lung disease and GOR. The evidence was of very low quality.

4.3.3.3.5 Severe chronic lung disease

One study evaluated the odds of developing GOR in infants with severe chronic lung disease. The study did not find an association. The evidence was of very low quality.

4.3.3.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in Section 4.3.10.

4.3.3.5 Recommendations

The recommendations covering risk-factors can be found in Section 4.3.11.

4.3.4 Neurodisabilities

Neurodisabilities have hugely differing aetiologies and manifestations. In addition, 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. Further, they may have other problems, such as severe kyphoscoliosis, severe constipation or seizure disorders, that can possibly affect gastrointestinal (GI) motility and intra-abdominal pressure making GOR or GORD more likely via a whole variety of potentially important mechanisms.

4.3.4.1 Description of included studies

Three observational studies were identified for this review (Fuloria et al., 2000; Ruigomez et al., 2010; Halpern et al., 1991). One was a case–control study (Fuloria et al., 2000), 1 a retrospective cohort (Ruigomez et al., 2010) and 1 a retrospective chart review (Halpern et al., 1991). Two studies were undertaken in the USA (Fuloria et al., 2000; Halpern et al., 1991) and the other in the UK (Ruigomez et al., 2010). Sample sizes ranged from 346 to

6677 children. The age of the subjects varied from newborns with a gestational age of 24 to 31 weeks in 1 study (Fuloria et al., 2000) and children aged 1 to 17 years in a second study (Ruigomez et al., 2010). The third study included children ranging from 1 week to 16 years (mean: 15 months).

One study reported on cerebral palsy (Fuloria et al., 2000), 1 on neurologic disabilities including various conditions (cerebral palsy, neurological syndromes with a motor component, various chromosomal anomalies, congenital central nervous system anomalies, mental retardation and delayed development, central nervous system neoplasm and neurological disorders due to neoplasm, trauma, encephalitis and extreme prematurity) (Ruigomez et al., 2010) and 1 on central nervous system (CNS) disease which also included a wide range of conditions (Halpern et al., 1991). The studies reported different outcomes such as GOR in 2 studies (Fuloria et al., 2000; Halpern et al., 1991) and GORD in the other (Ruigomez et al., 2010) defined in various ways. The settings of the studies varied, including a neonatal intensive care unit and primary care practices.

More details on each individual study can be found in the evidence tables (see Appendix I).

4.3.4.2 Evidence profile

Table 21: GRADE profile for the association between neurodevelopmental disorders and risk of developing GORD

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Neurodevelopmental disorders											
Prevalence and odds ratio for cerebral palsy in children with and without GOR[a]											
1 (Fuloria, 2000)	Retrospective case-control	Very serious[1,2]	None	Serious[3]	Very serious[4]	None	15/111 (14%)	31/235 (13%)	OR: 1.03 (0.53 to 1.99)*	-	Very low
Prevalence and odds ratio for neurological disabilities[b] in children with and without GORD[c]											
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[1,5]	None	None	None	None	107/1700 (6.3%)	72/4977 (1.4%)	Adjusted OR: 3.40 (2.50 to 4.70)[d]	-	Low
Prevalence and odds ratio for CNS disease[e] in children with and without GOR[f] – total population											
1 (Halpern et al., 1991)	Retrospective review	Very serious[1,2]	None	None	Very serious[4]	None	101/463 (21.8%)	31/149 (20.8%)	OR: 1.06 (0.68 to 1.67)*	-	Very low
Prevalence and odds ratio for CNS disease[e] in children with and without GOR[f] – subjects >1 year of age											
1 (Halpern et al., 1991)	Retrospective review	Very serious[1,2]	None	None	Serious[4]	None	31/69 (44.9%)	14/57 (24.6%)	OR: 2.51 (1.16 to 5.4)*	-	Very low
Prevalence and odds ratio for CNS disease[f] in children with and without GOR[f] – subjects <1 year of age											
1 (Halpern et al., 1991)	Retrospective review	Very serious[1,2]	None	None	Very serious[4]	None	70/394 (17.8%)	17/92 (18.5%)	OR: 0.95 (0.53 to 1.71)*	-	Very low

CI confidence interval, CNS central nervous system, GOR gastro-oesophageal reflux, GORD gastro-oesophageal disease, OR odds ratio

** Calculated by NCC-WCH technical team based on data reported in the article*

[a] Fuloria 2000: diagnostic criteria for GOR - defined as either treatment with anti-reflux medications (metaclopramide, bethanecol, cisparide, cimetidine or ranitidine) or a positive test for GOR. Tests for GOR included esophageal pH probe, upper gastrointestinal contrast studies and microscopic examination of tracheal aspirates for lipid laden macrophages. Tests for GOR were performed and treatment was initiated at the discretion of the attending neonatologist.

[b] Included cerebral palsy, neurological syndromes with motor component, chromosomal anomalies, congenital central nervous system anomalies, mental retardation and delayed development, central nervous system neoplasm, and neurological disorders due to neoplasm, trauma, encephalitis and extreme prematurity

[c] Ruigomez 2010: diagnostic criteria for GORD - identified by Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Non-specific symptoms such as epigastric pain to identify cases was not used unless they were recorded alongside reflux symptoms.

[d] OR adjusted for age, sex, year of diagnosis, visits to primary care physician in the previous year

[e] Includes mental-motor retardation: including cerebral palsy, developmental delay and mental retardation, seizure disorder, hydrocephalus, microcephaly, intracerebral haemorrhage, cortical blindness, abnormal head CT scan only, abnormal EEG without seizures, porencephalic cyst, spastic quadriplegia, cerebral dysgenesis, meningomyelocele, subarachnoid cyst, abnormal brainstem auditory evoked potential only, multiple CNS diseases, syndromes with CNS involvement.

[f] Halpern 1991: diagnostic criteria for GOR: initial evaluation included an extensive history and physical examination, barium oesophagram, upper gastrointestinal series and 18 to 24 hour esophageal pH monitoring. Documentation of GOR by an abnormal pH score derived from 18 to 24 hour esophageal pH monitoring.

[1] Retrospective study design

[2] Calculated by NCC-WCH, therefore unadjusted odds ratios

[3] Very low birth weight premature infants with chronic lung disease

[4] Confidence interval spans three possible interpretations

[5] Only 15.3% of GORD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control group had been tested for GORD

4.3.4.3 Evidence statements

See Table 21.

4.3.4.3.1 Neurodisabilities

Three studies evaluated the odds of children with neurodisabilities developing GORD. One reported a statistically significant association between a broad range of neurodisabilities (including children with cerebral palsy, neurological syndromes with a motor component, various chromosomal anomalies, congenital central nervous system anomalies, mental retardation and delayed development, central nervous system neoplasm and neurological disorders due to neoplasm, trauma, encephalitis and extreme prematurity) and GORD (evidence of low quality). The second study did not find a statistically significant association between cerebral palsy and GOR (very low quality evidence). The third study reported a statistically significant association between a broad range of CNS diseases (mental–motor retardation: including cerebral palsy, developmental delay and mental retardation, seizure disorder, hydrocephalus, microcephaly, intracerebral haemorrhage, cortical blindness, abnormal head CT scan only, abnormal EEG without seizures, porencephalic cyst, spastic quadriplegia, cerebral dysgenesis, meningomyelocele, subarachnoid cyst, abnormal brainstem auditory evoked potential only, multiple CNS diseases, syndromes with CNS involvement) and GOR in children aged more than 1 year but not for the total population or for children aged less than 1 year (very low quality evidence).

4.3.4.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.3.10.

4.3.4.5 Recommendations

The recommendations covering risk factors can be found in Section 4.3.11.

4.3.5 Prematurity

Extremely premature or low birth weight infants are, by definition, not physiologically completely ready to be outside the womb or feeding enterally. Infants in this group are likely to require very careful nutritional support that often requires a combination of enteral and parenteral feeding in the early stages of their postnatal care followed by a gradual normalisation of feeding with greater maturity. It is assumed that the frequent regurgitation and physiological reflux described in many post-term infants will be a very common problem in this population. This can be further complicated in some premature infants with additional difficulties that may put them at greater risk of emesis following other complications of prematurity, such as nectrotizing enterocolitis. What is less obvious is whether infants who have been delivered prematurely are at greater risk of GORD when they reach corrected postnatal ages during infancy and their subsequent childhood.

4.3.5.1 Description of included studies

Three observational studies were identified for this review (Deurloo et al., 2004; Forssell et al., 2012; Kohelet et al., 2004). Two were retrospective cohort studies (Deurloo et al., 2004; Kohelet et al., 2004) and 1 was a case–control study (Forssell et al., 2012). One study was undertaken in the Netherlands (Deurloo et al., 2004), 1 in Sweden (Forssell et al., 2012) and 1 in Israel (Kohelet et al., 2004). Sample sizes ranged from 134 to 10715. The age of the subjects varied; it included newborns in 2 studies (Kohelet et al., 2004; Deurloo et al., 2004) and children up to age 19 years in the third study (Forssell et al., 2012).

The definition of prematurity was reported in 3 studies (Deurloo et al., 2004; Forssell et al., 2012; Kohelet et al., 2004) and varied. One study (Forssell et al., 2012) examined both prematurity, defined as 33 to 36 weeks gestation, and extreme prematurity, defined as 32 weeks or less gestation. This study examined the association between prematurity and esophagitis at different ages. The studies reported different outcomes including esophagitis in 1 study (Forssell et al., 2012) and GOR in 2 studies (Deurloo et al., 2004; Kohelet et al., 2004). The settings of the studies included a paediatric surgical centre, medical centre and hospital.

More details on each individual study can be found in the evidence tables (see Appendix I).

4.3.5.2 Evidence profile

Table 22: GRADE profile for the association between prematurity and risk of developing GORD

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Prevalence and odds ratio for gestational age ≤32 weeks (versus 37 to 41 weeks) in children with and without subsequent oesophagitisa at the following ages[a]:											
≤9 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[1,2]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 6.82 (4.65 to 10.03)[b]	-	Moderate
10 to 19 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[1,2]	No serious	No serious	Serious[3]	None	NR	NR	Adjusted OR: 2.09 (1.18 to 3.70)[b]	-	Low
Prevalence and odds ratio for gestational age 33 to 36 weeks (versus 37 to 41 weeks) in children with and without oesophagitisa at the following ages[a]:											
≤9 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[1,2]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.75 (1.42 to 2.14)[b]	-	Moderate
10 to 19 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[1,2]	No serious	No serious	Serious[3]	None	NR	NR	Adjusted OR: 1.41 (1.10 to 1.80)[b]	-	Low
Prevalence and odds ratio for prematurity (25 to 36 weeks of gestation) in children with and without GOR[c]											
1 (Kohelet, 2004)	Retrospective cohort	Very serious[1,4]	No serious	No serious	Very serious[3]	None	18/62 (29%)	27/72 (38%)	OR: 0.68 (0.33 to 1.41)*	-	Very low
Prevalence and odds ratio for prematurity (<37 weeks gestation) in children with and without GOR[d]											
1 (Deurloo, 2004)	Retrospective cohort	Very serious[1,4]	No serious	Serious[5]	Serious[3]	None	32/73 (44%)	44/124 (35%)	OR: 1.42 (0.79 to 2.56)*	-	Very low
1 (Deurloo, 2004)	Retrospective cohort	Very serious[1,4]	No serious	Serious[5]	Serious[3]	None	32/73 (44%)	44/124 (35%)	OR: 1.42 (0.79 to 2.56)*	-	Very low

CI confidence interval, GOR gastro-oesophageal reflux, GORD gastro-oesophageal disease, NR not reported, OR odds ratio

** Calculated by NCC-WCH technical team based on data reported in the article*

[a] Forssell 2012: diagnostic criteria for esophagitis - cases of endoscopically verified esophagitis were ascertained through the Patient Register by combining the discharge diagnoses for esophagitis and the procedure codes for upper endoscopy. Confirmation of the diagnosis was based on the explicit diagnosis of esophagitis, combined with the described macroscopic findings at endoscopy that were found in the charts.

[b] OR adjusted for birth weight for gestational age, maternal age and birth order

[c] Kohelet 2004: diagnostic criteria for GOR - 24-hour distal esophageal pH monitoring. Reflux was considered pathologic if the proportion of total time with pH<4 during a 24-hour period exceeded 4%.

[d] Deurloo 2004: diagnostic criteria for GOR - Diagnosed either by clinical symptoms (n=30) or by 24 hour pH measurement (n=43).

[1] Retrospective study design

[2] Oesophagitis based on unverified clinical coding criteria

[3] Confidence interval spans multiple interpretations

[4] Unadjusted odds ratios

[5] Infants with oesophageal atresia

4.3.5.3 Evidence statements

See Table 22.

4.3.5.3.1 Prematurity

Three studies evaluated the odds of developing various outcomes such as esophagitis, GOR or eosinophilic esophagitis in infants who were premature.

One study reported a statistically significant association between prematurity (gestational age of 33 to 36 weeks) and the risk of developing esophagitis (two age groups analysed: 9 years or less and 10 to 19 years). This study also reported a statistically significant association between extreme prematurity (gestational age of 32 weeks or less) and esophagitis at 9 years or less and at 10 to 19 years.

The other 2 studies did not find a statistically significant association between prematurity (defined as 25 to 36 weeks of gestation in 1 study and less than 37 weeks gestation in the other) and GOR.

The evidence ranged from very low to moderate quality.

4.3.5.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.3.10.

4.3.5.5 Recommendations

The recommendations covering risk factors can be found in Section 4.3.11.

4.3.6 Surgical or congenital disorders

This section describes the available evidence in respect of structural or anatomical problems of the oesophagus and upper gastrointestinal system. The conditions that were targeted by the guideline development group were hiatus hernia (where there is a telescoping effect or invagination of the stomach back through the gastro-oesophageal junction), diaphragmatic hernia (where there is an abnormal weakness or discontinuity in the tissue plane between the thorax and abdomen which can result in the herniation of part of the gastro-intestinal tract into the thoracic space) and finally, oesophageal atresia (where there is a congenital abnormality in the development of the oesophagus with or without the trachea that invariably requires a complex surgical repair in infancy and may be linked with other complex congenital abnormalities in a variety of associations). All 3 abnormalities result in extremely disordered anatomy and function and so it is not surprising that symptoms and signs that are indistinguishable from GORD are likely to be observed at presentation but what is possibly less clear is whether problems are likely to persist after surgical correction.

4.3.6.1 Description of included studies

Three observational studies were identified for this review (Abrahams et al., 1970; Steward et al., 1993; Ruigomez et al., 2010). One was a prospective cohort study (Steward et al., 1993), 1 a retrospective cohort (Ruigomez et al., 2010) and 1 a case–control study (Abrahams et al., 1970). One study was undertaken in the UK (Ruigomez et al., 2010), 1 in Australia (Abrahams et al., 1970) and 1 in Northern Ireland (Steward et al., 1993). Sample sizes ranged from 79 to 6677 children. The age of the subjects varied from infants with a mean age of 28 months in 1 study (Steward et al., 1993) to children aged 1 to 17 years in another study (Ruigomez et al., 2010) and children up to the age of 16 years in the third study (Abrahams et al., 1970).

One study reported on hiatal hernia with reflux (Abrahams et al., 1970), 1 on hiatal hernia alone (Steward et al., 1993) and 1 on congenital and acquired hiatus and diaphragmatic hernia and separately on congenital esophageal disorders (Ruigomez et al., 2010). The studies reported different outcomes including erosive esophagitis in 1 study (Steward et al., 1993), GORD in 1 study (Ruigomez et al., 2010) and gastrointestinal symptoms in another study (Abrahams et al., 1970). The settings of the studies included a spastic centre, hospitals and primary care.

More details on each individual study can be found in the evidence tables (see Appendix I).

4.3.6.2 Evidence profile

Table 23: GRADE profile for the association between surgical/congenital disorders (hiatal hernia, diaphragmatic hernia, oesophageal atresia) and risk of developing GORD

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Hiatal hernia with reflux											
Prevalence and odds ratio for hiatal hernia with reflux in children with and without gastrointestinal symptoms[a]											
1 (Abrahams, 1970)	Prospective case-control	Serious[1]	None	Serious[2]	None	None	8/16 (50%)	5/63 (8%)	OR: 11.6 (3.04 to 44.29)*	-	Low
Hiatal hernia											
Prevalence and odds ratio for hiatal hernia in children with and without erosive oesophagitis[b]											
1 (Steward, 1993)	Propsective cohort	Serious[1]	None	No serious	Serious[3]	None	12/20 (60%)	25/75 (33%)	OR: 3.00 (1.09 to 8.28)*	-	Low
Hiatal and diaphragmatic hernia											
Prevalence and odds ratio for hiatus hernia (congenital and acquired hiatus and diaphragmatic hernia) in children with and without GORD[c]											
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[4,5]	None	None	None	None	13/1700 (0.8%)	6/4977 (0.1%)	Adjusted OR: 7.4 (2.7 to 20.3)[d]	-	Low
Oesophageal atresia											
Prevalence and odds ratio for congenital oesophageal disorders (oesophageal atresia, stenosis and traque-oesophageal fistula) in children with and without GORD[c]											
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[4,5]	None	None	None	None	8/1700 (0.5%)	5/4977 (0.1%)	Adjusted OR: 4.3 (1.3 to 14.1)[d]	-	Low

CI confidence interval, GORD gastro-oesophageal disease, OR odds ratio
** Calculated by NCC-WCH technical team based on data reported in the article*
[a] Abrahams 1970: diagnostic criteria for gastrointestinal symptoms - complaints referable to the gastro-intestinal tract (such as vomiting and haematemesis). Each patient was examined fluoroscopically, after the ingestion of 4 to 6 ozs of barium, in the supine position and then prone to see whether a hernia or reflux became visible.
[b] Steward 1993: diagnostic criteria for erosive oesophagitis – endoscopy, oesophagitis was defined by the demonstration of friability, erosions or ulceration of the mucosa
[c] Ruigomez 2010: diagnostic criteria for GORD - identified by Read codes for gastro-oesophageal reflux, reflux esophagitis, esophageal inflammation and heartburn. Non-specific symptoms such as epigastric pain to identify cases was not used unless they were recorded alongside reflux symptoms.
[d] OR adjusted for age, sex, year of diagnosis and visits to primary care physician in the previous year
[1] Unadjusted odds ratios
[2] All children with severe physical disability (cerebral palsy)
[3] Confidence interval spans multiple interpretations
[4] Retrospective study design
[5] Only 15.3% of GORD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control cohort had been tested for GOR

4.3.6.3 Evidence statements

See Table 23.

4.3.6.3.1 Hiatal hernia with reflux

One study evaluated the odds of developing gastrointestinal symptoms in infants with hiatal hernia. The study found a statistically significant association. The evidence was of low quality.

4.3.6.3.2 Hiatal hernia alone

One study evaluated the association between hiatal hernia and the odds of developing erosive oesophagitis. The study found a statistically significant association. The evidence was of low quality.

4.3.6.3.3 Hiatal and diaphragmatic hernia

One study evaluated the odds of developing GORD in infants with hiatus hernia (including both congenital and acquired hiatus and diaphragmatic hernia). The study found a statistically significant association. The evidence was of low quality.

4.3.6.3.4 Oesophageal atresia

One study evaluated the odds of developing GORD in infants with congenital oesophageal disorders (including oesophageal atresia, stenosis and tracheoesophageal fistula). The study found a statistically significant association. The evidence was of low quality.

4.3.6.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.3.10.

4.3.6.5 Recommendations

The recommendations covering risk factors can be found in Section 4.3.11.

4.3.7 Family history of GORD

It is integral to the medical clinical method to inquire regarding relevant family history. Patterns of potential inheritance or increased probability of recurrence have been recognised in many conditions in advance of more detailed genetic explanations. In this section the evidence in relation to GORD between generations is explored.

4.3.7.1 Description of included studies

One cross-sectional study was identified for this review (Murray et al., 2007). This study was undertaken in Northern Ireland and included 1133 adolescents (and their parents) selected from post-primary schools. The age of the subjects ranged from 13 to 17 years. This study reported on family history of epigastric pain, heartburn and acid regurgitation. Outcomes included epigastric pain, heartburn and acid regurgitation in the adolescent defined in various ways.

More details on the study can be found in the evidence tables (see Appendix I).

4.3.7.2 Evidence profile

Table 24: GRADE profile for the association between family history of GORD and risk of developing GORD

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Prevalence and odds ratio for a family history of epigastric pain in adolescents with and without epigastric pain[a] in the following categories:											
Either mother or father has epigastric pain											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[1]	None	14/52 (26.9%)	189/963 (19.6%)	Adjusted OR: 1.74 (0.82 to 3.69)[b]	-	Moderate
Both mother and father have epigastric pain											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[1]	None	4/52 (7.7%)	13/963 (1.3%)	Adjusted OR: 4.15 (0.78 to 22.2)[b]	-	Moderate
Prevalence and odds ratio for a family history of heartburn in adolescents with and without heartburna in the following categories:											
Either mother or father has heartburn											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[1]	None	13/32 (40.6%)	226/988 (22.9%)	Adjusted OR: 2.47 (0.99 to 6.16)[b]	-	Moderate
Both mother and father have heartburn											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	No serious	None	6/32 (18.8%)	42/988 (4.3%)	Adjusted OR: 5.71 (1.62 to 20.1)[b]	-	High
Prevalence and odds ratio for a family history of acid regurgitation in adolescents with and without acid regurgitation in the following categories:											
Either mother or father has acid regurgitation											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[1]	None	15/49 (30.6%)	147/965 (15.2%)	Adjusted OR: 2.54 (1.16 to 5.60)[b]	-	Moderate
Both mother and father have acid regurgitation											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	No serious	None	4/49 (8.2%)	10/965 (1.0%)	Adjusted OR: 6.89 (1.32 to 35.7)[b]	-	High

CI confidence interval, GORD gastro-oesophageal disease, OR odds ratio

[a] Murray 2007: diagnostic criteria - both adolescents and their parents completed a questionnaire including the following questions:

1) how often in the last 3 months have you had pain or discomfort in the place shown in the picture? (a diagram was included showing the epigastric area)

2) how often in the last 3 months have you had heartburn? (burning or ache behind the breastbone)

3) how often in the last 3 months have you got a very sour or acid tasting fluid at the back of your throat?

[b] OR adjusted for adolescent's age, sex, social class, household density (persons per room), BMI category, alcohol intake and smoking status. Analysis was also restricted to children living with both natural parents.

[1] Confidence interval spans multiple interpretations

4.3.7.3 Evidence statements

See Table 24.

4.3.7.3.1 Family history of epigastric pain

One study evaluated the association between family history of epigastric pain and epigastric pain in the adolescent. This study found that a history of epigastric pain in either or both parents is not significant in predicting the odds of epigastric pain in the adolescent. The evidence was of moderate quality.

4.3.7.3.2 Family history of heartburn

One study evaluated the association between family history of heartburn and heartburn in the adolescent. This study found that a history of heartburn in either parent is not statistically significant in predicting the risk of heartburn in the adolescent, but a history of heartburn in both parents is associated with the odds of heartburn in the adolescents. The evidence was of moderate and high quality, respectively.

4.3.7.3.3 Family history of acid regurgitation

One study evaluated the association between family history of acid regurgitation and acid regurgitation in the adolescent. This study found that a history of acid regurgitation in either or both parents is statistically significant in predicting the odds of acid regurgitation in the adolescent. The evidence was of moderate and high quality, respectively.

4.3.7.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.3.10.

4.3.7.5 Recommendations

The recommendations covering risk factors can be found in Section 4.3.11.

4.3.8 Obesity

Obesity is believed by many to increase the risk of developing GORD. The exact mechanism may vary and could include increased intra-abdominal pressure, lower oesophageal sphincter dysfunction or poor diet. The definition of different levels of obesity in children is dependent on the interpretation of the Body Mass Index with reference to age appropriate centile charts for boys and girls. In this section the evidence in relation to obesity as an isolated risk factor GORD is explored.

4.3.8.1 Description of included studies

Seven observational studies were identified for this review (Stordal et al., 2006; Murray et al., 2007; Koebnick et al., 2011; Quitadamo et al., 2012; Elitsur et al., 2009; El-Serag et al., 2001; Pashankar et al., 2009). One was a prospective cohort study (Quitadamo et al., 2012), 3 were cross-sectional studies (Murray et al., 2007; Koebnick et al., 2011; Elitsur et al., 2009) and three were case–control studies (Stordal et al., 2006; El-Serag et al., 2001; Pashankar et al., 2009). Four studies were undertaken in the USA (Koebnick et al., 2011; Elitsur et al., 2009; El-Serag et al., 2001; Pashankar et al., 2009), 1 in Norway (Stordal et al., 2006), 1 in Northern Ireland (Murray et al., 2007) and 1 in Italy (Quitadamo et al., 2012). Sample sizes for the analysis of this risk factor were reported in 3 studies and ranged from 153 to 9900. The age of the subjects varied: they were 7 to 16 years in 2 studies (Stordal et al., 2006; Pashankar et al., 2009), 2 to 18 years in 2 studies (Quitadamo et al., 2012; El-Serag et al.,

2001), 2 to 19 years in 1 study (Koebnick et al., 2011), 13 to 17 years in 1 study (Murray et al., 2007) and children with a mean age of 10.6 years in 1 study (Elitsur et al., 2009).

One study reported on overweight alone (Stordal et al., 2006), 2 studies on overweight or obesity (Quitadamo et al., 2012; Elitsur et al., 2009), 1 study on overweight and obesity separately (Murray et al., 2007), 1 study on obesity (Pashankar et al., 2009), 1 study on morbid obesity (El-Serag et al., 2001) and 1 study on overweight, moderate obesity and extreme obesity separately (Koebnick et al., 2011). The studies reported different outcomes including GORD in 3 studies (Koebnick et al., 2011; Elitsur et al., 2009; El-Serag et al., 2001), a positive reflux symptom score in 2 studies (Quitadamo et al., 2012; Pashankar et al., 2009), a positive GORD symptom score in 1 study (Stordal et al., 2006) and epigastric pain, heartburn and acid regurgitation in 1 study (Murray et al., 2007) defined in various ways. The settings of the studies included a paediatric outpatient's clinic, post-primary schools, medical offices, hospitals, a paediatric gastroenterology clinic and an obesity clinic.

More details on each individual study can be found in the evidence tables (see Appendix I).

4.3.8.2 Evidence profile

Table 25: GRADE profile for the association between obesity and risk of developing GORD

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Overweight											
Prevalence and odds ratio for overweight in children with and without GORD[a]											
1 (Stordal, 2006)	Prospective case control	Serious[1]	No serious	Serious[2]	Serious[3]	None	NR	NR	Adjusted OR: 1.6 (1.1 to 2.4)[b]	-	Very low
Prevalence and odds ratio for overweight in children with and without epigastric pain[c]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[3]	None	NR	NR	Adjusted OR: 1.09 (0.49 to 2.40)[d]	-	Low
Prevalence and odds ratio for overweight in children with and without heartburn[c]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[3]	None	NR	NR	Adjusted OR: 1.06 (0.35 to 3.21)[d]	-	Low
Prevalence and odds ratio for overweight in children with and without acid regurgitation[c]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[3]	None	NR	NR	Adjusted OR: 1.64 (0.72 to 3.72)[d]	-	Low
Prevalence and odds ratio for overweight in children with and without GORD[e] at the following ages:											
2 to 5 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 0.95 (0.85 to 1.07)[f]	-	Moderate
6 to 11 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 0.99 (0.87 to 1.12)[f]	-	Moderate
12 to 19 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.08 (1.01 to 1.15)[f]	-	Moderate
Overweight/Obesity											
Prevalence and odds ratio for overweight/obesity in children with and without a positive reflux score[g]											
1 (Quitadamo, 2012)	Prospective cohort	Serious[5]	No serious	No serious	No serious	None	29/49 (59%)	30/104 (29%)	OR: 3.58 (1.76 to 7.28)*	-	Moderate
Prevalence and odds ratio for overweight/obesity in children with and without GORD[h]											
1 (Elitsur, 2009)	Retrospective chart review	Very serious[4,6]	No serious	No serious	Serious[3]	None	237/491 (48%)	108/247 (44%)	OR: 1.2 (0.88 to 1.63)*	-	Very low

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Obesity											
Prevalence and odds ratio for obesity in children with and without a positive reflux symptom score[i]											
1 (Pashankar, 2009)	Prospective case-control	No serious	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 7.4 (1.7 to 32.5)[j]	-	High
Prevalence and odds ratio for obesity in children with and without epigastric pain[c]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[3]	None	NR	NR	Adjusted OR: 0.84 (0.20 to 3.65)k	-	Low
Prevalence and odds ratio for obesity in children with and without heartburnc											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[3]	None	NR	NR	Adjusted OR: 0.84 (0.11 to 6.60)[d]	-	Low
Prevalence and odds ratio for obesity in children with and without acid regurgitation[c]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[3]	None	NR	NR	Adjusted OR: 3.46 (1.24 to 9.69)[d]	-	Moderate
Moderate obesity (BMI for age ≥95th percentile or a BMI ≥30kg/m²)											
Prevalence and odds ratio for moderate obesity in children with and without GORD[e] at the following ages:											
2 to 5 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 0.92 (0.80 to 1.06)[f]	-	Moderate
6 to 11 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	Serious[3]	None	NR	NR	Adjusted OR: 1.16 (1.02 to 1.32)[f]	-	Low
12 to 19 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.16 (1.07 to 1.25)[f]	-	Moderate
Extreme/morbid obesity											
Prevalence and odds ratio for extreme obesity in children with and without GORD[e] at the following ages:											
2 to 5 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	Serious[3]	None	NR	NR	Adjusted OR: 1.26 (0.95 to 1.68)[f]	-	Low
6 to 11 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	Serious[3]	None	NR	NR	Adjusted OR: 1.32 (1.13 to 1.56)[f]	-	Low
12 to 19 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[4]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.40 (1.28 to 1.52)[f]	-	Moderate

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GORD	No GORD	Relative (95% CI)	Absolute (95% CI)	Quality
Prevalence and odds ratio for morbid obesity in children with and without GORD[k]											
1 (El-Serag, 2001)	Retrospective case-control	Very serious[4,7]	No serious	No serious	Serious[3]	None	NR/1980	NR/7920	Adjusted OR: 1.90 (1.17 to 3.02)[l]	-	Very low

BMI body mass index, CI confidence interval, GORD gastro-oesophageal disease, kg kilogram, m metre, NR not reported, OR odds ratio

[*] Calculated by NCC-WCH technical team based on data reported in the article

[a] Stordal 2007: diagnostic criteria for GORD - GORD if 3 or more points on a questionnaire. Overweight and obesity were defined as BMI corresponding to an adult BMI above 25 and 30, respectively.

[b] Odds ratio adjusted for age, gender and asthma

[c] Murray 2007: diagnostic criteria - both adolescents and their parents completed a questionnaire including the following questions:

1) how often in the last 3 months have you had pain or discomfort in the place shown in the picture? (a diagram was included showing the epigastric area)

2) how often in the last 3 months have you had heartburn? (burning or ache behind the breastbone)

3) how often in the last 3 months have you got a very sour or acid tasting fluid at the back of your throat?

BMI was calculated as body weight (kg) divided by the square of standing height (m). Adolescent BMI was categorised into normal, overweight and obese according to the age-sex specific thresholds of Cole et al).

[d] Odds ratio adjusted for age, sex, social class, household density (persons per room), smoking, alcohol and passive smoking

[e] Koebnick 2011: diagnostic criteria - International Classification of Disease codes (ICD-9 code 530.81). GORD diagnosis was validated in a random subsample of about 5% of cases (n=480) by confirming diagnosis codes for GORD from physician's notes in the electronic medical record. Overweight and obesity was defined based on the sex-specific BMI for age growth charts developed by the CDC and WHO definitions for overweight and obesity in adults. Normal weight: BMI for age ≥5th and <85th percentile. Overweight: BMI for age ≥85th percentile or a BMI ≥25kg/m². Moderately obese: BMI for age ≥95th percentile or a BMI ≥30kg/m². Extremely obese: BMI for age ≥1.2 x 95th percentile or a BMI ≥35kg/m²

[f] Odds ratio adjusted for sex, race and age within each age group

[g] Quitadamo 2012: diagnostic criteria for positive reflux score- during the clinic visit, children's esophageal symptoms (heartburn, epigastric pain, vomiting and regurgitation, irritability with meals, dysphagia and/or odynophagia, respiratory symptoms and hematemesis) during the preceding 2 months were recorded using a standardized questionnaire. The severity and frequency of symptoms were classified into different grades based on a scale used in previous studies. A score for each symptom and a total symptom score were calculated. Overweight/obesity: height, weight, BMI and waist circumference were determined for each participant. Based on the Institute of Medicine definitions, subjects were classified according to BMI as underweight - BMI<5th percentile, normal weight - BMI 5th to 85th percentile, overweight - BMI 85th to 95th percentile and obese - BMI >95th percentile and according to waist circumference in children with waist circumference <75th percentile, from 75th to 90th percentile and >90th percentile

[h] Elitsur 2009: diagnostic criteria for GORD – histology, the histological reports were based on assessment of at least 3 biopsies obtained from the distal esophagus. BMI status was defined as follows: normal weight – BMI <85th percentile, overweight - BMI between 85th and 95th percentiles, obese – BMI >95th percentile

[i] Pashakanar 2009 diagnostic criteria: All children were interviewed in person using a standard questionnaire (completed by parents if child younger than 10 years). The questionnaire consists of a history of any sickness in the last 2 weeks and 5 symptoms experienced over the last week (vomiting, nausea, heartburn, regurgitation and dysphagia). A score was given for each symptom and a validated total score of 3 or more was considered a positive reflux symptom score. Obesity: weight and height were measured by experienced nursing assistants. BMI calculated as weight divided by height². Obesity defined as BMI greater than 95th percentile for age and sex on growth charts from the Centre for Disease Control

[j] Odds ratio was adjusted for age, sex, race and caffeine exposure.

[k] El-Serag 2001: diagnostic criteria for GORD - based on ICD-9 coding of GORD (530.81, 530.10, 530.11, 530.19, 530.3). Morbid obesity diagnosed according to ICD-9 codes.

[l] Odds ratio adjusted for age, gender and ethnicity

[1] Presence of GORD based on questionnaire rather than objective diagnostic test

[2] Population included children with asthma

[3] Confidence interval spans multiple interpretations

[4] Retrospective study design

[5] *Positive reflux score not defined*
[6] *Unadjusted odds ratios*
[7] *Both the risk factor and outcome based on reliability of coding in medical records*

4.3.8.3 Evidence statements

See Table 25.

4.3.8.3.1 Overweight

Three studies evaluated the odds of developing symptoms of GOR in children and young people who were overweight. One study reported a statistically significant association between being overweight and a positive GORD symptom score. A second study did not find a statistically significant association between being overweight and the risk of developing epigastric pain, heartburn or acid regurgitation. A third study which looked at the association between being overweight and GORD at different ages found a statistically significant association at 12 to 19 years but not at 2 to 5 years or at 6 to 11 years. The evidence was of very low to low quality.

4.3.8.3.2 Overweight/obesity

Two studies evaluated the odds of developing a positive reflux score or GORD in children and young people who were overweight or obese. One study reported a statistically significant association between being overweight or obese and a positive reflux score, but the other did not find a statistically significant association between being overweight or obese and GORD. The evidence was of very low to moderate quality.

4.3.8.3.3 Obesity

Two studies evaluated the risk of developing various outcomes including a positive reflux symptom score, epigastric pain, heartburn and acid regurgitation in children and young people who were obese. One study reported a statistically significant association between obesity and a positive reflux symptom score. The other study which looked at the association between obesity and epigastric pain, heartburn or acid regurgitation found a statistically significant association between obesity and acid regurgitation but not between obesity and epigastric pain or heartburn. The evidence was of low to high quality.

4.3.8.3.4 Moderate obesity (BMI for age on or above 95th percentile or a BMI of 30kg/m² or more)

One study evaluated the risk of developing GORD at different ages (3 age groups analysed: 2 to 5 years, 6 to 11 years and 12 to 19 years) in children and young people who were moderately obese. The study found a statistically significant association at 6 to 11 years and at 12 to 19 years, but not at 2 to 5 years. The evidence was of very low to low quality.

4.3.8.3.5 Extreme/morbid obesity

Two studies evaluated the association between extreme or morbid obesity and the risk of developing GORD. One study reported a statistically significant association between morbid obesity and GORD. The other study which looked at the association between extreme obesity and the risk of developing GORD (3 age groups analysed: 2 to 5 years, 6 to 11 years and 12 to 19 years) found a statistically significant association at 6 to 11 years and at 12 to 19 years, but not at 2 to 5 years. The evidence was of very low to low quality.

4.3.8.4 Evidence to recommendations

The evidence to recommendations covering risk factors can be found in Section 4.3.10.

4.3.8.5 Recommendations

The recommendations covering risk factors can be found in Section 4.3.11.

4.3.9 Health economics profile

No health economic data was identified on risk factors and no health economic evaluation was undertaken.

4.3.10 Evidence to recommendations

4.3.10.1 Relative value placed on the risk factors considered

The guideline development group considered that it was important to recognise risk factors for gastro-oesophageal reflux disease. Depending on the size of the associated risk, this could help in deciding whether to undertake investigation, and if the risk factor was reversible, it could potentially inform the approach to therapy for GORD.

4.3.10.2 Consideration of clinicalusefulness of risk factor

No criteria were pre-specified for judging the usefulness of a risk factor. The guideline development group focused its attention on the quality of studies and level of imprecision reported in the results. It was noted that the available evidence was limited in quantity and quality and therefore the group relied on their clinical experience when making recommendations.

4.3.10.2.1 Chronic lung disease

Five studies on chronic lung disease were available, but the usefulness of this evidence was limited by the variation between studies in which lung condition was being investigated and the quality of analysis. The evidence suggested a possible association between cystic fibrosis (CF) and gastro-oesophageal reflux, but the guideline development group was concerned about the quality of the included studies and inconsistency between them. Interestingly, the group was aware that a significant proportion of children with CF are treated with PPIs for another reason (to potentiate the effect of their pancreatic enzyme replacement) which may also be treating some of the manifestations of GORD. The evidence for other lung conditions showed even greater uncertainty. The group therefore decided that no recommendation could be made for or against lung disease as a risk factor for GORD. Asthma is considered under a different section (see Section 5.2.14.1.9).

4.3.10.2.2 Congenital heart disease

Although the guideline development group considered the possibility that congenital heart disease might also be a risk factor for gastro-oesophageal reflux disease, no evidence was found to support this and so the recommendations do not include it as a risk factor.

4.3.10.2.3 Neurodisabilities

The guideline development group members were aware from their own clinical knowledge that severe regurgitation, vomiting or gastro-oesophageal reflux disease is an important complication in children with complex severe neurodisability, including more severe forms of cerebral palsy. Only 3 studies were identified that measured this risk factor, and of these, only 1 presented adjusted odds ratios. This supported the group's experience that neurodisability was a risk factor for developing GORD, and so it was recommended that this be included as a risk factor.

The group recognise that the literature is hampered by vague generalisations and a failure to look at specific diagnoses in assessing the problem. Similarly, children with these problems are often suffering a variety of problems that may be contributing to complex feeding problems, chest disease, pain, faltering growth and emesis. This makes the description of the problem as GOR or GORD of debatable value.

4.3.10.2.4 Prematurity

The guideline development group discussed the risk of GORD in premature infants and those who had a history of prematurity. As with other risk factors, there was limited data available. Of the 3 available studies, 2 did not find that premature infants were subsequently at greater risk of developing GOR, but these studies reported unadjusted odds ratios and the evidence was very low quality. The third study did report adjusted odd ratios and concluded prematurity was a risk factor for subsequent developing esophagitis. The group focused on this study as it reported an unambiguous complication of reflux and used robust methods to analyse the data. Based on this finding, the group recommended that prematurity be listed as a risk factor for subsequently developing GORD.

However, the guideline development group was unsure if this conclusion should apply to infants during the initial phase of prematurity. No studies were identified that could be assessed according to the chosen criteria and methodology on the premature infants while they were still premature (and being cared for on the neonatal unit). The evidence described above was based on children and young people who had been born prematurely and went on later to develop symptoms.

The group discussed their experience, which suggested that there were higher rates of overt reflux in premature infants for the reasons outlined in the section introduction; that is, it was proposed that higher rates of reflux are likely to be caused by the relative immaturity of gastrointestinal system in this group together with other factors. The group debated whether the higher rates of reflux observed was normal physiology or abnormal (pathology) and whether it would require treatment or if treatment offered to older infants was potentially harmful. No conclusion could be reached and no recommendation was made on the management of reflux in premature infants. Similarly, it was agreed that detailed suggestions in terms of complex feeding regimes for hospital neonatal units was beyond the scope of this guideline.

4.3.10.2.5 Surgical or congenital disorders

Evidence from 3 observational studies showed an association between congenital disorders and reflux symptoms. The evidence, though limited, matched the guideline development group's experience that congenital disorders were risk factors for developing GORD. Furthermore, the group highlighted that children with congenital disorders often developed severe GORD from a very early age, and that this required surgical correction. Given the evidence and their own clinical experience, the group felt it was appropriate to recommend that congenital disorders are a risk factor for GORD.

4.3.10.2.6 Family history of GORD

Only 1 observational study was found. This showed a link between family history of GORD and reports of GORD in children and young adults. The study was prospective and provided adjusted odds ratios, and was graded as moderate to high quality evidence. The results matched the guideline development group members' own experience of family history of GORD. The group interpreted the results to possibly suggest that common lifestyle factors within families, such as diet, could contribute to the observed link between parents and children reporting symptoms of GOR. The group thought it was unlikely that a simple genetic component could explain all the outcomes.

The included study focused on older children and young adults. Therefore, it was unknown what effect family history would have on younger children and infants. However, it was agreed by the group that lifestyle factors would take a considerable time to manifest themselves, so it would be older children and young adults where this finding would be most relevant.

The group concluded that a family history of GOR could be a useful risk factor and that a recommendation could be made on this.

4.3.10.2.7 Obesity

Results from 7 observational studies showed an association between weight and symptoms of GOR. The available studies were undertaken in older children and young adults. This finding matched the experience of guideline development group members that excess weight was associated with GORD. The group believed that excess weight was an issue that developed with age; therefore the results of this study were appropriate for the population of interest. There was a concern that obesity and GORD could both be linked to lifestyle, and this was not adjusted for in the analysis. However, it was concluded that obesity was still useful as a risk factor, and a recommendation could be made on obesity as a risk factor for GORD.

The group did not discuss what affect weight reduction would have on GORD. However, the group agreed that healthy eating, regular exercise and, where necessary, safe weight loss programmes are likely to be beneficial for all obese children and adults as they may reduce a number of potentially serious co-morbidities.

4.3.10.3 Consideration of clinical benefits and harms

Risk factors are important because when they are present, they may influence the decision to investigate or to treat for GORD. For example, recognition that neurodisability is an important risk factor could justify a decision to investigate or treat a child or young person who otherwise may not be investigated or treated for GORD. The decision to give a trial of acid suppression therapy should be influenced by the presence of a significant neurodisability as specified in Recommendation 30. Failure to recognise GORD could have significant consequences because effective treatments might be delayed. On the other hand, children and young people without risk factors should have a higher threshold for deciding to investigate or treat, because the likelihood of GORD is less. Unnecessary investigation can have adverse consequences. Endoscopy is usually performed under sedation or more frequently under general anaethesia in children, and there are small but associated risks. Oesophageal pH monitoring can be a somewhat distressing investigation, requiring placement of a naso-oesophogeal probe. Unnecessary treatment with drugs such as acid suppressing agents (for example PPIs, H_2RAs) is not high risk but nevertheless undesirable. Conversely, false negative clinical evaluation could result in delayed investigation or treatment.

4.3.10.4 Consideration of health benefits and resource uses

Discussion within the guideline development group highlighted that simple, sensitive and specific tests do not exist for this condition. Further, it is impractical to use diagnostic testing that is available for GORD in most clinical settings, and especially in primary care. The cost of equipment, training and time required would be prohibitive. Therefore, initial diagnosis has to be based on risk factors, symptoms and signs, and examination.

4.3.10.5 Quality of evidence

All the reviews were based on observational studies. The main sources of bias in these were: retrospective study design; no adjustment for confounding factors in roughly half of the studies; and imprecision in the results, which meant that usefulness of a risk factor was uncertain. The evidence was of very low to high quality.

4.3.10.6 Other issues

No equality issues were specified for this question.

4.3.11 Recommendations

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.

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.**

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)**

4.3.12 Research recommendations

No research recommendations in this area.

4.4 Indications for investigation and treatment

Healthcare professionals have to base their initial management decisions on the symptoms, signs and risk factors that are presented. The labels GOR and GORD (and other synonyms) are used to describe a number of specific conditions caused by the effects of reflux. In addition, reflux and vomiting are common symptoms in other potentially more serious conditions. The aim of these questions was to help healthcare professionals decide which symptoms, signs and risk factors indicated the need for which tests and treatments, if any.

4.4.1 Review questions

- Which symptoms, signs and risk factors indicate the need for which investigations?
- Which symptoms, signs and risk factors indicate the need for which treatment?

For full details see review protocol in Appendix E.

4.4.2 Description of included studies

It was agreed that undertaking a specific systematic review on these questions was unlikely to identify any additional useful information. Therefore, the guideline development group used the result of the reviews on natural course of overt regurgitation (see Section 4.1), symptoms and signs (see Section 4.2), and risk factors (see Section 4.3) in conjunction with their clinical experience to address these questions.

4.4.3 Evidence profile

None.

4.4.4 Evidence statements

None.

4.4.5 Health economics profile

No health economic data was identified on indications for investigation and treatment and no health economic evaluation was undertaken.

4.4.6 Evidence to recommendations

4.4.6.1 Relative value placed on the outcomes considered

The relative values placed on the outcomes considered are discussed elsewhere in the guideline in relation to natural course of overt regurgitation (see Section 4.1), symptoms and signs (see Section 4.2), and risk factors (see Section 4.3) in conjunction with their clinical experience to address these questions.

4.4.6.2 Consideration of clinical benefits and harms

The guideline development group discussed the fact that in certain areas there was a lack of consensus on when to perform specific investigations.The group considered a number of diagnostic tests that are commonly used to investigate the potential effect of reflux, these being: upper gastrointestinal contrast studies (typically, the barium meal); upper gastrointestinal endoscopy with biopsy; and oesophageal pH monitoring, which in recent years has often been performed with impedance monitoring (which can detect non-acid GOR). To undertake and interpret the results of these tests requires specialist training, which is beyond the remit of this guideline. The group therefore limited their discussion to the indications for undertaking such investigations. There were 2 main reasons why investigation might be undertaken: firstly, where the diagnosis of GORD was uncertain and needed confirmation or other diagnoses needed to be ruled out; and secondly, to assess the response to treatment (for example effective acid suppression or healing of oesophagitis). Establishing a correct diagnosis was clearly fundamentally important as there are conditions that can mimick GORD and may be serious in their own right, such as congenital intestinal malrotation. If symptoms persist despite treatment with an acid supressing agent (such as a PPI) this could be for a variety of reasons, but it is important to confirm that acid suppression has been effective. In children and young people with erosive oesophagitis it is impossible to know whether or not treatment has achieved oesophageal healing without performing an upper gastrointestinal biopsy. However, unnecessary investigation has potential adverse consequences and needs to be avoided.

4.4.6.3 Consideration of health benefits and resource uses

Early investigation can enable prompt initiation of effective treatments for GORD resulting in better patient outcomes. It can also avoid the use of unnecessary and ineffective treatments. However, it is important to avoid unnecessary investigation because this is associated with potential adverse effects for patients and carries with it significant resource implications. For example, most children with overt regurgitation do not require an upper gastrointestinal endoscopic examination. Identifying the indications for investigation was therefore an important priority for the guideline.

4.4.6.4 Quality of evidence

As detailed above, the recommendations for this review question were written from evidence results from the following reviews in conjunction with the experience of members of the guideline development group. For details on the quality of the evidence for the contributing

reviews refer to natural course of overt regurgitation (see Section 4.1), symptoms and signs (see Section 4.2), and risk factors (see Section 4.3) in conjunction with their clinical experience to address these questions.

4.4.6.5 Other considerations

No specific equality issues were raised in relation to this question.

The guideline development group agreed that upper gastrointestinal (GI) contrast studies were sometimes indicated when a condition other than GORD was suspected. For example, if a child had bile stained vomiting it would be important in order to rule out an obstructive disorder. This was particularly urgent in infants with bile stained vomiting in whom malrotation and volvulus are a special concern, and in such cases they recommended that an upper GI contrast study be performed urgently on the same day. In children and young people with GORD, an upper GI contrast study might be necessary to look for certain specific complications, such as an oesophageal stricture. The group therefore advised that an upper GI contrast be performed in those with GORD who complain of swallowing difficulty (dysphagia). The group considered progressively worsening or frequent forceful vomiting of feeds in young infants would be unusual and might indicate an alternative condition such as hypertrophic pyloric stenosis requiring referral and assessment on the same day as presentation. The group specifically advised that upper GI contrast studies have no role either in the diagnosis or assessment of severity of GORD. A contrast study does not accurately reflect the pathophysiological processes of GOR. Moreover, GOR is an episodic phenomenon in most individuals, whereas the contrast study provides a very limited timeframe of investigation. Avoidance of unnecessary radiation exposure was seen by the group as a very important priority.

The group agreed that upper GI endoscopy should be the main investigation for those with clinical symptoms suggestive of oesophagitis (oesophageal inflammation). They advised referral for consideration of an endoscopic examination in a variety of settings. This included those with retrosternal, epigastric or upper abdominal pain that needs ongoing medical therapy or is refractory to medical therapy, unexplained distress in children and young people with communication difficulties, and those with features of Sandifer's syndrome. Haematemesis was an important indication that may require assessment on the same day because it can be caused by erosive oesophagitis, among other explanations. An exception was the breastfed infant in whom heamatemesis was explained by blood swallowing associated with maternal nipple bleeding. In older children swallowed blood might also provide a benign explanation, such as having had a significant nosebleed. Those presenting with melaena (black, foul-smelling stool) should also be referred potentially for assessment on the same day, because this indicates a serious upper gastrointestinal haemorrage, although this would be an uncommon presentation of erosive oesophagitis. Unexplained iron-deficiency anaemia was an indication because, among other possibilities, erosive oesophagitis can sometimes be responsible for this condition. Children and young people with dysphagia should be referredfor endoscopy possibly on the same day because reflux oesophagitis can lead to oesophageal strictures, although other conditions may also be responsible. Infants and young children with faltering growth or feeding aversion can have a variety of explanations that require consideration, but the group concluded if these were otherwise unexplained, and occurred in the presence of overt regurgitation, reflux oesophagitis was a plausible explanation and would require investigation. Evidence from the review of the natural history of GOR indicated that most infants recover by age 1 year. In those in whom overt regurgitation persists, the group believed that an underlying problem with reflux oesophagitis might be contributory and so advised referral for possible endoscopy.

The guideline development group considered that an oesopheageal pH study, ideally combined with impedance monitoring, was an appropriate investigation for those with:

- suspected recurrent aspiration pneumonia

- unexplained apnoeas
- unexplained non-epileptic seizure-like events
- suspected diagnosis of Sandifer's syndrome
- unexplained upper airway inflammation
- dental erosion associated with neurodisability
- frequent otitis media.

It was also considered an appropriate investigation when considering moving forward to a possible need for fundoplication.

The oesopheageal pH study performed over a period of approximately 24 hours gives an ongoing indication of acid reflux into the oesophagus. The impedance study provides additional information, detecting episodes of non-acid GOR. If caused by reflux, the conditions listed above might well be associated with evidence of such reflux and in the case of episodic phenomena, such as aponeas and seizure-like events, it might even be possible to show a temporal association between reflux episodes and such events.

The group agreed that oesophageal pH monitoring without impedance monitoring was valuable in those where ensuring effective acid suppression was thought clinically important; for example if reflux oesophagitis was not responding as expected to acid suppression therapy.

The group recognised that urinary tract infection in infants can present with both vomiting/regurgitation and faltering growth. They also suspected that such infants might sometimes appear distressed. Such symptoms might mimick those of overt regurgitation due to GOR. The group therefore recommended that infants with those symptoms such be investigated for a possible urinary tract infection. They also recommended investigating for a urinary tract infection if overt regurgitation began for the first time in an infant over 8 weeks. Evidence from the natural history review indicated that onset after 8 weeks was somewhat uncommon.

4.4.7 Recommendations

15. **Do not offer an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of GORD in infants, children and young people.**

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.**

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.**

18. **Offer an upper GI contrast study for children and young people with a history of GORD presenting with dysphagia.**

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.**

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 R1)
- melaena (black, foul-smelling stool; assessment to take place on the same day if clinically indicated; also see Table R1)
- 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.

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 Chapter 9)
    - a suspected diagnosis of Sandifer’s syndrome.

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.**

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.

4.4.8 Research recommendations

No research recommendations in this area.

5 Initial management of GOR and GORD

5.1 Infant positioning

Positional management involves assessing if altering the position an infant is placed in reduces symptoms of GOR. Historically, it was considered good practice to place infants in the front (prone) or side position for sleep to help with GOR, but as the link between sudden infant death syndrome (SIDS) and placing infants to sleep on their front has become clear, this advice has been withdrawn. However, interest has remained in altering the angle at which infants may be positioned while in the back (supine) position.

5.1.1 Review question

What is the effectiveness of a clearly described positional intervention in comparison with no positional management and alternative clearly described positional interventions?

For full details see review protocol in Appendix E.

5.1.2 Description of included studies

The search strategy created for this review can be found in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profile below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Seven randomised controlled trials with a crossover design were included in this review (Bagucka et al., 1999; Bhat et al., 2007; Ewer et al., 1999; Orenstein et al., 1983a; Orenstein et al., 1983b; Orenstein et al., 1990; Tobin et al., 1997). Three studies were from the USA (Orenstein et al., 1983; Orenstein et al., 1983b; Orenstein et al., 1990), 2 from the UK (Bhat et al., 2007; Ewer et al., 1999), 1 from Australia (Tobin et al., 1997) and 1 from Belgium (Bagucka et al., 1999).

Sample sizes ranged from 9 to 90 infants. The age of the subjects included infants born prematurely in 2 studies (Bhat et al., 2007; Ewer et al., 1999) and infants less than 6 months in the other 5 studies (Bagucka et al., 1999; Orenstein et al., 1983; Orenstein 1983b; Orenstein et al., 1990; Tobin et al., 1997).

The settings of the studies included medical centres, an asthma centre, paediatric gastroenterology units, a neonatal intensive care unit and a clinical research centre.

The definition of GOR varied, including criteria such as oesophageal pH reflux index and histological criteria used to indicate the presence of oesophagitis. The studies examined a range of different positioning interventions – this variation meant that the data could not be meta-analysed. Though not explicitly stated in all studies, the type of position examined was sleeping and/or resting position in 4 studies (Orenstein et al., 1983a; Orenstein et al., 1983b; Orenstein et al., 1990; Tobin et al., 1997) and sleeping position in 2 studies (Bhat et al., 2007; Bagucka et al., 1999). In the seventh study (Ewer et al., 1999) position was not altered during or immediately after feeds.

More details on the individual studies can be found in the evidence tables (see Appendix I).

5.1.3 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

The following GRADE profiles are shown below:

- GRADE findings for comparison of prone with supine positioning
- GRADE findings for comparison of prone head elevated (at 30 to 45 degrees) positioning in harness with infant seat elevated at 60 degrees
- GRADE findings for comparison of head elevated prone positioning with flat prone positioning
- GRADE findings for comparison of infant seat elevated at 60 degrees with horizontal prone positioning
- GRADE findings for comparison of supine reversed Trendelenburg position of 10 degrees with flat supine positioning
- GRADE findings for comparison of prone with right lateral positioning
- GRADE findings for comparison of left lateral with right lateral positioning
- GRADE findings for comparison of prone with left lateral positioning
- GRADE findings for comparison of left lateral with supine positioning.

Table 26: GRADE profile for comparison of prone with supine positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	Supine	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Bhat et al 2007)	RCT – crossover	Very serious[1,2,3,4]	NA	Serious[5]	None	Yes[6]	n=21 Median (range): 0 (0 to 11.4)	n=21 Median (range): 3 (0 to 15.4)	NC	p=0.002	Very low
1 (Tobin et al 1997)	RCT – crossover	Serious[3,4]	NA	None	None	None	n=24 Mean (Standard deviation [SD]): 6.72 (5.2)	n=24 Mean (SD): 15.33 (11.4)	Mean Difference [MD]: −8.00 (−12.83 to −3.17)*	p<0.05	Moderate

CI confidence interval, MD mean difference, NA not available, NC not calculable, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] Method of randomisation not reported
[2] Unclear whether there was adequate concealment of allocation
[3] Unclear whether investigators were blinded to intervention
[4] Unclear whether investigators were blinded to confounding factors
[5] 12/21 subjects were oxygen dependent and had or subsequently fulfilled the diagnosis of BPD (oxygen dependency beyond 36 weeks postmenstrual age)
[6] Infants born premature

Table 27: GRADE profile for comparison of prone head elevated (at 30 to 45 degrees) positioning in harness with infant seat elevated at 60 degrees

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone head elevate position in harness	Infant seat	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Orenstein et al 1983)	RCT – crossover	Serious[1,2,3]	None	None	None	None	n=15 Mean (SD): 7.9 (8.9)	n=15 Mean (SD): 37.4 (24)	MD: −29.50 (42.46 to −16.54)*	p<0.001	Moderate
Number of episodes with pH<4.0											
1 (Orenstein et al 1983)	RCT – crossover	Serious[1,2,3]	None	None	None	None	n=15 Mean (SD): 5.2 (4.3)	n=15 Mean (SD): 19.6 (13.6)	MD: −14.40 (21.59 to −7.21)*	p<0.001	Moderate
Number of such episodes lasting longer than 5 minutes											
1 (Orenstein et al 1983)	RCT – crossover	Serious[1,2,3]	None	None	Serious[4]	None	n=15 Mean (SD): 0.6 (0.8)	n=15 Mean (SD): 1.9 (2.3)	MD: −1.30 (−2.54 to −0.06)*	p<0.05	Low

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone head elevate position in harness	Infant seat	Relative (95% CI)	Absolute (95% CI)	Quality
Duration of the longest episode in each 2 hour postprandial period											
1 (Orenstein et al 1983)	RCT – crossover	Serious[1,2,3]	None	None	Serious[4]	None	n=15 Mean (SD): 5.0 (6.6)	n=15 Mean (SD): 13.1 (19.4)	MD: −8.10 (−18.45 to 2.25)*	p<0.05	Low

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] Unclear whether there was adequate concealment of allocation
[2] Unclear whether investigators were blinded to intervention
[3] Unclear whether investigators were blinded to confounding factors
[4] Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)

Table 28: GRADE profile for comparison of head elevated prone positioning with flat prone positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Head elevated prone	Flat prone	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Orenstein et al 1990)	RCT – crossover	Serious[1,2]	None	None	Serious[3]	None	n=90 Mean (SD): 27.8 (30.4)	n=90 Mean (SD): 34.6 (31.3)	MD: −6.80 (−15.81 to 2.21)*	p=NS[a]	Low
Number of episodes with pH<4.0											
1 (Orenstein et al 1990)	RCT – crossover	Serious[1,2]	None	None	Serious[3]	None	n=90 Mean (SD): 6.2 (5.7)	n=90 Mean (SD): 7.8 (7.6)	MD: −1.60 (−3.56 to 0.36)*	p=NS[a]	Low
Mean duration of reflux episodes											
1 (Orenstein et al 1990)	RCT – crossover	Serious[1,2]	None	None	None	None	n=90 Mean (SD): 6.1 (9.5)	n=90 Mean (SD): 6.2 (8.5)	MD: −0.10 (−.2.74 to 2.54)*	p=NS[a]	Moderate
Number of reflux episodes lasting longer than 5 minutes											
1 (Orenstein et al 1990)	RCT – crossover	Serious[1,2]	None	None	None	None	n=90 Mean (SD): 1.3 (1.9)	n=90 Mean (SD): 1.5 (1.9)	MD: −0.20 (−0.75 to 0.35)*	p=NS[a]	Moderate
Duration of the longest reflux episode											
1 (Orenstein et al 1990)	RCT - crossover	Serious[1,2]	None	None	None	None	n=90 Mean (SD): 17.1 (22.8)	n=90 Mean (SD): 17.9 (20.9)	MD: −0.80 (−7.18 to 5.58)*	p=NS[a]	Moderate

CI confidence interval, MD mean difference, NS not significant, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[a] Significance defined as p<0.05
[1] Unclear whether there was adequate concealment of allocation
[2] Unclear whether investigators were blinded to confounding factors

[3] *Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)*

Table 29: GRADE profile for comparison of infant seat elevated at 60 degrees with horizontal prone positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infant seat	Horizontal prone	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Orenstein et al 1983b)	RCT – crossover	Serious[1,2,3]	None	None	Serious[4]	None	n= 9 Mean (SD): 28.2 (19.2)	n=9 Mean (SD): 12.8 (11.1)	MD: 15.00 (0.66 to 29.34)*	p=0.023	Low
Number of episodes with pH<4.0											
1 (Orenstein et al 1983b)	RCT – crossover	Serious[1,2,3]	None	None	Serious[4]	None	n=9 Mean (SD): 16.0 (7.2)	n=9 Mean (SD): 10.1 (6.9)	MD: 6.00 (−0.47 to 12.47)*	p=0.002	Low
Number of reflux episodes lasting longer than 5 minutes											
1 (Orenstein et al 1983b)	RCT – crossover	Serious[1,2,3]	None	None	Serious[4]	None	n=9 Mean (SD): 1.7 (1.8)	n=9 Mean (SD): 0.6 (0.9)	MD: 1.00 (−0.46 to 2.46)*	p=0.093	Low
Duration of the longest reflux episode in each 2 hour postprandial period											
1 (Orenstein et al 1983b)	RCT – crossover	Serious[1,2,3]	None	None	Serious[4]	None	n= 9 Mean (SD): 6.7 (3.9)	n=9 Mean (SD): 4.0 (2.4)	MD: 3.00 (0.08 to 5.92)*	p=0.079	Low

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] *Unclear whether there was adequate concealment of allocation*
[2] *Unclear whether investigators were blinded to intervention*
[3] *Unclear whether investigators were blinded to confounding factors*
[4] *Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)*

Table 30: GRADE profile for comparison of supine reversed Trendelenburg position of 10 degrees with flat supine positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supine reversed Trendelenburg	Flat supine	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Bagucka et al 1999)	RCT – crossover	Very serious[1,2,3,4]	None	None	Serious[5]	None	n=10 Mean (SD): 19.08 (13.10)	n=10 Mean (SD): 10.62 (6.40)	MD: 8.00 (−0.87 to 16.87)*	p=0.08	Very low
Number of episodes with pH<4.0											
1 (Bagucka et al 1999)	RCT – crossover	Very serious[1,2,3,4]	None	None	Very serious[6]	None	n=10 Mean (SD): 32.3 (8.00)	n=10 Mean (SD): 33.9 (15.6)	MD: −2.00 (−13.09 to 9.09)*	p=0.95	Very low

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supine reversed Trendelenburg	Flat supine	Relative (95% CI)	Absolute (95% CI)	Quality
Duration of the longest reflux episode											
1 (Bagucka et al 1999)	RCT – crossover	Very serious[1,2,3,4]	None	None	Serious[5]	None	n=10 Mean (SD): 38.9 (46.81)	n=10 Mean (SD): 17 (6.34)	MD: 22.00 (−7.37 to 51.37)*	p=0.16	Very low

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] Method of randomisation not reported
[2] Unclear whether there was adequate concealment of allocation
[3] Unclear whether investigators were blinded to intervention
[4] Unclear whether investigators were blinded to confounding factors
[5] Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)
[6] Confidence interval of standardised mean difference crosses 3 zones (very wide confidence interval)

Table 31: GRADE profile for comparison of prone with right lateral positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	Right lateral	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 6.3 (7.2)	n=18 Mean (SD): 29.4 (13.6)	MD: −23.10 (−30.20 to −16.00)*	p<0.05	Moderate
1 (Tobin et al 1997)	RCT – crossover	Serious[1,2]	None	None	None	None	n=24 Mean (SD): 6.72 (5.2)	n=24 Mean (SD): 12.02 (6.8)	MD: −5.00 (−8.44 to −1.56)*	p<0.05	Moderate
Number of episodes with pH<4.0											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 15.4 (11.9)	n=18 Mean (SD): 41.6 (19.5)	MD: −26.20 (−36.75 to −15.65)*	p<0.05	Moderate
Number of reflux episodes lasting longer than 5 minutes											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 1.1(1.7)	n=18 Mean (SD): 4.5 (3.4)	MD: −3.40 (−5.15 to −1.65)*	p<0.05	Moderate
Duration of the longest reflux episode											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 8.6 (9.3)	n=18 Mean (SD): 26 (16.5)	MD: −17.4 (−26.18 to −8.62)*	p<0.05	Moderate

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] Unclear whether investigators were blinded to intervention
[2] Unclear whether investigators were blinded to confounding factors
[3] Infants born premature

Table 32: GRADE profile for comparison of left lateral with right lateral positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Left lateral	Right lateral	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 11 (9.3)	n=18 Mean (SD): 29.4 (13.6)	MD: −18.4 (−26.01 to −10.79)*	p<0.05	Moderate
1 (Tobin et al 1997)	RCT – crossover	Serious[1,2]	None	None	None	None	n=24 Mean (SD): 7.69 (5)	n=24 Mean (SD): 12.02 (6.8)	MD: −4 (−7.44 to −0.56)*	p<0.05	Moderate
Number of episodes with pH<4.0											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 24.6 (14.8)	n=18 Mean (SD): 41.6 (19.5)	MD: −17.00 (−28.33 to −5.67)*	p<0.05	Moderate
Number of reflux episodes lasting longer than 5 minutes											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 1.8 (2.1)	n=18 Mean (SD): 4.5 (3.4)	MD: −2.70 (−4.55 to −0.85)*	p<0.05	Moderate
Duration of the longest reflux episode											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	None	Yes[3]	n=18 Mean (SD): 10 (10.2)	n=18 Mean (SD): 26 (16.5)	MD: −16 (−24.98 to −7.02)*	p<0.05	Moderate

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] Unclear whether investigators were blinded to intervention
[2] Unclear whether investigators were blinded to confounding factors
[3] Infants born premature

Table 33: GRADE profile for comparison of prone with left lateral positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	Left lateral	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	Serious[3]	Yes4	n=18 Mean (SD): 6.3 (7.2)	n=18 Mean (SD): 11 (9.3)	MD: −4.70 (−10.15 to 0.75)*	p<0.05	Low
1 (Tobin et al 1997)	RCT – crossover	Serious[1,2]	None	None	Serious[3]	None	n=24 Mean (SD): 6.72 (5.2)	n=24 Mean (SD): 7.69 (5.0)	MD: −1.00 (−3.83 to 1.83)*	NS	Low
Number of episodes with pH<4.0											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	Serious[3]	Yes[4]	n=18 Mean (SD): 15.4 (11.9)	n=18 Mean (SD): 24.6 (14.8)	MD: −9.20 (−17.98 to −0.42)*	p<0.05	Low

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	Left lateral	Relative (95% CI)	Absolute (95% CI)	Quality
Number of reflux episodes lasting longer than 5 minutes											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	Serious[3]	Yes[4]	n=18 Mean (SD): 1.1 (1.7)	n=18 Mean (SD): 1.8 (2.1)	MD: −0.70 (−1.95 to 0.55)*	p>0.05[a]	Low
Duration of the longest reflux episode											
1 (Ewer et al 1999)	RCT – crossover	Serious[1,2]	None	None	Very serious[5]	Yes[4]	n=18 Mean (SD): 8.6 (9.3)	n=18 Mean (SD): 10 (10.2)	MD: −1.40 (−7.78 to 4.98)*	p>0.05[a]	Very low

CI confidence interval, MD mean difference, NS not significant, p probability, RCT randomised controlled trial, SD standard deviation
[*] Calculated by NCC-WCH technical team based on data reported in the article
[a] Unclear reporting but seems as though p>0.05
[1] Unclear whether investigators were blinded to intervention
[2] Unclear whether investigators were blinded to confounding factors
[3] Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)
[4] Infants born premature
[5] Confidence interval of standardised mean difference crosses 3 zones (very wide confidence interval)

Table 34: GRADE profile for comparison of left lateral with supine positioning

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Left lateral	Supine	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux index (% of time with pH<4.0)											
1 (Tobin et al 1997)	RCT – crossover	Serious[1,2]	None	None	None	None	n=24 Mean (SD): 7.69 (5.0)	n=24 Mean (SD): 15.33 (11.4)	MD: −7.00 (−11.83 to −2.17)*	p<0.05	Moderate

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[1] Unclear whether investigators were blinded to intervention
[2] Unclear whether investigators were blinded to confounding factors

5.1.4 Evidence statements

See Table 26 to Table 34.

5.1.4.1 Prone versus supine positioning

5.1.4.1.1 Reflux index (percent of time with pH less than 4.0)

Two studies found that reflux index was lower (less acid reflux exposure) when infants were placed in the prone position compared with the supine position. The evidence for this finding ranged from moderate to very low quality.

5.1.4.2 Prone head-elevated (at 30 to 45 degrees) positioning in harness versus infant seat elevated at 60 degrees

5.1.4.2.1 Reflux index (percent of time with pH less than 4.0)

One study found that reflux index was lower (less acid reflux exposure) when infants were placed in the prone head elevated (at 30 to 45 degrees) position in harness compared with the infant seat elevated at 60 degrees. The evidence for this finding was of moderate quality.

5.1.4.2.2 Number of reflux episodes with pH less than 4.0

One study found that the number of reflux episodes with pH less than 4 was decreased when infants were placed in the prone head elevated (at 30 to 45 degrees) position in harness compared with the infant seat elevated at 60 degrees. The evidence for this finding was of moderate quality.

5.1.4.2.3 Number of reflux episodes lasting longer than 5 minutes

One study found that the number of reflux episodes lasting longer than 5 minutes was decreased when infants were placed in the prone head elevated (at 30 to 45 degrees) position in harness compared with the infant seat elevated at 60 degrees. The evidence for this finding was of low quality.

5.1.4.2.4 Duration of the longest episode (in each 2 hour postprandial period)

One study found that the duration of the longest reflux episode in each 2 hour postprandial period was decreased when infants were placed in the prone head elevated (at 30 to 45 degrees) position in harness compared with the infant seat elevated at 60 degrees. The evidence for this finding was of low quality.

5.1.4.3 Head-elevated prone positioning versus flat prone positioning

5.1.4.3.1 Reflux index (percent of time with pH less than 4.0)

One study did not find a significant difference in reflux index when infants were placed in the head elevated prone position compared with the flat prone position. The evidence for this finding was of low quality.

5.1.4.3.2 Number of episodes with pH less than 4.0

One study did not find a significant difference in the number of episodes with pH<4.0 when infants were placed in the head elevated prone position compared with the flat prone position. The evidence for this finding was of low quality.

5.1.4.3.3 Mean duration of reflux episodes

One study did not find a significant difference in the mean duration of reflux episodes when infants were placed in the head elevated prone position compared with the flat prone position. The evidence for this finding was of moderate quality.

5.1.4.3.4 Number of reflux episodes lasting longer than 5 minutes

One study did not find a significant difference in the number of reflux episodes lasting longer than 5 minutes when infants were placed in the head elevated prone position compared with the flat prone position. The evidence for this finding was of moderate quality.

5.1.4.3.5 Duration of the longest episode

One study did not find a significant difference in the duration of the longest reflux episode when infants were placed in the head elevated prone position compared with the flat prone position. The evidence for this finding was of moderate quality.

5.1.4.4 Infant seat elevated at 60 degrees versus horizontal prone positioning

5.1.4.4.1 Reflux index (percent of time with pH less than 4.0)

One study found that reflux index was increased when infants were placed in the infant seat elevated at 60 degrees compared with horizontal prone positioning. The evidence for this finding was of low quality.

5.1.4.4.2 Number of episodes with pH less than 4.0

One study found that the number of episodes with pH less than 4.0 was increased when infants were placed in the infant seat elevated at 60 degrees compared with horizontal prone positioning. The evidence for this finding was of low quality.

5.1.4.4.3 Number of reflux episodes lasting longer than 5 minutes

One study did not find a significant difference in the number of reflux episodes lasting longer than 5 minutes when infants were placed in the infant seat elevated at 60 degrees compared with horizontal prone positioning. The evidence for this finding was of low quality.

5.1.4.4.4 Duration of the longest episode in each 2 hour postprandial period

One study did not find a significant difference in the duration of the longest reflux episode when infants were placed in the infant seat elevated at 60 degrees compared with horizontal prone positioning. The evidence for this finding was of low quality.

5.1.4.5 Supine reversed Trendelenburg position of 10 degrees versus flat supine positioning

5.1.4.5.1 Reflux index (percent of time with pH less than 4.0)

One study did not find a significant difference in reflux index when infants were placed in the supine reversed Trendelenburg position of 10 degrees compared with the flat supine position. The evidence for this finding was of very low quality.

5.1.4.5.2 Number of episodes with pH less than 4.0

One study did not find a significant difference in the number of episodes with pH less than 4 when infants were placed in the supine reversed Trendelenburg position of 10 degrees compared with the flat supine position. The evidence for this finding was of very low quality.

5.1.4.5.3 Duration of the longest episode

One study did not find a statistically difference in the duration of the longest reflux episode when infants were placed in the supine reversed Trendelenburg position of 10 degrees compared with the flat supine position. The evidence for this finding was of very low quality.

5.1.4.6 Prone versus right lateral

5.1.4.6.1 Reflux index (percent of time with pH less than 4.0)

Two studies found that reflux index was lower (less acid reflux exposure) when infants were placed in the prone position compared with the right lateral position. The evidence for this finding was of moderate quality.

5.1.4.6.2 Number of episodes with pH less than 4.0

One study found that the number of episodes with pH less than 4 was decreased when infants were placed in the prone position compared with the right lateral position. The evidence was of moderate quality.

5.1.4.6.3 Number of episodes lasting longer than 5 minutes

One study found that the number of episodes lasting longer than 5 minutes was decreased when infants were placed in the prone position compared with the right lateral position. The evidence was of moderate quality.

5.1.4.6.4 Duration of the longest reflux episode

One study found that the duration of the longest reflux episode was decreased when infants were placed in the prone position compared with the right lateral position. The evidence was of moderate quality.

5.1.4.7 Left lateral versus right lateral

5.1.4.7.1 Reflux index (percent of time with pH less than 4.0)

Two studies found that reflux index was lower (less acid reflux exposure) when infants were placed in the left lateral position compared with the right lateral position. The evidence for this finding was of moderate quality.

5.1.4.7.2 Number of episodes with pH less than 4.0

One study found that the number of episodes with pH less than 4 was decreased when infants were placed in the left lateral compared with the right lateral position. The evidence was of moderate quality.

5.1.4.7.3 Number of episodes lasting longer than 5 minutes

One study found that the number of episodes lasting longer than 5 minutes was decreased when infants were placed in the left lateral position compared with the right lateral position. The evidence was of moderate quality.

5.1.4.7.4 Duration of the longest reflux episode

One study found that the duration of the longest reflux episode was decreased when infants were placed in the left lateral position compared with the right lateral position. The evidence was of moderate quality.

5.1.4.8 Prone versus left lateral

5.1.4.8.1 Reflux index (percent of time with pH less than 4.0)

One study found that reflux index was lower (less acid reflux exposure) when infants were placed in the prone position compared with the left lateral position. The evidence for this finding was of low quality. One other study did not find a significant difference in reflux index when infants were placed in the prone position compared with the left lateral position. The evidence for this finding was of low quality.

5.1.4.8.2 Number of episodes with pH less than 4.0

One study found that the number of episodes with pH less than 4 was decreased when infants were placed in the prone position compared with the left lateral position. The evidence was of low quality.

5.1.4.8.3 Number of episodes lasting longer than 5 minutes

One study did not find a significant difference in the number of episodes lasting longer than 5 minutes when infants were placed in the prone position compared with the left lateral position. The evidence was of low quality.

5.1.4.8.4 Duration of the longest reflux episode

One study did not find a significant difference in the duration of the longest reflux episode when infants were placed in the prone position compared with the left lateral position. The evidence was of very low quality.

5.1.4.9 Left lateral versus supine positioning

5.1.4.9.1 Reflux index (percent of time with pH less than 4.0)

One study found that reflux index was lower (less acid reflux exposure) when infants were placed in the left lateral position compared with supine positioning. The evidence for this finding was of moderate quality.

5.1.5 Health economics profile

No health economic data was identified on symptoms and signs, and no health economic evaluation was undertaken.

5.1.6 Evidence to recommendations

5.1.6.1 Relative value placed on the outcomes considered

The main application of positional management would be the reduction of overt reflux episodes in infants. Therefore, the guideline development group had prioritised the outcome of any change in frequency of overt gastro-oesophageal reflux. The group also considered reported changes in oesophageal acid reflux based on oesophageal pH monitoring.

5.1.6.2 Consideration of clinical benefits and harms

Seven randomised controlled were included in the review, and these reported data on 9 positions.

The guideline development group noted that the prone position improved reflux as measured by pH studies in infants when compared with both supine and right lateral positions. The left lateral position was found to be more effective in comparison with the supine position. When the left lateral position and prone position were compared, no statistical differences were

found. The group concluded from the evidence that the prone and left lateral positions have been shown in some studies to be effective at reducing acid reflux as measured by pH study in the infants studied. The data was limited to average pH change over 24 hours and it was unclear what effect there would be on reflux following feeding and on episodic bouts of reflux that infants may experience throughout the day.

The group discussed at length the Worldwide Public Health and Department of Health recommendations that infants should be put to sleep on their back for every sleep in order to reduce the risk of sudden infant death syndrome (SIDS). Further, the whole group accepted and recognised the dramatic effect this simple message has had over the last 25 years and the many hundreds of thousands of infant lives that have been saved.

As a result, the group 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. The statement that positional management should **not** be used in a sleeping infant (with GORD) entirely supports this guidance.

From their primary care experience, some members of the group reported that parents and carers of infants find that lying prone can be a helpful when used in some infants with GORD when they are both **awake and supervised**. This opportunity is entirely consistent with the 'Tummy Time' as widely advocated by health visitors across the UK and neatly described in the publication Protect your baby's natural head shape: tummy time to play, back to sleep from the Scottish NHS.

The group was also aware of situations where infants, particularly premature infants, are placed in a front (prone) position while sleeping on the neonatal intensive care unit (NICU) or special care baby unit (SCBU) in hospital to help relieve GOR, but this occurs only in circumstances when the infant is under electronically monitored constant nursing supervision with immediate access to full cardio-pulmonary resuscitation from trained professionals.

Therefore, the group recommended that positional management should **not** be used as a treatment for GOR in sleeping infants because any potential small individual benefit would almost certainly be outweighed by the very real risk of SIDS in the baby and were this dangerous practice to become widespread once again, it would quite possibly pose a risk to the much larger population of well infants with normal regurgitation and mild physiological GOR.

5.1.6.3 Consideration of health benefits and resource uses

While advice on positional management would have a minimal cost associated with it, this has to be offset against the potential costs associated with an increased risk in SIDS caused by its inappropriate use.

5.1.6.4 Quality of evidence

The review was based on RCT evidence. The outcome was entirely limited to pH study data. The quality of the evidence ranged from moderate to very low. The main sources of bias were: small sample size (with the largest study including 90 infants), lack of blinding of allocation to treatment, and imprecision in findings which meant the guideline development group could not make definitive conclusions from the results. Furthermore, the studies examined a variety of different positions and because of this variation the data could not be meta-analysed. Finally, the studies did not describe if assessment was during feeding or rest, which limited the interpretation of findings.

5.1.6.5 Other considerations

5.1.6.5.1 Positional management in older children

The positional management review and the Back to Sleep campaign only considered infants who are not able to independently change their position. As no evidence was available on the efficacy of positional management, such as elevation to head of the infant crib or the older child or young person's bed, the guideline development group did not make a recommendation for this group.

5.1.6.5.2 Positional management of children with neurodisability

No evidence was identified for children with neurodisability and therefore the guideline development group did not make a recommendation for this group.

5.1.6.5.3 Positional management supports

The guideline development group was aware of a number of commercially available positional management products that claim to reduce the frequency of reflux episodes when a child is sleeping or following a feed. The group stated that in order to consider any intervention, data from RCTs would be required to show clinical efficacy. As no RCT data was found for any product, the group concluded that no benefit could be demonstrated for any such products and therefore none should be recommended or offered in the NHS.

5.1.6.5.4 Infant sleeping position and risk of SIDS

Public health advice to always avoid the front (prone) sleeping position in infants started to become widespread in many countries and cultures across the world from the late 1980s. By the early 1990s it was becoming apparent that this single intervention had led to an immediate and dramatic fall in the number of cases of sudden infant death syndrome (SIDS). In a summary of UK data, the number of infant deaths caused by SIDS fell by nearly 70% in England and Wales between 1988 and 1992.

Subsequent work has clarified that all infants must be placed on their back at all times for sleep. This is because there remains an increased risk of SIDS when a baby is sleeping on its side compared with on its back (the supine position). This further change has led to an ongoing fall in the incidence of this syndrome. This advice is reflected in the practical guidance from the NHS on infant sleeping positioning: Sudden infant death syndrome in the section 'What can I do to help prevent SIDS?' (See http://www.nhs.uk/Conditions/Sudden-infant-death-syndrome/Pages/Introduction.aspx).

5.1.7 Recommendations

24. 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.

5.1.8 Research recommendations

No research recommendations in this area.

5.2 Feeding changes

This section evaluates the evidence on feed changes in relation to regurgitation and GOR for infants, children and young people. It is extremely common for parents and carers to receive advice on feed changes for a whole variety of perceived problems in early infancy. Regurgitation and assumed GOR are no different and the advice comes from a variety of sources including: books, publications, the internet, friends and family, as well as healthcare

professionals at all tiers of care. For infants who regurgitate, advice may include changing the way the feed is administrated by altering both the volume and the frequency of administration or by altering the content by either thickening the milk or changing the constituent parts, for example by using hydrolysed milk substitutes.

5.2.1 Review question

What is the effectiveness of a managed feeding regimen in comparison with a conventional, age appropriate, regimen in the management of overt GOR:

- To determine if smaller feeds can reduce overt reflux in children and young people.
- To determine if feed thickeners or pre-thickened formula can reduce overt reflux in children and young people.
- To determine if use of a formula free of cows' milk protein can reduce the frequency of overt reflux in children and young people.
- To determine if a maternal diet free of cows' milk and/or soya protein can reduce the frequency of overt reflux in children who are being breastfed.

For full details see review protocol in Appendix E.

5.2.2 Description of included studies

The search strategy created for this review can be found in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profile below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Fourteen comparative studies were included on thickened feeds (Iacono et al., 2002, Ostrom et al., 2006; Moukarzel et al., 2007, Xinias et al., 2005; Vanderhoof et al., 2003; Orentstein et al., 1986; Wenzl et al., 2003; Chao & Vandenplas, 2007a; Chao & Vandenplas, 2007b; Vandenplas et al., 1994; Miyzawa et al., 2006; Miyazawa et al., 2007; Miyazawa et al., 2008; Miyazawa et al., 2004), 1 study on elimination of cows' milk from diet (Borrelli et al., 2012) and 1 on volume of feeds (Sutphen & Dillard, 1988). No comparative studies were found on the effect elimination of cows' milk from the maternal diet on infant reflux symptoms. The type of thickening agents used varied, and included corn starch, rice starch (Enfamil) and locust bean. Miyzawa et al., 2006 and Miyazawa et al., 2007 used anti-regurgitant milk with varying concentrations of locust bean gum defined as: HL-450, antiregurgitant milk with 0.45 g/100 mL locust bean gum; HL-350, antiregurgitant milk with 0.35 g/100 mL locust bean gum; and HL-00, control milk with no locust bean gum.

Of the included studies, 4 were undertaken in the USA (Sutphen & Dillard, 1988; Orenstein et al., 1986; Vanderhoof et al., 2003; Ostrom et al., 2006), 4 in Japan (Miyazawa et al., 2006; Miyazawa et al., 2004; Miyazawa et al., 2007; Miyazawa et al., 2008), 2 in Taiwan (Chao & Vandenplas, 2007a; Chao & Vandenplas, 2007b), 1 in Lebanon (Moukarzel et al., 2007), 1 in Belgium (Vanderplas et al., 1994), 1 in Germany (Wenzl et al., 2003), 1 in the UK (Borrelli et al., 2012) and 1 in Italy (Iacono et al., 2002). There was 1 multinational study undertaken in Greece, Morocco, France and Belgium (Xinias et al., 2005).

The most common study design was a randomised controlled trial (RCT) (Miyazawa et al., 2004; Vanderhoof et al., 2003; Orenstein et al., 1986; Vanderplas et al., 1994; Ostorm et al., 2006; Moukarzel et al., 2007; Xinias et al., 2005; Iacono et al., 2002; Chao & Vandenplas, 2007a; Chao & Vandenplas, 2007b). Four studies used a crossover design (Miyzawa et al., 2006; Miyazawa et al., 2007; Miyazawa et al., 2008; Wenzl et al., 2003). Two studies were non-randomised trials (Borrelli et al., 2012; Sutphen and Dillard, 1988).

The definition of GOR varied between studies, but was most commonly based on frequency of overt regurgitation. The most common measurement used pH and/or impedance

monitoring. The duration of studies varied from a single feed (Sutphen and Dillard, 1998) to a duration of 8 weeks (Chao and Vandenplas, 2007).

Studies on thickened feeds and volumes included infants aged 6 months or less. A study on cows' milk protein elimination included children up to age 24 months.

Only 1 study examined a specific sub-group, which was children with cerebral palsy (Miyazawa et al., 2008).

5.2.3 Evidence profile

Study quality was assessed using the GRADE methodology. RCTs were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias. For non-randomised trials, the quality rating started at low and they were then downgraded if there were any potential sources of bias.

The following GRADE profiles are shown below:

- GRADE findings for comparison of thickened feeds with standard formula feeds for reduction in GOR related symptoms
- GRADE findings for comparison of thickened feeds with standard formula feeds for reduction in GOR related symptoms in children with cerebral palsy
- GRADE findings for comparison of cows' milk elimination diet on the symptoms of GOR
- GRADE findings for comparison of feeding volume on symptoms of GOR.

Table 35: GRADE profile for comparison of thickened feeds with standard formula feeds for reduction in GOR related symptoms.

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation: pH and/or impedance monitoring											
Number of infants without regurgitation											
1 (Iacono et al., 2002)	RCT	Serious[1,2]	None	None	None	None	28 of 82	12 of 84	Relative Risk: 2.39 [1.31, 4.37]	NA	Moderate
Number of episodes of regurgitation (per day or week)											
3 (4 arms) Moukarzel et al., 2007 Xinias et al., 2005 Miyazawa et al., 2006)	Meta analysis of RCTs	Serious[1,2]	Serious[3]	None	None	Yes[4]	-	-	Mean Difference: -2.00 [-4.65, 0.65]	NA	Low
Change in regurgitation frequency from baseline at one week											
1 (Vanderhoof et al., 2003)	RCT	Very serious[1,5]	None	None	Serious[6]	No	Change -6 (range ± 1)[a]	Change -6 (range ± 1)[a]	Non-significant[a]	NA	Very low
Episodes of emesis over a 90 minute period											
1 (Orenstein et al., 1986)	RCT; crossover	Very serious[7]	None	None	Serious[6]	No	1.2 (SD ±0.7)g	3.9 (SD ± 0.9)g	p=0.015[a]	NA	Very low
1 (Wenzl et al., 2003)	RCT; crossover	None	None	None	Serious[6]	No	1.07 (SD ± 1.69)[a]	4.86 (SD ±4.05[a]	p<0.003[a]	NA	Moderate
Frequency of regurgitation per day, median (IQR)											
1 (Miyazawa et al., 2004)	RCT; crossover within arms	Serious[1]	None	None	Serious[6]	Yes[8]	HL-350 Median 1.6 (IQR 0.8 to 2.0)[a]	HL-00 Median 3.5 (IQR 2.3 to 4.9)[a]	p=0.021[a]	NA	Low
1 (Miyazawa et al., 2004)	RCT; crossover within arms	Serious[1]	None	None	Serious[6]	Yes[8]	HL-450 Median 1.3 (IQR 0.6 to 2.3)[a]	HL-00 Median 2.9 (IQR 2.0 to 3.2)[a]	p=0.0003[a]	NA	Low
1 (Miyazawa et al., 2007)	RCT;	Serious[1]	None	None	Serious[6]	Yes[8]	HL-350 Median 2.3 (IQR 1.6 to 3.6)[a]	HL-00 Median 5.2 (IQR 3.7 to 7.8)[a]	p<0.01)[a]	NA	Low
Number of episodes of vomiting per day											
2 (Moukarzel et al., 2007 Xinias et al., 2005)	Meta analysis of RCTs	Serious[1]	None	None	None	Yes[4]	-	-	Mean difference: −0.97 [−1.54, −0.39]	NA	Moderate

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux measured using oesophageal pH or impedance monitoring											
Reflux Index (% time pH<4.0)											
3 (Moukarzel et al., 2007 Xinias et al., 2005 Vandenplas et al., 1994)	Meta-analysis of RCTs	Serious[1,2]	None	None	None	Yes[4]	-	-	Mean difference: −3.38 [−5.28, −1.48]	NA	Moderate
Resolution of faltering growth											
Weight gain (grams per day)											
4 (Chao & Vandenplas, 2007a Chao & Vandenplas, 2007b Xinias et al., 2005)	Meta analysis of RCTs	Very serious[1]	Serious[3]	None	None	Yes[4]	-	-	Mean Difference: 3.99 [1.66, 6.31]	NA	Low
Adverse events											
Discontinued due to diarrhoea											
1 (Iacono et al., 2002)	RCT	Serious[1,2]	None	None	None	No	14 of 82	0 of 84	∞	NA	Moderate
Reported adverse events (not specified)											
1 (Vanderhoof et al., 2003)	RCT	Very serious[1]	None	None	Serious[6]	No	-	-	No difference between groups[a]	NA	Very low
1 (Miyazawa et al., 2004)	RCT; crossover within arms	Serious[1]	None	None	Serious[6]	No	-	-	No difference between groups[a]	NA	Low
1 (Xinias et al., 2005)	RCT;	Serious[1]	None	None	Serious[6]	No	-	-	No difference between groups[a]	NA	Low
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, HL-00 control milk with no locust bean gum, HL-350 antiregurgitant milk with 0.35 g/100 ml locust bean gum, HL-450 antiregurgitant milk with 0.45 g/100 ml locust bean gum, IQR interquartile range, NA not available, p probability, RCT randomised controlled trial, SD standard deviation
[a] Result as reported in study
[1] Method of randomisation not described in detail
[2] High discontinuation rate
[3] High heterogeneity between studies
[4] Variation in viscosity of formulas and nutritional value of formulas
[5] Children assessed at 1 week and some given further treatment
[6] Imprecision could not be investigated due to way result have been reported and cross-over design
[7] Study based on response to a single feed. Method of investigation was scintigraphically
[8] It is unclear how these studies are linked. Numbers in each arm differ.

Table 36: GRADE profile for comparison of thickened feeds with standard formula feeds for reduction in GOR related symptoms in children with cerebral palsy

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
1 (Miyazawa et al., 2008)	RCT; crossover within arms	Serious[1]	None	None	Serious[2]	No	High pectin median 2.5 (IQR 1.0 to 5.0)	Standard feed median 1.0 (IQR 1.0 to 1.5)	P<0.05	NA	Low
1 (Miyazawa et al., 2008)	RCT; crossover within arms	Serious[1]	None	None	Serious[2]	No	Low pectin median 0.0 (0.0 to 0.5)	Standard feed median 0.0 (0.0 to 0.1)	NS	NA	Low
Reflux measured using oesophageal pH or impedance monitoring											
Not reported											
Resolution of faltering growth											
Not reported											
Adverse events											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, IQR interquartile range, NA not available, NS not significant, p probability, RCT randomised controlled trial
[1] Method of randomisation not described in detail
[2] Could not be calculated

Table 37: GRADE profile for comparison of thickened feeds (Soy milk and fibre) with standard formula feeds for reduction in GOR related symptoms.

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Number of infants without regurgitation											
1 (Ostrom et al., 2006)	RCT	Very serious[1,2]	None	Very serious[3]	Serious[4]	No	11 of 67	3 of 66	Relative risk: 3.61 [1.06, 12.36]	NA	Very low
Number of episodes of regurgitation											
1 (Ostrom et al., 2006)	RCT	Very serious[1,2]	None	Very serious[3]	None	No		-	Mean difference: −0.40 [−0.49, −0.31]	NA	Very low
Reflux measured using oesophageal pH or impedance monitoring											
Not reported											
Resolution of faltering growth											
Not reported											
Adverse events											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, NA not available, RCT randomised controlled trial
[1]Effect of cows' milk intolerance not controlled for in analysis
[2] 25% discontinuation rate across study
[3] 6 g/l of soy fibre was added to a soy based formula in the thickened arm of the trial. This was compared to a standard milk based formula. Thus it is unclear whether any treatment effects were due to elimination of cows' milk protein and/or any thickened feed
[4] Wide confidence intervals

Table 38: GRADE profile for comparison of thickened feeds with standard formula feeds plus positional management for reduction in GOR related symptoms

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Number of episodes of regurgitation and vomiting per day											
1 (Chao & Vandenplas, 2007b)	RCT	Serious[1,2]	None	Serious[3]	Serious[4]		-	-	Mean difference: −0.77 [−1.16, −0.38]	NA	Very low
Reflux measured using oesophageal pH or impedance monitoring											
Not reported											
Resolution of faltering growth											
Not reported											
Adverse events											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, NA not available, RCT randomised controlled trial
[1] Randomisation and concealment not described in detail
[2] 20% discontinuation from study
[3] Comparison group had positional management
[4] Wide confidence intervals

Table 39: GRADE profile for comparison of thickened feeds with 25% strengthened regular formula for reduction in GOR related symptoms.

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Number of episodes of regurgitation and vomiting per day											
1 (Chao & Vandenplas, 2007a)	RCT	Serious[1]	None	Serious[2]	None	Yes	-	-	Mean difference −1.96 [−2.34, −1.58]	NA	Very low

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thickened feed	Standard/comparator feed	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux measured using oesophageal pH or impedance monitoring											
Not reported											
Resolution of faltering growth											
Not reported											
Adverse events											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, NA not available, RCT randomised controlled trial
[1] Randomisation and concealment not described in detail
[2] Comparison group had partially strengthened formula.

Table 40: GRADE profile for comparison of cows' milk protein elimination with continued cows' milk diet on the symptoms of GORD

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Not reported											
Reflux measured using oesophageal pH or impedance monitoring											
Total number of reflux episodes											
1 (Borrelli et al., 2012)	Non-randomised clinical trial	Very serious[1]	None	None	Serious[2]	No	Amino acid formula: Median 65 (range 39 to 87.5)	Standard cows' milk: Median 105 (range 58 to 127.5)	p<0.001	NA	Very low
Reflux Index (% of time pH<4.0)											
1 (Borrelli et al., 2012)	Non-randomised clinical trial	Very serious[1]	None	None	Serious[2]	No	Amino acid formula: Median 3.4 (SD ± 2.6)	Standard cows' milk: Median 3.6 (SD ± 2.7)	NS	NA	Very low
Resolution of faltering growth											
Not reported											
Adverse events											
Not reported											
Parent reported reduction in infant distress											
Not reported											

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, NA not available, NS not significant, p probability, SD standard deviation
[1] Non-randomised study design and all children were known to have cows' milk allergy
[2] Could not be calculated

Table 41: GRADE profile for comparison of differing feeding volumes on symptoms of GOR

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Not reported											
Reflux measured using oesophageal pH or impedance monitoring											
Total number of reflux episodes											
1 (Sutphen & Dillard, 1988)	Non-randomised crossover clinical trial	Very serious[1,2]	None	None	Serious[3]	No	9 ml/kg mean 8.1 (SD 13.9)	18 ml/kg mean 14.3 (SD 12.5)	p=0.004	NA	Very low
1 (Sutphen & Dillard, 1988)	Non-randomised crossover clinical trial	Very serious[1,2]	None	None	Serious[3]	No	9 ml/kg mean 9.6 (SD 7.2)	27.3 ml/kg mean 24.4 (SD 20.2)	p=0.007	NA	Very low
Resolution of faltering growth											
Not reported											
Adverse events											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, kg kilogram, ml millilitre, N/A not available, OR odds ratio, p probability, SD standard deviation
[1] Non-randomised study design
[2] Variation in how study protocol was applied.
[3] Could not be calculated

5.2.4 Evidence statements

See Table 35 to Table 41.

5.2.4.1 Thickened feeds

Evidence from 14 comparative studies showed that thickened feeds reduced overt regurgitation and reflux acid exposure in infants. The quality of this evidence ranged from very low to moderate.

5.2.4.2 Cows' milk protein diet

One comparative study found that in a group of children aged 6 to 24 months eliminating cows' milk protein from their diet reduced the number of reflux episodes as measured by pH monitoring, but not the total time of acid reflux exposure as measuring by pH monitoring. This evidence was very low quality.

5.2.4.3 Feeding volumes

One comparative study found smaller volume feeds were associated with fewer reflux episodes (as measured by pH monitoring) than larger volume feeds. This evidence was very low quality.

5.2.5 Health economics profile

No health economic studies were identified for this question and no health economic modelling was undertaken. Therefore, only cost data was considered (see Appendix A: Health economics).

5.2.6 Evidence to recommendations

5.2.6.1 Relative value placed on the outcomes considered

The guideline development group confirmed that it is very common in both primary and secondary care for the suggestion to be made to parents and carers that feed content and administration be changed for infants who appear to have significant regurgitation, as well as for children with similar problems who are dependent on enteral feeding. The primary outcome for this evidence was the reduction of reflux episodes by observation and, if this is not reported, when measured by pH monitoring.

5.2.6.2 Consideration of clinical benefits and harms

The guideline development group was aware that frequent regurgitation is very common in infants and is a normal physiological event. This has been defined with reference to the available evidence already in this guideline and is included in recommendations that are discussed in an earlier chapter. Therefore, the group recommended that before any alterations are made to feed administration (for example to volume or frequency, or to content of feed), it should be clarified whether the infant or child has a 'significant' problem with regurgitation; that is, one which is outside what may be expected for the normal population at that particular age. This is information that can be collected relatively easily by healthcare professionals at all levels by taking a detailed history, but may be augmented by suggesting that worried parents keep a detailed diary of regurgitation episodes, together with the feed details, over several consecutive days. This not only helps the healthcare professional get a clearer idea of the range of the problem but can also help clarify to parents

that symptoms can vary from day to day and improve the accuracy of their recall of symptoms.

Owing to the limitations of the studies identified, the discussion mainly concerns young infants prior to weaning and concentrates on formula fed infants for the simple reason that breastfed babies essentially feed 'on demand' and it is therefore almost impossible to make specific changes to the feed regime of an exclusively breastfed infant. Similarly, no studies comparing breastfed to formula fed infants were identified, so although the guideline development group unanimously advocate exclusive breastfeeding for all young infants wherever possible, it is impossible to say whether GOR is more likely with either method of feeding.

5.2.6.2.1 Thickened feeds

The reviewed evidence supported the experience of the guideline development group that there can be a benefit in thickening feeds for the treatment of overt reflux. The data shows a significant cessation of reflux and a reduction in the number of reflux episodes (per day and per week) in infants using thickened feeds compared with those infants not using them. Similar findings were reported when utilising pH indices, indicating a relief from acid exposure in the oesophagus. This benefit was demonstrated in feeds thickened with soy and fibre. In children with cerebral palsy, significant reduction was found in the frequency of overt regurgitation when a high pectin thickening agent was used. These results matched the group's own experience when using thickened feeds to manage GOR.

The group discussed the practicalities of using feed thickeners. They noted that there are number of feed thickening products available; both on prescription and over the counter. These products vary across commercial brands but are basically either pre-thickened formulae or products added to formula milk. The group was aware that both types of thickened feeds are associated with difficulties in achieving a successful feed, with reported resistance to the texture from the child and the increased viscosity effecting the feeding time. However, these difficulties did not outweigh the benefits of reducing reflux.

Based on the available evidence and their experience, the group recommended that feed thickeners should be used as an early, effective and cheap strategy to treat GOR.

The group considered whether thickening agents could be used for breastfeeding infants. However, difficulty in effective administration of thickeners to breastfed infants makes their use impractical. Alginates can be given to breastfed infants according to well-established methods of administration (see Section 1.1.2.2).

5.2.6.2.2 Cows' milk (protein) elimination

A single non-randomised clinical trial reported a significant increase in the frequency of overt reflux episodes in a group of infants with known cows' milk allergy (CMA) when they underwent a challenge test compared with when they were on an amino acid formula. There was, however, no statistical difference in the effect of cows' milk protein elimination on the pH reflux index. All the infants in this study had confirmed CMA and the guideline development group concluded that this result was of little relevance in general situations where CMA status is not known. No RCTs addressing the question as defined in the guideline development group protocol had been identified, so discussion was then based on clinical experience in the absence of available evidence.

The group's experience was that cows' milk protein and soya protein elimination with the use of either a change in maternal diet for breastfed infants or an expensive extensively hydrolysed feed or amino acid based feed for bottle fed infants is very widespread practice in the UK for a wide variety of perceived problems in infancy.

The logical reason for the elimination of cows' milk or soya milk based products would be a diagnosis of cows' milk or soya protein allergy. However, it was accepted by the guideline

development group that the area is controversial and not helped by the absence of any sensitive or specific diagnostic test for this form of non-IgE mediated hypersensitivity.

In these situations it was the experience of the group that in infants where cows' milk protein allergy is suspected, it is very common practice in both primary and secondary care to carry out an empirical trial of up to a fortnight of an extensively hydrolysed or amino acid based feed for bottle fed infants with regurgitation with or without reported distress. This practice consumes a significant financial resource in total across the UK.

The group concluded that, based on RCTs, there is no evidence base to support or refute the efficacy of this practice in the treatment of suspected GORD. Furthermore, given that these milks are prescribed for children, as opposed to standard formula milks that are purchased by the parents or carers in most cases, it is possible that once an infant has been started on a prescribed milk substitute there is likely to be a disincentive to revert to the original feed unless the infant is either noticeably worse or suffering side effects, such as refusing the substitute or regurgitating even more. The group postulated this may account for why, once infants have been started on prescribed milk substitutes, it becomes practically impossible for healthcare professionals to accurately gauge their true effect, or even stop the feed to assess the effect. The group therefore felt that there is a pressing need for large, well designed, blinded RCTs to address this important question and identified this issue as research recommendation.

Finally, it has also been hypothesised that an elimination of cows' milk in the mother's diet can be beneficial for the treatment of GOR in breastfed infants, but no data was found to support this. The group therefore concluded that no recommendation could be made on this.

5.2.6.2.3 Feed volume

Although daily infant requirements for volume of feeds are often discussed on product packaging, healthcare professionals usually recommend a total volume of around 150 ml/kg body weight per day divided across a number of feeds (for example 6 to 8) every 24 hours. This figure is a useful 'rule of thumb' once feeding is well established for term infants, and remains reasonably accurate up until weaning when infants begin to take an increased component of their nutrition and energy as solid feed. Breastfed babies, however, mainly feed 'on demand' frequently in the first few weeks of life.

The guideline development group noted a single non-randomised crossover study, which found that a feed volume of 9 ml/kg per feed (lower than most infants would typically receive) was effective at reducing reflux episodes (according to a short-term, post feed pH monitor) when compared with a larger feed volume. This study did not report a daily feed regimen that was effective in comparison with a more conventional feeding schedule (that is, a feeding schedule of more frequent feeds of smaller volume that would keep to appropriate total daily feed volume).

This evidence matched the group's own experience, which is that in infants who are inadvertently overfed an increased feed volume can appear to cause or potentiate regurgitation. However, it was the group's opinion that if the feeding volume for individual feeds must be decreased, then an adequate total volume should be maintained (generally accepted as 150 ml/kg per day) and, therefore, that the number of feeds may need to increase.

Ultimately, it is essential that babies remain adequately hydrated and receive sufficient and appropriate nutrition. All infants have minor individual differences, so calculations on feed volumes and calorific requirements are of secondary importance compared with monitoring a baby's growth, which in the UK is monitored in primary care, augmented where necessary by secondary referral.

The group concluded that altering feed volume and frequency was an effective and easily modifiable intervention with few, if any, adverse effects, assuming babies continue to receive an effective overall total quantity of feed and nutrition and that they continue to thrive and develop normally.

5.2.6.2.4 Key conclusions

Based on the reviewed evidence, its experience and subsequent discussion, the guideline development group outlined a stepped care management sequence for formula fed infants who had GOR causing significant distress. The group recommended that following an intitial feeding assessment, feed volumes could be reduced but only if they were clearly excessive. Then, infants should be offered smaller, more frequent feeds without reducing a total daily volume intake unless judged that the feeds were already small and frequent. Then, if the symptoms persisted, a trial of thickened formula should be given. If these measures did not improve the infant's symptoms, the guideline development group recommended that the thickened formula be discontinued and a trial of an alginate preparation be given (see Section 5.3.7).

For breastfed infants, the group agreed an initial detailed feeding and regurgitation feeding history is equally vital, with appropriate skilled support for breastfeeding technique, including positioning and attachment.

5.2.6.3 Consideration of health benefits and resource uses

The guideline development group noted that many types of feeding thickeners are available, both commercially in over-the-counter products and also on prescription. There was, however, not enough comparative data to allow assessment of the health gain in order to determine which thickening agent was the most cost effective. Therefore the type of thickener that should be offered is not recommended and can be left to the discretion of the pharmacist healthcare professional, taking into account patient preference, local acquisition cost and route of delivery.

5.2.6.4 Quality of evidence

Fourteen studies on thickening of feeds were included in the review. All the studies were randomised. The main biases in these studies were variations in agents used to thicken feeds and in outcomes that were measured. The evidence showed a consistent pattern that use of thickeners reduced levels of overt reflux and associated symptoms in infants. Only a single non-randomised study was identified for each of the 2 questions on feeding volume and cows' milk. The very low quality and lack of available evidence means that a strong recommendation could not be made for these interventions.

5.2.6.5 Other considerations

5.2.6.5.1 Breastfeeding

The benefits of breastfeeding for infants are recognised as being beyond any doubt. The evidence review did not investigate the merits of breastfeeding in comparison with formula feeding for GORD. It is the opinion of the guideline development group that, whenever possible, every infant should be breastfed.

5.2.7 Recommendations

25. 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.

26. 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).

5.2.8 Research recommendations

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

Why this is important

There is a widespread belief that GOR and/or GORD in formula-fed infants is often caused by intolerance to cows' milk. As a result, health professionals often prescribe a trial of hydrolysed formula as a substitute for cows' milk formula. This has resource implications because hydrolysed formula is more expensive than cows' milk formula. Additionally, there is no evidence on the clinical or cost effectiveness of this approach. Therefore, it is proposed that a randomised controlled trial is undertaken to explore this question. It is important to consider 2 population subgroups:

- infants with a personal or family history of atopic conditions
- infants whose GOR and/or GORD has not responded to the initial management outlined in this guideline (up to and including alginates).

5.3 Aliginates and antacids

Alginates and antacids are prescribed to treat symptoms of gastro-oesophageal reflux disease (GORD).

Commonly used alginates include Gaviscon Infant and other compound alginates such as Gaviscon, Gaviscon Advance, Gastrocote and Peptac. Of these, only Gaviscon Infant can be used in younger children. The mode of action of Gaviscon Infant is considered to be physical – its summary of product characteristics states that by reacting with acidic gastric contents the alginate forms a viscous gel that stabilises stomach activity, so reducing the incidence of gastro-oesophageal reflux. Gaviscon Infant is not designed to reduce gastric acidity.

Alginate preparations used in older children form a viscous gel which acts as a raft that floats on the stomach contents and may reduce the symptoms of reflux. Alginates taken in combination with an antacid increase the viscosity of the stomach contents and can protect the oesophageal mucosa from acid reflux.

The sodium content of alginates may vary between preparations and this should be borne in mind when used for infants and children with renal impairment or cardiac co-morbidities. Aluminium has been removed from more recent formulations of Gaviscon Infant.

Antacids aim to reduce the likelihood of acid related symptoms, such as heartburn or dyspepsia. Commonly used antacids often contain either sodium/potassium bicarbonate, or aluminium, magnesium or calcium salts, and are designed to neutralise acid, but are not designed to increase viscosity of gastric contents. Aluminium-containing antacids should not be used in children with renal impairment or in infants as accumulation may lead to increased plasma concentrations.

The guideline development group reviewed the evidence for the effectiveness of antacids and alginates in managing GORD symptoms in children and young people.

5.3.1 Review question

How effective are antacids/alginates compared with placebo in the treatment of GOR/GORD?

For full details see review protocol in Appendix E.

5.3.2 Description of included studies

The search strategy created for this review can be found in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profiles below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Four randomised controlled trials were included in this review (Buts et al., 1987; Del Buono et al., 2005; Forbes et al., 1986; Miller et al 1999). Two studies were from the UK (Del Buono et al., 2005; Miller et al., 1999), 1 from Belgium (Buts et al., 1987) and 1 from Australia (Forbes et al., 1986). The guideline development group was also aware of a protocol for an ongoing Cochrane review (Tighe et al., 2010). No studies were identified on the use of antacids for the management of GOR or GORD in children and young adults.

Sample sizes ranged from 20 to 90 patients. The age of the subjects varied, including infants less than 6 months in 1 study (Miller et al., 1999), infants under 12 months in 1 study (Del Buono et al., 2005), children up to the age of 3 years in 1 study (Buts et al., 1987) and children up to the age of 17 years in 1 study (Forbes et al., 1986).

The settings of the studies were reported in 2 studies; these included a gastroenterology department and general practices.

The studies examined a range of different Gaviscon formulations, described in the original research as:

- Gaviscon infant liquid: alginic acid with antacid; 10 ml 4 times a day for infants, 20 ml 4 times a day for older children (Forbes et al., 1986).
- Gaviscon: aluminium-containing alginate preparation; 2 g of alginate per sachet (Buts et al., 1987)
- Infant Gaviscon: the currently available formulation as per BNFc. 225 mg sodium alginate and 87.5 mg magnesium alginate. In breastfed Infants under 4.5 kg (10 lb) – 1 sachet. In breastfed Infants over 4.5 kg (10 lb) – 2 sachets. In bottle-fed infants 1 sachet per 115 ml (4 fl oz) of feed. The authors state that this preparation was aluminium–free (Miller et al., 1999).
- Infant Gaviscon: consisting of sodium and magnesium alginate (225 mg sodium alginate and 87.5 mg magnesium alginate in 225 ml milk) and mannitol but no bicarbonate (Del Buono et al., 2005).

The majority of the studies (Buts et al., 1987; Del Buono et al., 2005; Forbes et al., 1986) monitored for oesophageal reflux either using pH or impedance monitoring, or both, over a 24 hour period. In addition the studies variously reported: cessation of, or days free of, overt regurgitation; reduced frequency of overt regurgitation; adverse outcomes; and parent reported reduction in infant distress. The GRADE profile reports the exact outcome reported in the studies. None reported on the other prioritised outcomes.

The differing ages of the populations, the varied formulations of Gaviscon employed and different outcomes reported in the studies meant that meta-analysis of the data was inappropriate.

5.3.3 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

The following GRADE profiles are shown below:

- GRADE findings for comparison of aluminium free infant Gaviscon (sodium alginate) with placebo
- GRADE findings for comparison of Gaviscon (alginate) with placebo
- GRADE findings for Gaviscon infant liquid (alginic acid with antacid) with placebo
- GRADE findings for infant Gaviscon (sodium and magnesium alginate and mannitol but no bicarbonate) with placebo.

Table 42: GRADE profile for comparison of aluminium-free infant Gaviscon (sodium alginate) with placebo in infants aged less than 6 months.

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aluminium free Infant Gaviscon (sodium alginate)	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Cessation (or symptom free days) of overt regurgitation											
Reported as at least 10% symptom free days, %											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Serious[6]	None	13/42 (31%)	5/46 (11%)	p=0.027[a] Odds ratio [OR] (95%CI): 3.68 (1.18 to 11.44)*	-	Very low
Reduced frequency of overt regurgitation											
Reported as median number of vomiting/regurgitation episodes in the previous 24 hours											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Serious[7]	None	n=42 Median (range): 3.0 (0 to 22)	n=46 Median (range): 5.0 (0 to 37)	p=0.009[a]	-	Very low
Reported as mean frequency of vomiting/regurgitation episodes after 14 days											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Serious[7]	None	n=42 Mean: 4.5 (Standard deviation [SD] not reported)	n=46 Mean: 6.2 (SD not reported)	p=0.056[a]	-	Very low
Adverse outcomes, n (%)											
Functional diarrhoea											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Very serious[8]	None	6/42 (14.3%)	5/46 (10.9%)	p>0.1[b] OR (95%CI): 1.37 (0.38 to 4.86)*	-	Very low
Teething syndrome											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Very serious[8]	None	5/42 (11.9%)	3/46 (6.5%)	p>0.1[b] OR (95%CI): 1.94 (0.43 to 8.66)*	-	Very low
Diarrhoea not otherwise specified											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Very serious[8]	None	1/42 (2.4%)	4/46 (8.7%)	p>0.1[b] OR (95%CI): 0.26 (0.03 to 2.39)*	-	Very low

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aluminium free Infant Gaviscon (sodium alginate)	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Constipation											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Very serious[8]	None	4/42 (9.5%)	1/46 (2.2%)	p>0.1[b] OR (95%CI): 4.74 (0.51 to 44.20) *	-	Very low
Acute nasopharyngitis											
1 (Miller et al 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Very serious[8]	None	3/42 (7.1%)	1/46 (2.2%)	p>0.1[b] OR (95%CI): 3.46 (0.35 to 34.64)*	-	Very low
Colic[c]											
1 (Miller et al., 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Very serious[8]	None	2/42 (4.8%)	3/46 (6.5%)	p>0.1[b] OR (95% CI): 0.72 (0.11 to 4.51)*	-	Very low
Parent reported reduction in infant distress											
Reported as parent/guardian assessment of symptoms, n (%)											
1 (Miller et al., 1999)	RCT	Very serious [1,2,3,4,5]	None	None	Serious[7]	None	Very good + good: 33/41 Acceptable, poor + very poor: 8/41	Very good + good: 21/44 Acceptable, poor + very poor: 23/44	Chi squared equals 8.468[a] p=0.0036[a]	-	Very low

CI confidence interval, OR odds ratio, p probability, RCT randomised controlled trial, SD standard deviation
[*] *Calculated by NCC-WCH technical team based on data reported in the article*
[a] *As reported in the study (Wilcoxon rank sum test)*
[b] *As reported in article (chi square or Fisher's exact test, as appropriate)*
[c] *Reported as adverse event in paper*
[1] *Randomisation not described in detail*
[2] *Unclear whether there was adequate allocation concealment*
[3] *Unclear whether investigators were blinded to intervention*
[4] *Unclear whether investigators were blinded to confounding factors*
[5] *20 withdrawals (alginate, n=7; placebo, n=13; p>0.2) due primarily to adverse events (alginate, n=4; placebo, n=7) and lack of efficacy (alginate, n=2; placebo, n=3)*
[6] *Wide confidence interval (CI crosses 2 zones)*
[7] *Imprecision could not be investigated due to way result has been reported*
[8] *Very wide confidence interval (CI spans 3 zones)*

Table 43: GRADE profile for comparison of Gaviscon (alginate) with placebo in children aged up to 3 years

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gaviscon (alginate)	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux measured using oesophageal pH measurement											
Total number of reflux episodes (oesophageal pH<4 for at least 25 seconds) in 24 hours											
1 (Buts et al 1987)	RCT	Serious[1,2,3,4,5]	None	None	Serious[6]	None	n=10 Mean (SD): 56.0 (53.1)	n=10 Mean (SD): 90.6 (46.5)	p-value for after Gaviscon versus before Gaviscon: p<0.05[a] p-value for after placebo versus before placebo: NS[a] Mean Difference [MD] (95%CI): −35.00 (−78.50 to 8.50)*	-	Low
Number of reflux episodes greater than 5 minutes											
1 (Buts et al 1987)	RCT	Serious[1,2,3,4,5]	None	None	None	None	n=10 Mean (SD): 1.2 (0.6)	n=10 Mean (SD): 4.6 (2.8)	p-value for after Gaviscon versus before Gaviscon: p<0.05[a] p-value for after placebo versus before placebo: NS[a] MD (95%CI): −4.00 (−5.96 to −2.04)*	-	Moderate
Percent total reflux (Reflux Index)											
1 (Buts et al 1987)	RCT	Serious[1,2,3,4,5]	None	None	None	None	n=10 Mean (SD): 6.1 (0.9)	n=10 Mean (SD): 10.1 (4.4)	p value for after Gaviscon versus before Gaviscon: p<0.05[a] p value for after placebo versus before placebo: NS[a] MD (95% CI): −4.00 (−6.56 to −1.44)*	-	Moderate
Adverse outcomes (events not specified), n (%)											
1 (Buts et al 1987)	RCT	Serious[1,2,3,4,5]	None	None	Serious[7]	None	n=10 0/10 (0%)	n=10 0/10 (0%)	-	-	Low

CI confidence interval, MD mean difference, p probability, RCT randomised controlled trial, SD standard deviation
** Calculated by NCC-WCH technical team based on data reported in the article*
[a] As reported in study
[1] Randomisation method not described in detail
[2] Alternate allocation to treatments
[3] Not all subjects endoscoped
[4] Unclear whether investigators were blinded to intervention
[5] Unclear whether investigators were blinded to confounding factors
[6] Wide confidence interval (confidence interval of SMD crosses 2 zones)
[7] Imprecision could not be investigated due to way result have been reported

Table 44: GRADE profile for Gaviscon infant liquid (alginic acid with antacid) with placebo in children and young adults aged up to 17 years.

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gaviscon infant liquid (alginic acid with antacid)	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux measured using oesophageal pH measurement											
Number of episodes of GOR (esophageal pH<4) in 24 hours											
1 (Forbes et al 1986)	RCT	Serious[1,2,3,4]	None	None	Serious[5]	None	n=10 Mean (SD): 81 (72.7)	n=10 Mean (SD): 49 (34.8)	p: NS[a] MD (95% CI): 32.00 (−18.18 to 82.18)*	-	Low
Total duration of acid reflux in minutes											
1 (Forbes et al 1986)	RCT	Serious[1,2,3,4]	None	None	Very serious[6]	None	n=10 Mean (SD): 74 (123.3)	n=10 Mean (SD): 96 (34.8)	p: NS[a] MD (95% CI): −22.00 (−101.26 to 57.26)*	-	Very low
Adverse outcomes (events not specified), n (%)											
1 (Forbes et al 1986)	RCT	Very serious[1,2,3,4]	None	None	Not assessed[7]	None	n=10 0/10 (0%)	n=10 0/10 (0%)	-	-	Very low

CI confidence interval, GOR gastro-oesophageal reflux, MD mean difference, NS not significant, p probability, RCT randomised controlled trial, SD standard deviation

[*] *Calculated by NCC-WCH technical team based on data reported in the article*

[a] *As reported in the study (Wilcoxon signed rank test)*

[1] *Method of randomisation not described in detail*

[2] *Unclear whether there was adequate allocation concealment*

[3] *Not all subjects endoscoped*

[4] *Unclear whether investigators were blinded to confounding factors*

[5] *Wide confidence interval (confidence interval of SMD crosses 2 zones)*

[6] *Very wide confidence interval (confidence interval of SMD crosses 3 zones)*

[7] *Imprecision could not be investigated due to way result have been reported*

Table 45: GRADE profile for infant Gaviscon (sodium and magnesium alginate and mannitol but no bicarbonate) with placebo in infants aged up to 12 months.

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infant Gaviscon (sodium and magnesium alginate and mannitol)	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Reflux measured using intra-oesophageal impedance and dual channel pH monitoring											
Number of reflux events per hour											
1 (Del Buono et al 2005)	RCT	Very serious [1,2,3,4]	None	None	Not assessed[5]	None	-	Median difference (placebo –Gaviscon infant), range: 0.06 (−1.20 to 3.80)	p=0.784[a]	-	Very low
Number of acid reflux events per hour											
1 (Del Buono et al 2005)	RCT	Very serious [1,2,3,4]	None	None	Not assessed[5]	None	-	Median difference (placebo –Gaviscon infant), range: −0.02 (−0.55 to 3.94)	p=0.940[a]	-	Very low
Total reflux time per hour (seconds per hour)											
1 (Del Buono et al 2005)	RCT	Serious [1,2,3,4]	None	None	Not assessed[5]	None	-	Median difference (placebo –Gaviscon infant), range: −7.6 (−38.5 to 111.8)	p=0.096[a]	-	Very low

CI confidence interval, p probability, RCT randomised controlled trial
[a] As reported in study (Wilcoxon signed rank test)
[1] Method of randomisation not described in detail
[2] Unclear whether groups were comparable at baseline (baseline characteristics not reported)
[3] Unclear whether groups were comparable for dropout (numbers not reported)
[4] Unclear whether groups were comparable for missing data (numbers not reported)
[5] Imprecision could not be investigated due to way result have been reported

5.3.4 Evidence statements

See Table 42 to

Table 45.

5.3.4.1 Aluminium free infant Gaviscon versus placebo

5.3.4.1.1 Cessation of symptom free days of overt regurgitation

Reported as at least 10% symptom free days

One study found that the percentage of infants with at least 10% symptom free days was higher in infants receiving aluminium free infant Gaviscon compared with infants receiving placebo. This finding was statistically significant. The evidence for this finding was of very low quality.

5.3.4.1.2 Reduced frequency of overt regurgitation

Reported as median number of vomiting/regurgitation episodes in the previous 24 hours

One study found that the median number of vomiting/regurgitation episodes in the previous 24 hours was lower in infants receiving aluminium free infant Gaviscon compared with infants receiving placebo. This finding was statistically significant. The evidence for this finding was of very low quality.

Reported as mean frequency of vomiting/regurgitation episodes after 14 days

One study did not find a statistically significant difference in the mean frequency of vomiting/regurgitation episodes after 14 days in infants receiving aluminium free infant Gaviscon compared with infants receiving placebo. The evidence for this finding was of low quality.

5.3.4.1.3 Adverse outcomes

Functional diarrhoea, diarrhoea not otherwise specified, constipation, acute nasopharyngitis and colic

One study did not find a statistically significant difference in the occurrence of any of the above adverse outcomes (reported separately) in infants receiving aluminium free infant Gaviscon compared with infants receiving placebo. The evidence for this finding was of very low quality.

5.3.4.1.4 Parent reported reduction in infant distress

Reported as parent/guardian assessment of symptoms

One study found that parent assessment of symptoms was significantly better in infants receiving aluminium free infant Gaviscon compared with infants receiving placebo. The evidence for this finding was of low quality.

5.3.4.2 Gaviscon versus placebo

5.3.4.2.1 Reflux measured using oesophageal pH monitoring

Total number of reflux episodes (24 hours)

One study did not find a statistically significant difference in the total number of reflux episodes in infants receiving Gaviscon (alginate) compared with infants receiving placebo. The evidence was of low quality.

Number of reflux episodes greater than 5 minutes

One study found that the number of reflux episodes greater than 5 minutes was lower in infants receiving Gaviscon (alginate) compared with infants receiving placebo. This finding was statistically significant. The evidence was of moderate quality.

Reflux index (reported as the percentage of time the oesophageal pH was less than 4)

One study found that the percentage of total reflux (reflux index) was lower in infants receiving Gaviscon (alginate) compared with infants receiving placebo. This finding was statistically significant. The evidence was of moderate quality.

5.3.4.2.2 Adverse outcomes – not specified

One study found no adverse events were observed in infants receiving Gaviscon (alginate) or placebo. The evidence was of moderate quality.

5.3.4.3 Gaviscon infant liquid versus placebo

5.3.4.3.1 Reflux measured using oesophageal pH measurement

Number of episodes of GOR (oesophageal pH less than 4) in 24 hours

One study did not find a statistically significant difference in the number of episodes of GOR in infants receiving Gaviscon Infant Liquid (alginic acid with antacid) compared with infants receiving placebo. The evidence was of low quality.

Total duration of acid reflux in minutes

One study did not find a statistically significant difference in the total duration of acid reflux in infants receiving Gaviscon Infant Liquid (alginic acid with antacid) compared with infants receiving placebo. The evidence was of very low quality.

5.3.4.3.2 Adverse outcomes – not specified

One study found no adverse events were observed in infants receiving Gaviscon Infant Liquid (alginic acid with antacid) or placebo. The evidence was of moderate quality.

5.3.4.4 Infant Gaviscon versus placebo

5.3.4.4.1 Reflux measured using intra-oesophageal impedance and dual channel pH monitoring

Number of reflux events per hour

One study did not find a statistically significant difference in the number of reflux events per hour in infants receiving Gaviscon Infant compared with infants receiving placebo. The evidence was of moderate quality.

Number of acid reflux events per hour

One study did not find a statistically significant difference in the number of acid reflux events per hour in infants receiving Gaviscon Infant compared with infants receiving placebo. The evidence was of moderate quality.

Total reflux time per hour

One study found a statistically significant difference in the total reflux time per hour in infants receiving Gaviscon Infant compared with infants receiving placebo. The evidence was of moderate quality.

5.3.5 Health economics profile

No health economic studies were identified for this question and the available data was not suitable for health economic modelling. Therefore, only cost data was considered (see Appendix A: Health economics).

5.3.6 Evidence to recommendations

5.3.6.1 Relative value placed on the outcomes considered

Of the outcomes prioritised by the guideline development group, cessation of regurgitation and reduced frequency of overt regurgitation were considered the most important from a clinical perspective. Overt regurgitation is a very common reason for administration of Gaviscon Infant to infants and these outcomes were therefore of key importance in the assessment of efficacy. Detection and characterisation of oesophageal reflux using oesophageal pH or impedance monitoring was also considered important. Although this was only an indirect marker of efficacy, the information provided could nevertheless help in considering the likely effectiveness of these agents in various clinical circumstances. The guideline development group listed a number of outcomes reported by parent (parents reported reduction in infant distress, improvement in validated reflux questionnaire and parent satisfaction with this intervention) which they considered of clinical relevance. They also sought information on resolution of faltering growth as this is commonly believed to be associated with GOR or GORD in some infants. Finally, they considered adverse outcomes to be important when recommending treatment for potentially mild symptoms.

5.3.6.2 Consideration of clinical benefits and harms

In infants who have not been weaned the only preparation of alginates available for prescription is Gaviscon Infant. Gaviscon Infant is delivered as a powder mixed with a small amount of warm water. As Gaviscon Infant can be administered with water following conventional feeds, it can used in women who exclusively breastfeed, unlike feed thickening agents.

Each unit dose sachet of Gaviscon Infant contains 0.65 g powder (225 mg sodium alginate and 87.5 mg magnesium alginate). It is intended for use in children aged up to 2 years. It contains mannitol and colloidal silica as excipients.

The studies included in the evidence review used differing preparations of alginate, as outlined above; an aluminium free infant Gaviscon (sodium alginate) reported in Miller et al. (1999), Gaviscon (alginate) reported in Buts et al. (1987), Gaviscon infant liquid (alginic acid with antacid) reported in Forbes et al. (1986) and Infant Gaviscon (sodium and magnesium alginate and mannitol but no bicarbonate) reported in Del Buono et al. (2005). Each of the preparations was compared with a placebo formula.

The guideline development group noted that the preparations currently available were quantitatively different from those used in 2 of the studies identified. The Gaviscon liquid formula preparation reported in Forbes et al. (1986) was no longer in use. Similarly, the Gaviscon product used in the study by Buts et al. (1987) differed in its composition from the currently used product. The group considered these differences to be important and hence that the findings of these studies were no longer relevant. The group therefore focused on the studies by Miller et al. (1999) and Del Buono et al. (2005).

The study by Miller et al. (1999) showed that the number of regurgitation episodes in a 24 hour period was statistically lower in those treated with Gaviscon Infant compared with those treated with placebo, but the frequency of regurgitation episodes was not statistically different at 14 days of treatment. No statistical difference was found in the incidence of adverse events. Finally, although the study reported a statistically significant benefit in attaining 10% symptom free days, the group did not consider this outcome to have clinical relevance.

The study by Del Buono et al. (2005) used dual impedance and pH monitoring to assess acid reflux events over 24 hours, the difference in the number of reflux events per hour, the total reflux time in seconds per hour (using impedance monitoring) and the number of acid reflux events per hour (using oesophageal pH monitoring). The study reported that the number of reflux events, the number of acid reflux events and the total reflux time per hour did not change significantly with Gaviscon treatment. The group noted that outcomes were based on oesophageal measurements, no data on regurgitation events was reported and the data from the impedance was not suitable as a proxy for this outcome. In addition, the dosage described in the study appeared to be lower than that recommended by the manufacturer and this could influence the findings.

The guideline development group noted that there would be no benefit in offering an alginate for any reason beyond reducing the frequency of regurgitation. There was no evidence identified for alginates providing any benefit in the treatment of conditions associated with gastro-oesophageal reflux disease, for example erosive oesophagitis. The group noted that neither Miller et al. (1999) nor Del Buono et al. (2005) included children older than 1 year (infants in the studies were up to 12 months and 6 months, respectively) and has only made recommendations for the use of alginates in infants.

The group was concerned that alginates are prescribed to infants where the benefit would be limited or where the regurgitation is not problematic and, in most cases, would resolve naturally itself (see Chapter 5). Therefore the use of alginates should only be recommended where the regurgitation is problematic and would not be adequately treated with conservative management options and parental advice. The group concluded that although the evidence was limited, with only the Millar et al. (1999) study examining frequency of overt reflux, it matched their clinical experience. The group recommended that an alginate be offered as a therapeutic trial for 1–2 weeks, but there was not enough evidence of benefit to empirically offer an alginate for longer. A review at 1–2 weeks should be offered to all infants given treatment. To minimise cost and inconvenience to patients, their families and carers, and professionals, the review can happen via telephone or at a face-to-face consultation. After this therapeutic trial, the infant's condition should be reviewed and the need for ongoing treatment should be agreed upon. The effect of an alginate should be evident: if, after 1 or 2 weeks, there is no improvement in symptoms then treatment with alginates can be discontinued and the potential adverse effects and cost of the failed alginate intervention would be minimised.

The main alternative treatments for alginates in bottle fed infants are changes to feeds, most notably feed thickening agents. No studies were identified that compared alginates to any recommended feed thickening agent. In the absence of comparative evidence, the guideline development group considered a rational sequence of interventions should be tried for formula fed infants with frequent regurgitation associated with marked distress – including changes to feed volume and frequency and, if necessary, the use of a thickened formula (see Section 5.2.7). They recommended a trial of alginate therapy for those in whom symptoms persisted despite those interventions. The rationale for offering alginates in this setting was that feed thickeners are a cheaper intervention than alginates, so 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 (such as feed thickeners). The group highlighted that this order of treatment should only be applied

in infants that are bottle fed. Feeding changes are not appropriate in breastfed infants and in this situation alginates should be considered earlier. The group noted that a method for administering Infant Gaviscon to breastfed infants was available for parents (see Section J.1 of Appendix J).

No evidence was identified for the use of antacids to treat problematic overt regurgitation in children or young people. Furthermore, the group noted that the pharmacological action of an antacid would not have any benefit in reducing the frequency of overt regurgitation. Antacids could theoretically provide short-term relief for heartburn, a commonly reported symptom of GOR in older children. The group recommended that antacids and antacid/alginate combinations should be offered to young people suffering from heartburn. This is extrapolated from NICE guideline on dyspepsia and gastro-oesophageal reflux disease. Antacids should only be offered in young people who have gone through puberty as the effect in younger children is unknown and therefore recommendations made based on adult evidence are inappropriate.

5.3.6.3 Consideration of health benefits and resource uses

A description of the treatment costs associated with treatment are provided in Appendix A: Health economics.

5.3.6.4 Quality of evidence

Four randomised controlled trials were identified for this review. The quality of the evidence ranged from moderate to very low. The different ages of the study population, varying formulations of Gaviscon and different outcomes reported by the studies meant that the data could not be meta-analysed. Sample size was small and ranged from 20 to 90 infants or children. The other sources of bias included poorly defined methods of randomisation and analysis, serious imprecision in results and failure of studies to report 95% confidence intervals (CIs) or ranges which meant that imprecision could not be calculated in some studies. These limited the guideline development group's ability to make clear conclusions based on the evidence.

5.3.7 Recommendations

27. **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.**

28. **In formula-fed infants, if the stepped-care approach is unsuccessful (see recommendation 26), 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.**

5.3.8 Research recommendations

No research recommendations in this area.

6 Pharmacological treatment of GORD

6.1 H_2 receptor antagonists, proton pump inhibitors and prokinetics

Drug treatments are usually considered for GORD after attempting more conservative treatments, such as feeding changes in infants or use of alginates. The groups of medications being investigated in this chapter are broadly divided into those which may promote gastric emptying and enhance upper gut motility (pro-kinetics) and those which reduce gastric acid secretion (the H_2 receptor antagonists or the more recent proton pump inhibitors).

Before prescribing any drug treatment, it is important, ethical and logical that healthcare professionals adhere to the principle of 'first, do no harm' by always considering the indications, contra-indications, possible complications and potential interactions of the agent they are recommending. The treatment principles for GORD are no different and it was for these reasons that a previously widely used medication (Cisapride) was removed from the available treatment options because of concern about rare but very serious side effects (heart arrhythmia). Also, when caring for infants or small children the practical issues of drug administration become very important, particularly considering the availability of acceptable and reasonably priced preparations for these age groups.

6.1.1 Review question

What is the comparative effectiveness of the following treatments for GOR/GORD?

- How effective are H_2-receptor antagonists (H_2RAs) compared with placebo in the treatment of GOR/GORD?
- How effective are proton pump inhibitors (PPIs) compared with placebo and one another in the treatment of GOR/GORD?
- How effective are H_2 receptor antagonists compared with proton pump inhibitors in the treatment of GOR/GORD?
- How effective are prokinetic agents compared with placebo in the treatment of GOR/GORD?

For full details see review protocol in Appendix E.

6.1.2 Description of included studies

The search strategy created for this review can be found in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profiles below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Fifteen studies were included in this review (Cucchiara et al., 1989; Cucchiara et al., 1993; Simone et al., 1997; Leung et al., 1984; Bines et al., 1992; Carroccio et al., 1994; Cresi et al., 2008; Bellissant et al., 1997; Tolia et al., 1989; Omari et al., 2007; Moore et al., 2003; Winter et al., 2012; Orenstein et al., 2009; Davidson et al., 2013; Hussain et al , 2014).

All the studies included were randomised controlled trials (RCTs), with 3 using a crossover design (Omari et al., 2007; Moore et al., 2003; Tolia et al., 1989).

The definition of GOR/GORD varied between studies, and included criteria based on pH monitoring, endoscopic findings, non-response to treatment or reported GORD symptoms.

Six studies assessed the effect of PPIs (Omari et al., 2007; Orenstein et al., 2009; Winter et al 2012; Moore et al., 2003; Davidson et al., 2013; Hussain et al , 2014), 2 studies assessed the effect of H_2 receptor antagonists (Simeone et al., 1997; Cucchiara et al., 1989) and 6 studies examined prokinetics (Tolia et al., 1989; Bines et al., 1992; Bellissant et al., 1997; Cresci et al., 2008; Carroccio et al., 1994; Leung et al., 1984). However, the use of prokinetics is increasingly restricted, with Cisapride being withdrawn from use in the UK and use of domperidone being limited in many areas due to concerns about increased risk of cardiac events (see below). One trial was identified that compared PPIs with H_2 receptor antagonists (Cucchiara et al., 1993). No evidence comparing different PPIs was found.

Five studies were undertaken in the USA (Orenstein et al; Winter et al 2012; Tolia et al., 1989; Bines et al., 1992; Hussain et al., 2014), 5 in Italy (Cresci et al., 2008; Carroccio et al., 1994; Simeone et al., 1997; Cucchiara et al., 1989; Cucchiara et al., 1993), 2 in Australia (Moore et al., 2003; Davidson et al., 2013) and 1 each in France, Sweden, Australia and Canada (Leung et al., 1984; Omari et al., 2007; Bellissant et al., 1997).

The age of children entered into studies varied as follows:

- range 4 to 51 weeks (Orenstein et al., 2009)
- range 34 to 40 weeks postmenstrual age (Omari et al., 2007)
- range 3 to 10.2 months (Moore et al., 2003)
- mean 4.9 months (SD 2.6) and mean 4.9 months (SD 3.2) in each treatment group (Winter et al., 2012)
- range 0.5 to 12 years (Simeone et al., 1997)
- mean 29.03 months (SD 39.73) (Cucchiara et al., 1989)
- range 21 to 1215 days (Leung et al., 1984)
- range 0.5 to 11.3 years (Bines et al., 1992)
- range 1 to 19 months (Carroccio et al., 1993)
- mean 122 days (SD 79) (Bellissant et al., 1997)
- mean 24.7 days (SD 13.7) (Cresi et al., 2008)
- range 1 to 9 months (Tolia et al., 1989)
- mean 48.1 days (SD 29.8) (Davidson et al., 2013)
- range 1 to 11 months (Hussain et al., 2014).

One study was included that compared H_2 receptor antagonists with PPIs (Cucchiara et al., 1993). The study compared high dose ranitidine plus omeprazole in the management of GORD refractory with lower dose ranitidine.

The only setting mentioned in studies was the paediatric unit within hospitals.

Further details about each study are shown in the evidence tables.

6.1.3 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

The following GRADE profiles are shown below:

- comparison of PPIs with placebo for the management of GORD in infants
- comparison of H_2 receptor antagonists with placebo for the management of GORD in infants
- comparison of prokinetics with placebo for the management of GORD in infants
- comparison of PPIs compared with H_2 receptor antagonists.

Table 46: GRADE profile for comparison of PPIs with placebo for the management of GORD in infants.

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proton pump inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Regurgitation (Change % of feeds per week)											
1 (Orenstein et al., 2009)	RCT	Serious[1]	None	None	Not assessed [2]	None	Lansoprazole: N=81, -14%	n=81, -11%	NS[a]	NA	Moderate
Frequency of vomiting											
1 (Omari et al., 2007)	RCT, Crossover	Very serious [1,3]	None	None	Not assessed [2]	None	Omeprazole: Median 8.5 (IQR 7 to 22.8)	Median 6.5 (IQR 3 to 14.3)	NS[a]	NA	Low
Vomiting											
1 (Davidson et al., 2013)	RCT	Serious [4]	None	Serious [5]	Very serious [6]	None	Esomeprazole: Mean 5.21 (SD 6.75)	Mean 4.87 (SD 5.93)	MD 0.34 [-3.15, 3.83]	NA	Very low
Frequency of regurgitation											
1 (Hussain et al., 2014)	RCT	Very serious [1,7]	None	Serious[8]	Not assessed [2]	None	Raberprazole: NR	NR	NS[a]	NA	Very low
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
Number of acid GOR episodes											
1 (Omari et al., 2007)	RCT, Crossover	Very serious [1,3]	None	None	Not assessed [2]	None	Omeprazole: 59.6 (SE 26.7)	119.4 (SE 20.9)	p<0.05[a]	NA	Low
Number of acid GOR episodes lasting longer than 5 minutes											
1 (Omari et al., 2007)	RCT, Crossover	Very serious [1,3]	None	None	Not assessed [2]	None	Omeprazole: 3.0 (SE 2.0))	8.0 (SE 2.1	p<0.01[a]	NA	Low
Longest acid GOR episode (minutes)											
1 (Omari et al., 2007)	RCT, Crossover	Very serious [1,3]	None	None	Not assessed [2]	None	Omeprazole: 16.3 (SE 8.0)	48.6 (SE 10.1)	p<0.01[a]	NA	Low
% time pH<4.0											
1 (Omari et al., 2007)	RCT, Crossover	Very serious [1,3]	None	None	Not assessed [2]	None	Omeprazole: 4.9 (SE 3.4)	19.0 (SE 4.5)	p<0.01[a]	NA	Low
1 (Moore et al., 2003)	RCT, Crossover	Serious [1,9]	None	Serious[10]	Not assessed [2]	None	Omeprazole: 1.0 (SD 1.3)	5.3 (SD 4.9)	p<0.01[a]	NA	Low
Resolution of oesophagitis											
Not reported											
Resolution of faltering growth											
Not reported											

Quality assessment							Number of infants		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proton pump inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Adverse outcomes											
Adverse events											
1 (Orenstein et al., 2009)	RCT	Serious[1]	None	None	None	None	Lansoprazole: 50[b]	37b	NS[a]	NA	Moderate
1 (Hussain et al., 2014)	RCT	Very serious [1,7]	None	Serious[8]	None	None	Rebeprazole: 83/178	42/89	NS[a]	NA	Very low
Serious adverse events											
1 (Orenstein et al., 2009)	RCT	Serious[1]	None	None	None	None	Lansoprazole: 10 [c]	2m	p=0.032 [a]	NA	Moderate
1 (Omari et al., 2007)	RCT, Crossover	Very serious [1,7]	None	None	None	None	Omeprazole: 0	0	NS[a]	NA	Low
1 (Davidson et al., 2013)	RCT	SeriousI[4]	None	Serious[5]	None	None	Esomeprazole: 6	9	NS[a]	NA	Low
Parent reported reduction in infant distress											
Global severity index (parent reported improved at 4 weeks)											
1 (Orenstein et al., 2009)	RCT	Serious[1]	None	None	Not assessed [2]	None	Lansoprazole: 45	44	NS[a]	NA	Moderate
Improvement in validated reflux questionnaire											
Visual Analogue Scale by parents of infants irritability											
1 (Moore et al)	RCT, Crossover	Serious[9]	None	Serious[10]	Not assessed [2]	None	Omeprazole: 5.0 (SD 3.1)	5.9 (SD 2.1)	p=0.214[a]	NA	Low
I-GORQ-R											
1 (Hussain et al., 2014)	RCT	Very serious[1,7]	None	Serious[8]	Not assessed [2]	None	Raberprazole: NR	NR	NS[a]	NA	Very low
Parent satisfaction with this intervention											
Responder rate (>50% reduction in feeding or crying symptoms from baseline)											
1 (Orenstein et al., 2009)	RCT	Serious[1]	None	None	Not assessed [2]	None	Lansoprazole 44%	44%	NS[a]	NA	Moderate
Discontinued due to non-efficacy											
1 (Orenstein et al., 2009)	RCT	Serious[1]	None	None	Very serious [11]	None	Lansoprazole: 28 of 81	29 of 81	RR: 0.97 [0.64, 1.47]	NA	Very low
Discontinued due to worsening symptoms											
1 (Winter et al., 2012)	RCT	Serious[12]	None	Serious[13]	Very serious[11]	None	Esomeprazole: 15 of 39	20 of 41	RR: 0.79 [0.48, 1.31]	NA	Very low

CI confidence interval, GOR gastro-oesophageal reflux, IQR interquartile range, NA not available, NR not reported, NS not significant, p probability, RCT randomised controlled trial, RR relative risk, SD standard deviation, SE standard error

[a] *As reported in the study.*

[b] *Reported events were: Infection – URI, ear, LRTI, viral, constipation, eczema, fever, respiratory tract congestion, rhinorrhea, candidiasis, diarrhea, vomiting.*

[c] *Reported events were: Lower respiratory infection, diarrhea, Ileua, dehydration, otitis media, upper respiratory infection, epididymal infection, arachnoid cyst, febrile convulsion, klebsiella infection.*
[1] *Poor reporting of results that not all GRADE items could be assessed*
[2] *Reporting of results did not allow imprecision to be calculated.*
[3] *Small sample size; no washout period during crossover between treatments.*
[4] *Groups unbalanced at baseline; small sample size*
[5] *Study included neonates only*
[6] *SMD confidence intervals cross several categories on Cohen effect size. MD presented in table as more relevant.*
[7] *Method of randomisation not described in detail*
[8] *Only included infants in whom PPIs were effective in a pre-randomisation phase.*
[9] *Method of randomisation not explained in detail; no washout period; results from before crossover*
[10] *Infants had GORD and were irritable.*
[11] *Confidence intervals cross several +/- 0.25 RR*
[12] *Method of randomisation and concealment not explained in detail.*
[13] *Infants had to respond to treatment to enter the randomised part of the study.*

Table 47: GRADE profile for comparison of H_2 receptor antagonists with placebo for the management of GORD in infants and children.

Quality assessment							Number of infants and children		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	Comparator	Relative (95% CI)	Absolute (95% CI)	
Reduced frequency of overt regurgitation											
Regurgitation at 4 weeks											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Mean 1.3 (SD 1.1)	Mean 2.2 (SD 1.3)	NA[a]	NA	Very low
Vomiting at 4 weeks											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Mean 0.8 (SD 0.9)	Mean 2.1 (SD 1.1)	NA[b]	NA	Very low
Regurgitation at 8 weeks											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Mean 0.3 (SD 0.7)	Mean 1.7 (SD 1.4)	NA[a]	NA	Very low
Vomiting at 8 weeks											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Mean 0.4 (SD 0.7)	Mean 1.6 (SD 1.7)	NA[b]	NA	Very low
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
% of reflux episodes (Reflux Index)											
1 (Simeone et al., 1997)	RCT	Very serious [1]	None	None	Not assessed[2]	None	Nizatidine: Median 4.3 (range 1.5 to 11.2)	Median 10.4 (4.1 to 18.8)	NA[c]	NA	Very low

Quality assessment							Number of infants and children		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	Comparator	Relative (95% CI)	Absolute (95% CI)	
Number of reflux episodes											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Median 85.8 (range 42 to 227)	Median 123 (range 32 to 360)	NA[c]	NA	Low
Number of reflux episodes >5 minutes											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Median 1.7 (range 0 to 6)	Median 5.4 (range 2 to 10)	NA[c]	NA	Very low
Duration time of longest episode											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Nizatidine: Median 11.8 (range 4 to 40)	Median 25.1 (range 3 to 73)	NA[c]	NA	Very low
Resolution of oesophagitis - endoscope											
Esophagitis score[e]											
1 (Cucchiara et al., 1989)	RCT	Serious[3]	None	None	Not assessed[2]	None	Cimetidine: Mean 1.6 (SD 2.43)	Mean SD 5.43 (3.81)	NA[d]	NA	Low
Esophagitis score improved[e]											
1 (Cucchiara et al., 1989)	RCT	Serious[3]	None	None	Serious[4]	None	Cimetidine: 16 of 17	9 of 15	RR 1.57 [1.02, 2.41]	NA	Low
Endoscopy score normal[f]											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Very serious[4]	None	Nizatidine: 5 of 12	2 of 12	RR 2.50 [0.60, 10.46]	NA	Very low
Histology score normal[g]											
1 (Simeone et al., 1997)	RCT	Very serious[1]	None	None	Serious[4]	None	Nizatidine: 9 of 12	3 of 12	RR 3.00 [1.07, 8.43]	NA	Very low
Resolution of faltering growth – Not reported											
Adverse outcomes											
1 (Cucchiara et al., 1989)	RCT	Serious[3]	None	None	None	None	Cimetidine: 0	0	NS[h]	NA	Moderate
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Clinical score											
1 (Cucchiara et al., 1989)	RCT	Serious[3]	None	None	Not assessed[2]	None	Cimetidine: Mean 5.00 (SD 4.36)	Mean 9.46 (SD 4.86)	NA[d]	NA	Low

Quality assessment							Number of infants and children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
% improvement in clinical score from baseline											
1 (Cucchiara et al., 1989)	RCT	Very serious[3]	None	None	Not assessed[2]	None	Cimetidine: Mean - 67.39% (SD 23.17)	Mean - 29.57% (SD 30.31)	p<0.01[h]	NA	Very low
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, H_2RA H2 receptor antagonists, GORD gastro-oesophageal disease, MD mean difference, NA not available, NS not significant, p probability, RCT randomised controlled trial, RR relative risk, SD standard deviation
[a] Based on a categorical score 0 to 3 so cannot be analysed as a continuous variable. Reduced from baseline in intervention group but not placebo.
[b] Based on a categorical score 0 to 3 so cannot be analysed a continuous variable. Significantly reduced from baseline in both groups by 8 weeks.
[c] No comparative results presented. Significantly reduced in treatment group compared to baseline, but not the placebo group.
[d] Based on a categorical score 0 to 9 so cannot be analysed a continuous variable. Reduced from baseline in intervention group but not placebo.
[e] Scored from 0 to 9 – normal mucosa, mild degree, moderate degree, severe degree
[f] Classified as "Normal, erithema and edema, erythema and friability, erosions."
[g] Classified as "Normal, mild or moderate histology."
[h] As reported by authors
[1] Method of randomisation not explained in detail. Small sample size. High dropout rate (26%). Poor reporting of study results so GRADE items could not be assessed.
[2] Reporting of results did not allow imprecision to be calculated.
[3] Method of randomisation and allocation concealment not explained in detail. Poor reporting of study results so GRADE items could not be assessed.
[4] Confidence interval spans multiple interpretations

Table 48: GRADE profile for comparison of prokinetics (metoclopramide and domperidone) with placebo for the management of GORD in infants and children

Quality assessment							Number of infants and children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prokinetic	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
1 (Leung et al., 1984)	RCT	Very serious[1]	None	None	Not assessed[2]	None	Metoclopramide: 1.6 (SD 2.0)	Not reported	p<0.05[a]	NA	Very low
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
% of reflux episodes <4.0											
1 (Bines et al., 1992)	RCT	Very serious[3]	None	None	Not assessed[2]	None	Domperidone: Mean 11.8 (SD not reported)	Mean 15.9 (SD not reported)	NS[a]	NA	Very low
1 (Carroccio et al., 1993)	RCT	Serious[4]	None	None	Not assessed[2]	None	Domperidone: Median 8 (range 2 to 35)	Median 9 (range 3 to 40)	NS[a]	NA	Low

Quality assessment							Number of infants and children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prokinetic	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
1 (Bellissant et al., 1997)	RCT	Serious[4]	None	None	Very serious[5]	None	Metoclopramide: Mean 6.7 (SD 9.2)	Mean 8.1 (SD 11.7)	MD −1.40 [−7.99, 5.19]	NA	Very low
1 (Tolia et al., 1989)	RCT, crossover	Very serious[6]	None	None	Not assessed[2]	None	Metoclopramide: Median 10.3 (range 2.4 to 22.8)	Median 13.4 (2.8 to 30.5)	p<0.001[a]	NA	Low
Number of reflux episodes <4.0											
1 (Bines et al., 1992)	RCT	Very serious[3]	None	None	Not assessed[2]	None	Domperidone: 26 (SD not reporter)	28 (SD not reported)	p=0.001[a]	NA	Very low
1 (Carroccio et al., 1993)	RCT	Serious[4]	None	None	Not assessed[2]	None	Domperidone: median 48.5 (range 2 to 181)	Median 68 (range 38 to 130)	N/S[a]	NA	Moderate
1 (Cresi et al., 2008)	RCT	Serious[4]	None	None	Not assessed[2]	None	Domperidone: NR	NR	p<0.05[a]	NA	Low
1 (Bellissant et al., 1997)	RCT	Serious[4]	None	None	Very serious[5]	None	Metoclopramide: 63 (SD 136)	43 (SD 26)	MD 20.00 [−42.20, 82.20]	NA	Very low
1 (Tolia et al., 1989)	RCT, crossover	Very serious[6]	None	None	Not assessed[2]	None	Metoclopramide: 25.0 (SD 3.4)	22.4 (SD 2.5)	NS[a]	NA	Moderate
Duration time of longest episode											
1 (Bines et al., 1992)	RCT	Very serious[3]	None	None	Not assessed[2]	None	Domperidone: 12.6	20.9	NS[a]	NA	Very low
1 (Carroccio et al., 1993)	RCT	Serious[4]	None	None	Not assessed[2]	None	Domperidone: Median 16 (range 2 to 51)	Median 33.5 (range 8 to 103)	NS[a]	NA	Low
1 (Bellissant et al., 1997)	RCT	Serious[4]	None	None	Very serious[6]	None	Metoclopramide: Mean 18 (SD 30)	Mean 15 (SD 17)	MD 3.00 [−12.41, 18.41]	NA	Very low
Number of reflux episodes >5 minutes											
1 (Carroccio et al., 1993)	RCT	Serious[4]	None	None	Not assessed[2]	None	Domperidone: Median 7.5 (range 0 to 16)	Median 6 (range 1 to 20)	NS[a]	NA	Low
1 (Bellissant et al., 1997)	RCT	Serious[4]	None	None	Serious[7]	None	Metoclopramide: Mean 1.9 (SD 3.0)	Mean 3.0 (SD 3.5)	MD −1.10 [−3.14, 0.94]	NA	Low
1 (Tolia et al., 1989)	RCT, crossover	Very serious[5]	None	None	Not assessed[2]	None	Metoclopramide: 2.6 (SD 0.5)	2.0 (SD 0.3)	NS[a]	NA	Low
Resolution of oesophagitis											
Not reported											
Resolution of faltering growth											
Not reported											

Quality assessment							Number of infants and children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prokinetic	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Adverse outcomes											
Diarrhoea											
1 (Bines et al., 1992)	RCT	Very serious[3]	None	None	None	None	Domperidone: 4	2	NS[a]	NA	Low
Any adverse event											
1 (Carroccio et al., 1993)	RCT	Serious[4]	None	None	None	None	Domperidone: 0	0	NS[a]	NA	Moderate
1 (Tolia et al., 1989)	RCT, crossover	Very serious[5]	None	None	None	None	Metoclopramide: 0	0	NS[a]	NA	Low
Any adverse event leading to discontinuation											
1 (Bellissant et al., 1997)	RCT	Serious[4]	None	None	None	None	Metoclopramide: 3 of 19	1 of 20	NS[a]	NA	Moderate
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, MD mean difference, NA not available, NR not reported, NS not significant, p probability, RCT randomised controlled trial, SD standard deviation

[a] As reported in the study

[1] Method of randomisation and concealment not described. Control group treatment not explained. Reason for unbalanced groups not explained. Poor reporting of data so not all GRADE items could be assessed.

[2] Data not reported so imprecision could not be calculated

[3] Method of randomisation and concealment not described in detail. Small sample size (<10 per arm). Poor reporting of data so not all GRADE items could be assessed.

[4] Method of concealment not described in detail. Poor reporting of data so not all GRADE items could be assessed.

[5] wide confidence intervals - SMD crosses +/- 0.5 effect size

[6] No washout period between cross-over. Method of randomisation and allocation not explained in detail. Individual periods not reported so reanalysis could not be undertaken.

[7] wide confidence intervals – SMD crosses -0.5 and 0 effect size

Table 49: GRADE profile for comparison of proton pump inhibitors compared with H_2 receptor antagonists for managing gastro-oesophageal reflux symptoms in infants and children

Quality assessment							Number of infants and children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	PPI	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Not reported											
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
Oesophageal pH<4.0 % improvement from baseline (measured with: 24-hour combined intraoesophageal and intragastric pH monitor; Better indicated by higher values)											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2,3,4,5]	None	Serious[6]	Not assessed[7]	None	Median 59.6 (range 2 to 83.4)	Median 61.9 (range 34 to 99)	NS[a]	-	Very low
Intragastric pH<2.0 (minutes) % improvement from baseline (measured with: 24-hour combined intraoesophageal and intragastric pH monitor; Median range of scores: 0-100; Better indicated by higher values)											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2,3,4]	None	Serious[6]	Not assessed[7]	None	Median 26.2 (range 0.35 to 95.6)	Median 61.5 (range 7.2 to 98.4)	NS[a]	-	Very low
Intragastric pH<4.0 % improvement from baseline (measured with: 24-hour combined intraoesophageal and intragastric pH monitor; range of scores: 0-100; Better indicated by higher values)											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2,3,4]	None	Serious[6]	Not assessed[7]	None	Median 22.3 (range 2.1 to 72.8)	Median 29.0 (range 16.4 to 62.8)	NS[a]	-	Very low
Median intragastric pH % improvement from baseline (Better indicated by higher values)											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2,3,4]	None	Serious[6]	Not assessed[7]	None	Median 37.4 (range 0 to 56.7)	Median 60.1 (range 9.3 to 81)	P<0.05[a]	-	Very low
Resolution of oesophagitis											
Healing of oesophagitis (grade 0 to 2 on histology score) - ranitidine vs omeprazole											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2]	None	Serious[6]	Very serious[8]	None	8/13 (61.5%)	9/12 (75%)	RR 0.82 (0.48 to 1.41)	-	Very low
Resolution of faltering growth											
Not reported											
Adverse events requiring discontinuation											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2]	none	Serious[6]	None	none	0/13 (0%)	0/12 (0%)	NS[a]	-	Very low
Parent reported reduction in infant distress											
Not reported											
Improvement in validated reflux questionnaire											
60% or more decrease in symptom score - ranitidine vs omeprazole											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2]	None	Serious[6]	Very serious[8]	None	9/13 (69.2%)	10/12 (83.3%)	RR 0.83 (0.53 to 1.29)	-	Very low

Quality assessment							Number of infants and children		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	PPI	Relative (95% CI)	Absolute (95% CI)	
GOR symptoms score (range of scores: 0-45; Better indicated by lower values)											
1 (Cucchiara et al., 1993)	Randomised trials	Very serious[1,2,3,4]	None	Serious[6]	Not assessed[7]	None	Median 9.0	Median 9.0	NS[a]	-	Very low
Parent satisfaction with this intervention											
Not reported											

CI confidence interval, GOR gastro-oesophageal reflux, H_2RA H2 receptor antagonists, NA not available, NS not significant, p probability, PPI proton pump inhibitor, RR relative risk, vs versus

[a] As reported in study
[1] High dropout rate
[2] Method of randomisation not defined
[3] Small sample size
[4] Data reported as medians due to skewness
[5] Poor reporting
[6] Study examining children who had failed previous treatment
[7] imprecision not assessed
[8] Wide confidence intervals crossing no effect and ± 0.25

6.1.4 Evidence statements

See Table 46 to

Table 49.

6.1.4.1 Proton pump inhibitors compared with placebo

Six studies were included in this review.

6.1.4.1.1 Reduced frequency of overt regurgitation in infants.

Four studies found that frequency of overt regurgitation did not differ in infants who received PPI compared with infants who received placebo for the treatment of pH confirmed GORD. The evidence was of moderate to very low quality.

6.1.4.1.2 Reflux measured using oesophageal pH monitoring or impedance monitoring

Two studies found that pH monitoring measures of reflux (reflux index, number of reflux episodes, duration of longest reflux episode, number of reflux episodes lasting longer than 5 minutes) were reduced in infants who received PPIs compared with those who received placebo for the treatment of pH confirmed GORD. The evidence was of moderate to low quality.

6.1.4.1.3 Resolution of oesophagitis

Not reported.

6.1.4.1.4 Resolution of faltering growth

Not reported.

6.1.4.1.5 Adverse outcomes

Four studies found that adverse events did not differ in infants who received PPI compared with those who received placebo for the treatment of pH confirmed GORD, but one of the studies reported a higher rate of serious adverse events in those receiving PPI compared with those receiving placebo treatment. The evidence was of moderate to very low quality.

6.1.4.1.6 Parent reported reduction in infant distress

One study found that parent-reported reduction in distress did not differ for infants who received PPI compared with those who received placebo for the treatment of pH confirmed GORD. The evidence was of moderate quality.

6.1.4.1.7 Improvement in validated reflux questionnaire

Two studies found that irritability score did not differ in infants who received PPI compared with those who received placebo for the treatment of pH confirmed GORD. The evidence was of high to very low quality.

6.1.4.1.8 Parent satisfaction with this intervention

Two studies found no difference in discontinuation rates in infants who received PPI compared with those who received placebo for the treatment of pH confirmed GORD. The evidence for these findings was from moderate to very low quality.

6.1.4.2 H_2 receptor antagonists compared with placebo in infants and children

6.1.4.2.1 Reduced frequency of overt regurgitation

One study found that compared with baseline figures, regurgitation and vomiting were reduced more in infants and children who received H_2 receptor antagonists than those receiving placebo. The evidence for these findings was of very low quality.

6.1.4.2.2 Reflux measured using oesophageal pH-monitoring or impedance monitoring

One study found that compared with baseline figures, pH monitoring indices were reduced more in infants and children who received H_2 receptor antagonists than those receiving placebo. The evidence ranged from low to very low quality.

6.1.4.2.3 Resolution of oesophagitis

Two studies found that endoscopic and histological features of oesophagitis were reduced in infants and children who received H_2 receptor antagonists compared with those who received placebo. The quality of the evidence for this finding was low to very low.

6.1.4.2.4 Resolution of faltering growth

Not reported.

6.1.4.2.5 Adverse outcomes

One study found no difference in adverse events reported by parents whose infants and children received H_2 receptor antagonists or placebo. The evidence was of moderate quality.

6.1.4.2.6 Parent reported reduction in infant distress

Not reported.

6.1.4.2.7 Improvement in validated reflux questionnaire

One study found that the improvement in clinical score was greater in infants and children who received H_2 receptor antagonists compared with those who received placebo. This evidence was of low and very low quality.

6.1.4.2.8 Parent satisfaction with this intervention

Not reported.

6.1.4.3 Prokinetics (metoclopramide or domperidone) compared with placebo

6.1.4.3.1 Reduced frequency of overt regurgitation

One study found that frequency of regurgitation was reduced in infants and children who received prokinetics compared with those who received placebo. The evidence for this finding was very low quality.

6.1.4.3.2 Reflux measured using oesophageal pH monitoring or impedance monitoring

Three studies found that there was no difference in pH outcomes in infants and children who received prokinetics compared with those who received placebo. Two studies found that pH monitoring outcomes were improved in infants and children who received prokinetics compared with those who received placebo. The quality of the evidence for this finding was moderate to very low.

6.1.4.3.3 Resolution of oesophagitis

Not reported.

6.1.4.3.4 Resolution of faltering growth

Not reported.

6.1.4.3.5 Adverse outcomes

Four studies reported no difference in adverse events between infants and children who received prokinetics or placebo. The quality of the evidence for this finding was moderate and low.

6.1.4.3.6 Parent reported reduction in infant distress

Not reported.

6.1.4.3.7 Improvement in validated reflux questionnaire

Not reported.

6.1.4.3.8 Parent satisfaction with this intervention

Not reported.

6.1.4.4 H_2 receptor antagonists compared with PPIs

6.1.4.4.1 Reduced frequency of overt regurgitation

Not reported.

6.1.4.4.2 Reflux measured using oesophageal pH monitoring or impedance monitoring

Oesophageal pH less than 4.0 (% improvement from baseline)

One study found no statistically significant difference in improvement based on oesophageal pH less than 4.0 between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

Intragastric pH less than 2.0 (% improvement from baseline)

One study found no statistically significant difference in improvement based on intragastric pH less than 2.0 between infants children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

Intragastric pH less than 4.0 (% improvement from baseline)

One study found no statistically significant difference in improvement based on intragastric pH less than 4.0 between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

Median intragastric pH (% improvement from baseline)

One study found no statistically significant difference in median intragastric pH between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

6.1.4.4.3 Resolution of oesophagitis

One study found no statistically significant difference in oesophagitis healing between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor

antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

6.1.4.4.4 Resolution of faltering growth

Not reported.

6.1.4.4.5 Adverse outcomes

One study found no statistically significant difference in reported adverse events requiring discontinuation of treatment between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

6.1.4.4.6 Parent reported reduction in infant distress

Not reported.

6.1.4.4.7 Improvement in validated reflux questionnaire

60% or more decrease in symptom score

One study found no statistically significant difference in 60% or more decrease in symptom score between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor antagonists) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

GOR symptoms score – percentage improvement from baseline

One study found no statistically significant difference in GOR symptom score between infants and children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with those with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

6.1.4.4.8 Parent satisfaction with this intervention

Not reported.

6.1.5 Health economics profile

No health economic studies were identified for this review and the available data was insufficient for economic modelling to be undertaken. Therefore, only cost data was considered (see Appendix A: Health economics).

6.1.6 Evidence to recommendations

6.1.6.1 Relative value placed on the outcomes considered

The primary outcomes outlined by the guideline development group were cessation of overt regurgitation or reduced frequency of overt regurgitation, and resolution of oesophagitis based on endoscopic findings. If data on these were not available, then reflux measured using oesophageal pH or impedance monitoring would be used.

The group also outlined a number of parent reported outcomes (parent reported reduction in infant distress, improvement in validated reflux questionnaire and parent satisfaction with this intervention) plus resolution of faltering growth and adverse outcomes. The same outcomes were used across all the reviews for H_2 receptor antagonists, proton pump inhibitors and prokinetics.

6.1.6.2 Consideration of clinical benefits and harms

The guideline development group considered the potential adverse effects associated with drugs commonly used in the treatment of overt regurgitation and other forms of GORD when making its recommendations. Acid suppressing agents, such as H2 receptor antagonists and proton pump inhibitors, are generally well tolerated but do have potential side effects. Long-term acid suppression might have adverse consequences. Acid, for example, has a protective effect against bacterial gastrointestinal infection and studies have shown an increased incidence of salmonella infection in people using such agents. It is important, therefore, that widespread unnecessary usage be avoided, and that where these drugs are used, unnecessarily long-term usage be avoided. Other agents, such as metoclopramide and domperidone, which act as pro-kinetic agents do have significant associated adverse effects, such as neurological symptoms (dyskinetic effects). There are concerns with domperidone regarding potential dysrrhythmias. The group was therefore concerned that these should only be considered for use following specialist advice.

6.1.6.2.1 H2 receptor antagonists

One RCT reported outcomes for overt regurgitation but none of these was found to be statistically significant. Two RCTs reported outcomes relating to the resolution of oesophagitis or improvement in histology scores: both studies showed significant benefit with either nizatidine or cimetidine compared with placebo. One RCT found no incidences of adverse outcomes with cimetidine.

The guideline development group noted that no studies were identified that used ranitidine, which is the most commonly prescribed H_2 receptor antagonist agent in the UK. However, it was the clinical opinion of the group members that the effects of all H_2 receptor antagonists are similar and that the data found for one type of H_2 receptor antagonist treatment could be applied to all H_2 receptor antagonist treatments.

The group's own experience matched the evidence. The group agreed that H_2 receptor antagonists were of benefit for the management of reflux oesophagitis, but should not be used to manage the frequency of overt regurgitation. Therefore, it is important to be able to identify those children and young people who had reflux oesophagitis in order that this treatment be used appropriately.

6.1.6.2.2 Proton pump inhibitors

Three RCTs reported no statistically significant difference for PPIs when compared with placebo for outcomes related to reducing regurgitation. Two RCTs did, however, find statistically significant outcomes related to the number of acid reflux events (measured by pH monitoring and/or impedance monitoring) showing a benefit of PPIs when compared with placebo. As with H_2 receptor antagonists, clinical experience led the guideline development group to conclude that all PPIs have a similar effect and therefore outcomes found for one drug would apply to others. The group agreed with the evidence and concluded that PPIs could be used to manage reflux oesophagitis, but should not be used to manage the frequency of overt regurgitation.

In addition, the group discussed the use of PPIs to manage heartburn in young people. The group had not outlined this as a specific outcome for the review, but was aware that it was the most common reflux related symptom reported by young people and adults. The group highlighted evidence shown in RCTs examining the effectiveness of PPIs on heartburn in an adult population. The group therefore recommended that a PPI could be offered to children and young people complaining of heartburn. However, the group emphasised that this should be for a trial of 4 weeks to avoid unnecessary long-term use: this should be followed by review and consideration of the need for referral for a possible endoscopy if the outcome of treatment was either failure to resolve or recurrence of symptoms on cessation.

Following from this recommendation and extending the above argument to infants and very young children who could have symptoms of reflux oesophagitis, the guideline development group concluded that it was not unreasonable in some instances to treat infants with either an H_2 receptor antagonist or PPI without endoscopic evidence for reflux oesophagitis. The clinical presentation would usually be an infant with obvious, frequent regurgitation and one or more of:

- severe (otherwise) unexplained feeding difficulty or aversion
- distressed behaviour
- otherwise unexplained faltering growth.

The group concluded that where the primary or secondary care physician concluded that the clinical picture may be resulting from reflux oesophagitis, it would be wrong to refrain from an empirical trial of treatment pending a potentially lengthy referral process for consideration of an upper gastrointestinal endoscopy and biopsy under general anaesthetic in a tertiary gastroenterology unit. However, the group very clearly stipulated that such treatment must be reviewed regularly with a low threshold for referral for endoscopy to guide subsequent treatment.

A major point of discussion for the guideline development group was the administration of PPIs to young children. Clearly, it is impractical and inappropriate to offer tablets, pills or capsules to infants or very young children, and the only practical solution in most parts of the UK is to make an emulsion out of one of the adult preparations using either water or sodium bicarbonate. This is difficult for parents or carers and often unpleasant for the infants and children. The group was unable to comprehend why a liquid preparation is readily and cheaply available in the US but not in the UK: instead, liquid preparations of PPI can be prepared in the UK but only very occasionally and at great cost. Because of these administration issues, it is often more convenient and practical to use Ranitidine in the treatment of reflux oesophagitis for infants and young children, moving to a PPI as an alternative if Ranitidine does not appear to have been successful.

6.1.6.2.3 Proton pump inhibitors compared with H_2 receptor antagonists

Evidence from 1 RCT found no difference in outcome between PPIs and H_2 receptor antagonists, but both improved symptom scores.

The guideline development group agreed with these findings of the review. It was their experience that in most cases the use of a PPI or a H_2 receptor antagonist will have similar outcomes as they are both acid supressing agents (although the pharmacological mechanisms differ). The group concluded that the decision of which to use should be based on practical considerations, such as administration and local acquisition costs.

6.1.6.2.4 Prokinetics

Evidence from RCTs was available for domperidone and metoclopramide, but these reported mixed results in terms of efficacy. One RCT found a statistically significant reduction in overt regurgitation and another 2 RCTs reported reduced acid reflux episodes based on 24 hour pH monitoring. However, the 3 other RCTs found no difference in acid reflux episodes. In addition, only 1 of the 5 RCTs that used pH monitoring reported any difference on other measures, such as reflux index, duration of longest episode of reflux or number of episodes lasting longer than 5 minutes. The guideline development group did note that there is some clinical opinion that domperidone has an effect in reducing the frequency of regurgitation in patients where all other interventions have failed, and this is normally in high risk groups, for example children with a neurodisability.

The group was aware of specific safety advice for domperidone and metoclopramide. In August 2013, the European Medicines Agency released a statement that the risk of neurological adverse events (such as short-term extrapyramidal disorders and tardive

dyskinesia) for metoclopramide outweighed the benefit when taken for a prolonged amount of time at a high dose. In April 2014, the Medicines and Healthcare products Regulatory Authority (MHRA) released a statement that there was a small risk of adverse cardiac events (specifically serious ventricular arrhythmia and sudden cardiac death) with the use of domperidone. The risk was observed in people older than 60 years, those with pre-existing cardiac disease, those taking CYP3A4 inhibitors and adults taking more than 30 mg as a daily oral dose. The group concluded that if metoclopramide or domperidone were used then caution should be taken and therefore initiation of treatment should only be offered by healthcare professionals who can make individual assessments on the cardiac risk and potential benefit on a case by case basis.

The guideline development group concluded that if domperidone and metoclopramide were to be offered, then they should be only be offered to reduce regurgitation frequency and only after other interventions have been tried and there is agreement for its use by specialist paediatric healthcare professionals.

The group noted a number of agents with prokinetic properties that have been described in the wider literature: erythromycin, bethanechol or baclofen. However, no robust RCT evidence was identified for these drugs and the pharmacodynamics of these agents differ from domperidone and metoclopramide. The group knew that erythromycin was also in widespread use in the NHS and was being used in similar indications as a prokinetic. However, the group was not aware of bethanechol or baclofen being used to manage GORD in children or young people.

6.1.6.3 Consideration of health benefits and resource uses

The guideline development group was aware that PPIs and H_2 receptor antagonists were commonly prescribed to manage GORD in children and young people. The available evidence showed that these agents did help to manage certain manifestations of GORD, such as oesophagitis and heartburn. The group's main concerns were that these agents were often used for long periods of time and sometimes used inappropriately to manage symptoms such as regurgitation, vomiting, distressed behaviour or even faltering growth, and therefore their use would not be cost effective in that context. Consequently, the group outlined recommendations that should ensure appropriate and limited use of PPIs and H_2 receptor antagonists. As the available evidence did not allow detailed health economic modelling to be undertaken, the group could not specify which individual preparation to use on the basis of cost effectiveness and concluded, therefore, that cost and practical application should be taken into account. This is explicitly recognised in the recommendation on choosing between PPIs and H_2 receptor antagonists, which notes that local procurement costs should be a factor in the decision. In the case of PPIs, the group highlighted that liquid preparation was the simplest to administer in practice to young children, but also the most costly (see Appendix A: Health economics).

6.1.6.4 Quality of evidence

All studies included used an RCT design. The main sources of bias were that methods of randomisation and concealment were not described in detail. Reporting of outcomes varied between studies, which meant that re-analysis and meta-analysis could not be undertaken. Only 1 study had a sample size of over 100 and the majority include less than 50 infants. Imprecision could not be calculated for most studies due to the method of reporting (confidence intervals not presented or non-calculable) and this limited the interpretation of the evidence.

6.1.7 Recommendations

29. **Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom.**

30. **Consider a 4-week trial of a PPI or H_2RA 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.

31. **Consider a 4-week trial of a PPI or H_2RA for children and young people with persistent heartburn, retrosternal or epigastric pain.**

32. **Assess the response to the 4-week trial of the PPI or H_2RA, and consider referral to a specialist for possible endoscopy if the symptoms:**
    - do not resolve **or**
    - recur after stopping the treatment.

33. **When choosing between PPIs and H_2RAs, 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.

34. **Offer PPI or H_2RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis, and consider repeat endoscopic examinations as necessary to guide subsequent treatment.**

35. **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.**

6.1.8 Research recommendations

No research recommendations in this area.

7 Enteral tube feeding for GORD

7.1 Intra-gastric and intra-jejunal tube feeding

Enteral tube feeding involves the artificial delivery of nutrition directly into the gastrointestinal tract without the need for swallowing. In temporary or short-term situations this is most commonly via a nasogastric tube (NGT) into the stomach but can be via a naso-jejunal tube (NJT) into the proximal small bowel. This form of feeding may be partial or exclusive and where it is indicated in the long term should be delivered via a more permanent device such as a gastrostomy or jejunostomy.

This chapter reviews the possible use of enteral feeding as a specific intervention in the management of GORD in infants, children and young people. This chapter does not investigate the reciprocal question of whether enteral tube feeding exacerbates GOR or GORD and neither does it provide a comprehensive account of the indications, contra-indications and complications of enteral feeding.

Several groups, including pre-term neonates and children with complex neurodisabilities, commonly receive enteral feeding. This is often because of immature or poorly developed swallow mechanisms, sometimes in the context of an inability to adequately protect their airway. Alternatively, some groups of children have additional energy requirements over and above what they manage to take by mouth, for example children with cystic fibrosis, metabolic disease or chronic liver, kidney or heart disease. In these cases they can receive supplemental nutrition via the enteral route. To further complicate matters, some of these groups include the populations of children at greatest risk of significant regurgitation and GORD. However, it is emphasised that although swallowing, airway protection or energy deficit problems and GORD can be linked, they remain distinct problems even when in the same child. Therefore, in a child with GORD enteral tube feeding is frequently used as a supportive treatment for a reason other than primary treatment for GORD.

Enteral tube feeding can only really be considered as a primary, specific intervention for GORD in the following three limited situations:

- The nasogastric delivery of small volume frequent feeds or the nasogastric delivery of continuous thickened feed in cases of such extreme regurgitation that effective net calorific intake, and therefore growth, is compromised; or to reduce the possibility of aspiration of the refluxed feed by dividing the necessary volume and quantity across a longer over all feeding time.
- In order to bypass the oesophagus in cases of feed refusal due to pain and distress which can very occasionally occur as a result of severe oesophagitis pending effective treatment and resolution; or to bypass a stricture caused by severe oesophagitis until effective treatment has been instigated.
- In extreme cases of regurgitation or GORD, jejunal feeding may be used as both a treatment and an empirical trial where other simpler therapeutic interventions have been unsuccessful via either an NJT or a gastro-jejunal device. This intervention may be pending or instead of fundoplication surgery.

7.1.1 Review question

How effective is enteral tube feeding in the management of GOR/GORD?

For full details see review protocol in Appendix E.

7.1.2 Description of included studies

No comparative studies were identified that met the inclusion criteria or outcomes outlined by the guideline development group.

The continued use of enteral tube feeding for problems of weight gain, aspiration or swallowing/dysphagia was not considered, particularly in relation to children with complex neurodisability and/or co-morbidity.

7.1.3 Evidence profile

There was no evidence identified in this area.

7.1.4 Evidence statements

There was no evidence identified to show how effective enteral tube feeding is in the management of GOR/GORD.

7.1.5 Health economics profile

No health economic studies were identified for this review and the available evidence meant that no health economic modelling could be undertaken. Therefore, only cost data was considered (see Appendix A: Health economics).

7.1.6 Evidence to recommendations

7.1.6.1 Relative value placed on the outcomes considered

The primary outcomes outlined by the guideline development group related to resolution of complications associated with gastro-oesophageal reflux for which enteral tube feeding was given, namely: faltering growth; pulmonary aspiration; and overt regurgitation.

Secondary outcomes were: parent reported reduction in infant distress; resolution of gastro-oesophageal reflux measured by oesophageal pH or impedance monitoring; adverse outcomes; improvement in validated reflux questionnaire; parent satisfaction with the intervention.

7.1.6.2 Consideration of clinical benefits and harms

No evidence was identified that met the predefined inclusion criteria and the guideline development group was unaware of any studies that could be included. Therefore, discussion was based on the group's own experience and knowledge of evidence from related areas. The group reiterated that the remit of discussion was enteral tube feeding as an effective treatment for GORD and not its use for other conditions, such as swallowing problems, as described in the introduction.

Enteral tube feeding as a treatment for GORD is a highly specialised and individualised intervention that would only be used in the most severe cases to alleviate extremely troublesome symptoms or complications of GORD, such as severe faltering growth, oral feed refusal or to decrease the risk of aspiration pneumonia.

The group stressed that enteral tube feeding was not a cure for GORD, but provided relief from symptoms and, in particular, allowed weight gain. This can give healthcare professionals time to investigate other possible causes of the symptoms and consider further treatment, such as fundoplication surgery.

Based on this discussion it was agreed that enteral tube feeding should ideally be a bridging measure that should only be considered in the child or young person with severe GORD that is causing:

- severe feed aversion that limits intake and growth
- an oesophageal stricture
- faltering growth
- aspiration pneumonia.

It is was recognised and highlighted by the guideline development group that there are potential harms related to tube feeding that should be considered before commencement. It was the experience of the group that feeding exclusively via an enteral tube can create behavioural issues relating to oral food aversion when tube feeding is stopped. Enteral tube feeding can disrupt normal feeding behaviour and therefore can lead to long-term feeding difficulties.It was agreed that as a precautionary measure, oral stimulation should be continued throughout enteral tube feeding treatment. Dependent on the individual, the group felt a variety of tastes and textures should be explored.

The group was aware of a continuing debate about whether enteral feeding into the stomach increased reflux in certain groups. A number of research papers had investigated higher levels of reflux following the insertion of a gastric enteral feeding tube and the need to consider undertaking a fundoplication to prevent this. It was outlined by the group that using enteral tube feeding in children with faltering growth can result in the child receiving a quantity of feed that they had not previously been used to, and that this could potentially cause reflux. The group concluded that in the first instance the quantity and timing of feeding should be monitored to avoid this, as per the guideline recommendation for formula feeding.

The group was also concerned that without a clear plan for the discontinuation of enteral tube feeding for GORD, it could unnecessarily be used as a long-term therapy. The group therefore concluded that predefined outcome criteria for when the tube is removed should be agreed before commencement of treatment.

Given the disruption and artificial nature of this intervention and the need, typically, for an inpatient admission pending discharge to the community with an appropriate supporting team, the group advised that a gastroenterology specialist be involved in reviewing the indication for this management decision.

The guideline development group recognised certain circumstances in which jejunal feeding might be preferable to providing intra-gastric tube feeds. In some infants, children and young people receiving intra-gastric feeding, GOR may continue to be a significant concern to the degree that they are not able to tolerate it, resulting, for example, in very frequent overt regurgitation. Also, there are circumstances in which it is judged that reflux is associated with a high risk of pulmonary aspiration. By delivering the feed into the jejunum, the risk of reflux may be significantly less. The group recognised that placement of jejunal tubes can be difficult and displacement of such tubes may pose problems. This was not, therefore, a procedure to be undertaken unless there were clear indications. However, the group recognised its value in the above circumstances.

7.1.6.3 Consideration of health benefits and resource uses

The guideline development group outlined that the main costs were related to staff time and equipment required, but noted that there were costs associated with not using enteral tube feeding as the child or young person would still require feeding.

The group recommended that enteral tube feeding should not be used as a long-term treatment for GORD, and that its use should be part of a clear management strategy outlined by a gastroenterology specialist. This would minimise the costs associated with its use.

7.1.6.4 Quality of evidence

No evidence was identified that met the predefined inclusion criteria for this review question. Therefore, recommendations were based on the guideline development group's experience and knowledge.

7.1.6.5 Other considerations

The guideline development group acknowledged that in most situations the children and young people requiring enteral tube feeding would have pre-existing co-morbidities, such as neurodisabilities, and that the management of GORD would form part of the individualised management strategy for each child or young person.

7.1.7 Recommendations

36. **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.

37. **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.

38. **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.

39. **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.

7.1.8 Research recommendations

No research recommendations in this area.

8 Surgery for GORD

8.1 Fundoplication

Fundoplication is a surgical procedure designed to reduce or eliminate reflux of gastric contents into the oesophagus. It is usually considered to be indicated for infants, children or young people with severe GORD which is refractory to conventional medical treatment or as an anti-vomiting procedure in children with complex, severe neurodisabilities, often in the context of an unsafe airway protection mechanism in a child who is already dependent on enteral feeding. In many cases fundoplication surgery takes place at the same time as the insertion of a gastrostomy feeding device, but the indication and more general discussion of enteral feeding is not considered in further detail within this chapter.

There are many variations of technique, but the common principles are firstly to ensure the stomach and distal oesophagus lie entirely within the abdomen, secondly to repair any abnormal laxity of the oesophageal hiatus and thirdly to wrap the distal oesophagus with the fundus of the stomach. The operation is believed to work by increasing pressure on the wrapped oesophagus as the stomach distends.

Among the more detailed variations in technique is whether the wrap is completely or only partially encircling the oesophagus. Complete wraps may be expected to give better protection from reflux but more side effects, such as dysphagia and gas bloat. Conversely, partial wraps may provide poorer reflux protection but fewer side effects.

Historically, the operation was performed using an open techniques, but this is now less common as minimally invasive techniques, also known as laparoscopic or keyhole surgery, have become available. The potential advantages of laparoscopic surgery include less pain, much shorter recovery times, a smaller risk of future adhesions and improved cosmesis.

The operation is performed relatively frequently, but there are several potential complications. The creation of the high pressure zone in the oesophagus will cause dysphagia (difficulty in swallowing), particularly of solid foods. Typically, this symptom will resolve over the first 6 months after the procedure, but a restricted diet may initially be required. Frequently, children are unable to burp following the procedure. This leads to episodes of stomach distension, causing discomfort, particularly in relation to feeds. This is termed ‘gas bloat’. While this symptom also tends to improve with time, it can be a cause of marked distress. Retching can be an intractable symptom following fundoplication, particularly in neurologically impaired children, although it is not possible to accurately predict prior to surgery which children will be most troubled by this symptom.

The aim of this review is to determine the effectiveness and place of fundoplication in the managed of GORD in children and young people.

8.1.1 Review question

How effective is fundoplication surgery in the treatment of GOR/GORD?

- To determine if fundoplication surgery can effectively treat GORD in children and young people.
- To determine if fundoplication surgery can effectively treat specific sub-groups of children and young people with GORD
- To compare the effectiveness of the following types of fundoplication:
  - open fundoplication
  - laparoscopic fundoplication

For full details see the review protocol in Appendix E.

8.1.2 Description of included studies

The search strategy created for this review can be found in Appendix F. A summary of the studies identified for this guideline is available in Appendix G. Evidence from the included studies is summarised in the GRADE profiles below and in the evidence tables in Appendix I. For full details of excluded studies see Appendix H.

Four comparative studies met the inclusion criteria for this review: 2 were randomised controlled trials (RCTs) (McHoney et al., 2011; Knatten et al., 2012) and 2 were observational studies (Diaz et al., 2005; Srivastava et al., 2009). Observational studies were restricted to those where case-mix adjustment had been undertaken by the authors in order to overcome underlying differences in study populations.

Three of the studies compared open fundoplication with laparoscopic fundoplication (McHoney et al., 2011; Knatten et al., 2012; Diaz et al., 2005) and 1 study compared fundoplication with gastrojejunal feeding tubes (Srivastava et al., 2009).

Sample sizes ranged from 44 to 456. Studies included children aged up to 5 years.

Two studies were undertaken in the USA (Diaz et al., 2005; Srivastava et al., 2009), 1 in the UK (McHoney et al., 2011) and 1 in Norway (Knatten et al., 2012).

8.1.3 Evidence profile

Study quality was assessed using the GRADE methodology. RCTs were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Table 50: GRADE profile for RCT comparison of Open Nissen Fundoplication (ONF) with Laparoscopic Nissen Fundoplication (LNF)

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ONF	LNF	Relative (95% CI)	Absolute (95% CI)	Quality
Cessation (or symptom free days) of overt regurgitation											
Reported as late postoperative recurrence of GORD, n/N, % (exact follow-up time point not reported)											
1 (McHoney et al., 2011)	RCT	Serious[1]	None	Serious	Very serious[2]	Yes[3]	3/18 (16.7%)	1/14 (7.1%)	Odds ratio [OR] (95% CI): 2.60 (0.24-28.14)*	9.5% (−17.1 to 32.8)[a]	Very low
Adverse outcomes											
Reported as early postoperative incidence of infection, n/N, % (exact follow-up time point not reported)											
1 (McHoney et al., 2011)	RCT	Serious[4]	None	None	Very serious[2]	Yes[3]	1/20 (5%)	3/19 (16%)	OR (95% CI): 0.28 (0.03-2.97)*	−10.8 (−33 to 10.5)[a]	Very low
Reported as patients with complications occurring in the first 30 days after surgery, n/N, %											
1 (Knatten et al., 2012)	RCT	Very serious[5,6,7,8]	None	None	Very serious[2]	Yes[9]	24/44 (55%)	24/44 (55%)	OR (95% CI): 1 (0.43-2.31)*	-	Very low
Reported as postoperative complications (total number of complications) occurring in the first 30 days, n (44 children in each arm)											
1 (Knatten et al., 2012)	RCT	Very serious[5,6,7,8]	None	None	Not assessed[10]	Yes[9]	31	34	NA	-	Very low
Reported as postoperative grade I complications l (number of complications) occurring in the first 30 days, n (44 children in each arm)											
1 (Knatten et al., 2012)	RCT	Very serious[5,6,7,8]	None	None	Not assessed[10]	Yes[9]	11	11	NA	-	Very low
Reported as postoperative grade II complications m (number of complications) occurring in the first 30 days, n (44 children in each arm)											
1 (Knatten et al., 2012)	RCT	Very serious[5,6,7,8]	None	None	Not assessed[10]	Yes[9]	18	17	NA	-	Very low
Reported as postoperative grade IIIb complications n (number of complications) occurring in the first 30 days, n (44 children in each arm)											
1 (Knatten et al., 2012)	RCT	Very serious[5,6,7,8]	None	None	Not assessed[1]	Yes[9]	2	6	NA	-	Very low
Reported as patients readmitted to hospital because of complications after discharge, n/N, %											
1 (Knatten et al., 2012)	RCT	Very serious [5,6,7]	None	None	Very serious[2]	Yes[9]	11/44 (25%)	12/44 (27%)	OR (95% CI): 0.89 (0.34-2.30)*	-	Very low
Reported as early postoperative incidence of gastric paresis, n/N, % (exact follow-up time point not reported)											
1 (McHoney et al., 2011)	RCT	Serious[4]	None	None	Very serious[2]	Yes[3]	2/20 (16%)	3/19 (11%)	OR (95% CI): 1.42 (0.21-9.52)*	−5.8% (−28.7 to 16.8)[a]	Very low

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ONF	LNF	Relative (95% CI)	Absolute (95% CI)	Quality
Reported as late postoperative incidence of dysphagia, n/N, % (exact follow-up time point not reported)											
1 (McHoney et al., 2011)	RCT	Serious[4]	None	None	Not assessed[10]	Yes3	0/16 (0%)	1/16 (6.3%)	-	−6.3% (−28.3 to 13.8) p=0.14 [a]	Moderate
Reported as late postoperative incidence of retching o, n/N, %											
1 (McHoney et al., 2011)	RCT	Very serious[1,11]	None	None	Very serious[2]	Yes3	10/18 (55.6)	1/16 (6.3%)	OR (95% CI): 18.75 (2.02 - 173.94)*	49.3% (18.3 to 69.8)[a]	Very low
Reported as mean time to full feed in days, mean (CI)											
1 (McHoney et al., 2011)	RCT	None	None	Serious	Not assessed[10]	None	2 (2 to 4)	2 (2 to 4)	p=0.85[a]	-	Low
Resolution of erosive oesophagitis (endoscopic and histologic)											
Not reported											
Resolution of reflux symptoms – for example, heartburn, retrosternal or epigastric pain, waterbrash											
Not reported											
Resolution of faltering growth											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Resolution of faltering growth											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Oesophageal reflux measured by oesophageal pH measurement or impedance monitoring											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with the intervention											
Not reported											

CI confidence interval, GORD gastro-oesophageal reflux disease, LNF Laparoscopic Nissen Fundoplication, ONF Open Nissen Fundoplication, OR odds ratio, NA not available, p probability, RCT randomised controlled trial

** Calculated by NCC-WCH technical team based on data reported in the article*

[a] As reported by study authors

[1] Unbalanced drop-out in the LNF arm, reasons not reported

[2] Wide confidence interval (CI crosses three zones)

[3] The study was not adequately powered for the clinical outcomes

[4] Unclear whether a valid and reliable method was used to assess outcome

[5] No adequate concealment

[6] No blinding of the patients or postoperative care staff

[7] Unclear whether the groups received same level of care

[8] *Unclear whether a valid and reliable method was used to assess outcome*
[9] *The study was not adequately powered for its primary outcome reoccurrence and result not reported; for adverse outcomes, a post hoc power calculation was performed*
[10] *Data was not presented in a way that allowed imprecision to be calculated.*
[11] *Subjective outcome reported by parents postoperatively*

Table 51: GRADE profile for observational comparison of Laparoscopic Nissen Fundoplication (LNF) with Open Nissen Fundoplication (LNF)

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNF	ONF	Relative (95% CI)	Absolute (95% CI)	Quality
Adverse outcomes											
Reported as patients undergoing reoperation, n/N (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Serious[1,2]	None	Serious	Very serious[3]	None	43/306 (14%)	12/150 (8%)	Odds ratio [OR] (95% CI): 1.88 (0.96-3.68)[a,b]	-	Very low
Reported as frequency of short-term acute bleeding, n (%),											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2,4]	None	None	Not assessed[5]	None	1 (0.8%)	0	p=0.67[a]	-	Very low
Reported as frequency of short-term acute respiratory problem, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2,4]	None	None	Not assessed[5]	None	4 (1.3%)	12 (8%)	p=0.046[a]	-	Very low
Reported as frequency of acute infection, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2,4]	None	None	Not assessed[5]	None	3 (0.9%)	2 (1.3%)	p=0.53[a]	-	Very low
Reported as frequency of acute prolonged ileus, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2,4]	None	None	Not assessed[5]	None	4 (1.3%)	14 (9.3%)	p=0.0003[a]	-	Very low
Reported as acute other, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2,4]	None	None	Not assessed[5]	None	6 (1.9)	6 (4%)	p=0.2[a]	-	Very low
Reported as total frequency of acute complications, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2,4]	None	None	Not assessed[5]	None	18 (5.9%)	34 (22.7%)	p=0.0001[a]	-	Very low
Reported as potential risk factors (LNF versus ONF) associated with reoperation											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2]	None	None	Very serious[3]	None	-	-	OR (95% CI): 1.68 (0.84-3.3) P=0.1427 [a,c]	-	Very low
Reported as the probability of survival (defined as those who did not require reoperation) and respective reoperation rate at 12 months after initial operation (LNF versus ONF)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2]	None	None	Very serious[3]	None	Survival/reoperation, n (%): 274 (89.5%)/ 32 (10.5%)[d]	Survival/reoperation, n (%): 144 (96%)/ 6 (4.0%)[d]	OR (95% CI): 2.80 (1.15-6.86)*	-	Very low

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNF	ONF	Relative (95% CI)	Absolute (95% CI)	Quality
Reported as the probability of survival (defined as those who did not require reoperation) and respective reoperation rate at 24 months after initial operation (LNF versus ONF)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2]	None	None	Very serious[3]	None	Survival/reoperation, n (%): 265 (86.6%)/41 (13.4%)[d]	Survival/reoperation, n (%): 140 (93.3%)/10 (6.7%)[d]	OR (95% CI): 2.17 (1.05-4.45)*	-	Very low
Reported as the probability of survival (defined as those who did not require reoperation) and respective reoperation rate at 36 months after initial operation (LNF versus ONF)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[1,2]	None	None	Very serious[3]	None	Survival/reoperation, n (%): 262 (85.6%)/44 (14.4%)[d,e]	Survival/reoperation, n (%): 138 (91.9%)/12 (8.1%)[d]	OR (95% CI): 1.93 (0.99-3.78)*	-	Very low
Cessation (or symptom free days) of overt regurgitation											
Not reported											
Resolution of erosive oesophagitis (endoscopic and histologic)											
Not reported											
Resolution of reflux symptoms – for example, heartburn, retrosternal or epigastric pain, waterbrash											
Not reported											
Resolution of faltering growth											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Resolution of faltering growth											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Oesophageal reflux measured by oesophageal pH measurement or impedance monitoring											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with the intervention											
Not reported											

CI confidence interval, LNF Laparoscopic Nissen Fundoplication, ONF Open Nissen Fundoplication, OR odds ratio, p probability

[*] *Calculated by NCC-WCH technical team based on data reported in the article*

[a] *As reported by study authors*

[b] *Unadjusted odds ratio*

[c] *Odds ratio adjusted for age, gender, neurological impairment, chronic respiratory condition, cardiac disease, prematurity, and reflux alone*

[d] *Number of patients undergoing reoperation at 36 months different from what previously reported, which was 43, due to discrepancies in percentage reported by study authors and rounding in calculations.*

[e] *Percentage as reported by study authors, number of patients calculated by NCC-WCH*
[1] *Intervention groups were not comparable at baseline in terms of undergoing diagnoses*
[2] *Unclear whether there were systematic differences between groups in the care provided*
[3] *Confidence interval crosses three zones*
[4] *Unclear how outcomes were ascertained, diagnosed or verified*
[5] *Data was not presented in the paper in a format that allowed imprecision to be assessed.*

Table 52: GRADE profile for observational comparison of fundoplication with gastro-jejunal feeding tube (GJT)

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fundoplication	GJT	Relative (95% CI)	Absolute (95% CI)	Quality
Adverse outcome											
Reported as death a during the following 10 years (median length of follow-up 3.4 years), n/N (%)											
1 (Srivastava et al. 2009)	Retrospective cohort study[a]	Very serious[1,2,3]	None	None	None	None	40/323 (12%)	9/43 (21%)	Hazard ratio [HR], (95% CI): 0.30 (0.12-0.73)[b]	-	Very low
Reported as aspirational pneumonia (AP) during the following years (median length of follow-up 3.4 years), n/N, (%)											
1 (Srivastava et al. 2009)	Retrospective cohort studya	Very serious [1,2,3,4]	None	None	Very serious[5]	None	48/323 (15%)	7/43 (16%)	HR (95% CI): 0.71 (0.21-1.69)[c]	-	Very low
Cessation (or symptom free days) of overt regurgitation											
Not reported											
Resolution of erosive oesophagitis (endoscopic and histologic)											
Not reported											
Resolution of reflux symptoms – for example, heartburn, retrosternal or epigastric pain, waterbrash											
Not reported											
Resolution of faltering growth											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Resolution of faltering growth											
Not reported											
Parent reported reduction in infant distress											
Not reported											
Oesophageal reflux measured by oesophageal pH measurement or impedance monitoring											
Not reported											
Improvement in validated reflux questionnaire											
Not reported											
Parent satisfaction with the intervention											
Not reported											

CI confidence interval, GJT gastro-jejunal feeding tube, HR hazard ratio
[a] *Study subjects were children with neurologic impairment and GORD*
[b] *Adjusted hazard ratio : the Cox model was stratified by age (patients >1 year versus patients ≤1 year) while adjusting for propensity scores for surgery indication and baseline heterogeneities*

[c] Adjusted hazard ratio from Cox model adjusting for propensity scores for surgery indication and baseline heterogeneities
[1] Intervention groups were not comparable at baseline in terms of comorbidities
[2] Confounders including propensity for surgical indication were adjusted for in analyses, but there still could be other unmeasured confounders
[3] Unclear whether the groups received same level of care before and after surgery
[4] The distinction between AP caused by primary aspiration (for example secretions) or secondary aspiration (for example refluxed GORD) could not be made because of the nature of the retrospective study
[5] Confidence interval crosses three zones

8.1.4 Evidence statements

See Table 50 to Table 52

8.1.4.1 Fundoplication compared to laparoscopic fundoplication

One study was unable to determine if there was a difference in frequency of overt regurgitation in children treated with open fundoplication compared with those treated with laparoscopic fundoplication. The quality of evidence for this finding was very low.

One study reported a significant benefit of the laparoscopic approach compared to the open approach with regards to the incidence of late post-operative retching. The quality of this evidence was very low.

Results from 1 RCT study found no difference in short-term adverse events. The quality of the evidence was low to very low.

Results from one retrospective observational study found that rates of reoperation at 12 and 24 months post-operation were higher in children who had undergone laparoscopic fundoplication compared with those who had undergone open fundoplication, but not at 36 months. The evidence was of very low quality. The same study found that the risk of acute complications was higher in children who underwent open fundoplication compared to children who underwent laparoscopic fundoplication. The evidence was of very low quality.

No data was found for other outcomes.

8.1.4.2 Open compared to gastrojejunal feeding tubes

One study found that long-term mortality was reduced in children who had undergone fundoplication compared with children who had tube feeding, but there was no difference in the risk of developing aspirational pneumonia. The evidence for these findings was very low quality.

No data was found for other outcomes.

8.1.5 Health economics profile

No health economic studies were identified for this question and the data was unsuitable for health economic modelling. Therefore, only cost data was considered (see Appendix A: Health economics).

8.1.6 Evidence to recommendations

8.1.6.1 Relative value placed on the outcomes considered

Fundoplication surgery is usually undertaken after other options have failed and is used to manage a number of reflux related complications, including severe vomiting, erosive oesophagitis and faltering growth. Therefore, the guideline development group outlined outcomes that addressed specific conditions (change in frequency of overt regurgitation, resolution of erosive oesophagitis and resolution of faltering growth) and more general outcomes that allowed comparison with medical treatments (improvement in validated reflux questionnaire, resolution of reflux symptoms and adverse outcomes). Furthermore, both objective (oesophageal reflux measured by oesophageal pHmeasurement, ideally with impedance monitoring) and subjective (parent reported reduction in infant distress and parent satisfaction with the intervention) outcomes were included.

8.1.6.2 Consideration of clinical benefits and harms

The guideline development group noted that the available evidence on fundoplication was limited in quantity, quality and scope, with few of the outcomes outlined by the group being reported. Therefore, the majority of the discussion was based on the group's own experience.

The group discussed whether fundoplication can be effective in the treatment of GORD in children and young people. Only 1 study was identified and this reported on the safety of fundoplication compared to gastro-jejunal feeding. It showed a lower mortality rate in the 10 years following the operation. However, no evidence was identified that compared the effectiveness of fundoplication with other medical management to treat GORD in children. There are no RCTs to date on other approaches, such as endoscopic anti-reflux procedures, in children.

It was highlighted that fundoplication is generally used in the situation where medical management has failed and symptoms and complications of GORD are severe. Alternatively, fundoplication may be used as an anti-vomiting procedure in the case of children with complex, severe neurodisabilities who require impractical enteral feeding regimes to maintain growth because of severe vomiting and/or to limit the possibility of aspiration episodes in the context of an unsafe airway protection mechanism. It was the experience of the group's members that fundoplication surgery can be an effective option for reducing the symptoms of GORD in these groups of children. However, as with any invasive intervention, the benefits, risks and potential complications must be weighed up very carefully.

Given the agreement that fundoplication surgery is beneficial in certain children, the group focused its discussion on which tests should be required prior to surgery to help clinicians within the multidisciplinary team to identify those children and young people who would benefit. During discussion, concern was expressed that surgery can sometimes be undertaken without adequate prior investigation, appropriate medical management and careful, expert analysis of the options.

It is recognised by the guideline development group that a variety of assessment models exist for children who are referred for consideration of fundoplication surgery. Rather than attempt to define the individual experts who should be involved in the decision making process, the group concluded that it was important that an upper GI endoscopy (with biopsies) is always carried out to prior to surgery during the referral process. In addition, the group concluded that consideration must be given to the potential benefit of having additional information from either or both pH and impedance monitoring and an upper GI contrast study. Having undergone these investigations, the results would then need to be analysed by an appropriate professional with expertise in the area and considered in the clinical context of the child in question. This will help ensure the diagnosis is correct and that the symptoms cannot be explained by an alternative disease which could be treated differently. Similarly, these tests will help ensure that the referral is genuinely indicated, help avoid potential future complications and ensure that the benefits are likely to outweigh the risks for the particular child and their family or carers.

Finally, the group assessed the evidence comparing laparoscopic with open fundoplication to treat GORD in children and young people. The available evidence from 3 low quality studies showed no difference in outcomes: based on this, the group did not believe a recommendation could be made on which method should be used. However, it was the experience of the group that open fundoplication had a number of disadvantages compared with laparoscopic surgery due to the larger wound, the main ones being greater pain and discomfort, longer length of stay and longer recovery period. Further, it is likely that there would be a decreased risk of developing adhesions (a relatively common long-term complication of an open laparotomy). As a result, it was debated whether equivalence in reported outcomes ought to logically favour the laparoscopic approach given its obvious

benefits, unless the results of 'open' surgery are clearly superior to 'laparoscopic' surgery in any specific case.

8.1.6.3 Consideration of health benefits and resource uses

No published health economic evaluations were identified in the literature search conducted for this review question. There is evidence to suggest that the long-term treatment of GORD in adults is cost effective compared to medical management. However, the guideline development group's view was that this evidence did not address the review question and was not transferable to the treatment of children suffering from GORD as the physiological impact of treatments is different in children compared with adults, and the underlying cause of GORD or severe regurgitation may be different in children (in whom, for example, it may be caused by evolving dysmotility in cerebral palsy) compared with adults (in whom, for example, it may be caused by lifestyle).

No studies were identified that evaluated the comparative cost effectiveness of surgical management of GORD in children, either comparing different types of surgery or comparing surgical procedures with long-term medical management. The different options for surgical management are not alternatives to one another (alternative options for the same condition) because they are designed to treat different physiological causes of GORD. For specific groups of children (such as those with neurodisability) or those with specific symptoms, surgical management may be considered the only option to treat GORD as the only alternative would be managing the symptoms of GORD on a long-term basis.

Similarly, there is no published economic evaluation comparing laparoscopic with open surgery. There was evidence that laparoscopic surgery had a shorter length of stay, but this had to be balanced against a greater risk of revision surgery being required.

The costs associated with different types of surgical techniques are outlined in Appendix A: Health economics.

8.1.6.4 Quality of evidence

Only 4 comparative studies were identified for this review – 2 RCTs and 2 retrospective observational studies. Unfortunately, none of the studies clearly answered the main question of whether fundoplication is effective in the treatment of GORD in infants, children and young adults.

Potential bias in the RCTs included being unable to blind allocation and inadequate power to detect differences in the primary outcome. Intention to treat was not used in either of the studies. In 1 study this was because the study was not adequately powered for its primary outcome so no result for this outcome was reported, nor was intention to treat (ITT) analysis performed for the outcome (adverse events) that the guideline development group was interested in. The second study did not perform ITT as the aim of the study was to assess the effects of the actual operation performed. In the observational studies, biases included retrospective design and high loss to follow-up. This was not differential loss between the groups.

Given the limited amount and quality of the evidence available, it is not possible to make strong recommendations on the use of fundoplication.

8.1.6.5 Other considerations

No specific equality issues were raised in relation to this question.

8.1.7 Recommendations

40. Offer an upper GI endoscopy with oesophageal biopsies for infants, children and young people before deciding whether to offer fundoplication for presumed GORD.

41. 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.

42. 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.

8.1.8 Research recommendations

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

Why this is important

Fundoplication is used to manage severe GORD. At present, there is limited evidence that overt regurgitation is reduced after surgery. However, this has not been objectively measured. In addition, the effect of surgery on occult reflux has not been assessed. This is important because surgery may be masking a continuing problem. The proposed study would monitor regurgitation before and after fundoplication using oesophageal pH monitoring. This may help health professionals identify which infants, children and young people will benefit from surgery.

9 Glossary and abbreviations

9.1 Glossary

Term	Description
Abdominal distension	Outward expansion beyond the normal girth of the abdomen – caused by accumulation in the abdomen of substances such as gas or liquid or faeces.
Abdominal mass	Discrete or diffuse enlargement or swelling in the abdomen.
Alginates	A polysaccharide found in seaweed which can absorb water or react with enzymes found in the stomach such as pepsin. Alginates are used to reduce reflux by increasing the viscosity of stomach contents.
Anaemia	A low blood haemoglobin concentration which is below age-specific normal ranges.
Antacid	Alkaline agents that raise the pH in the stomach by neutralising acid produced in the stomach.
Apnoea	Abrupt cessation of breathing.
Aspiration pneumonia	An inflammation of the lungs precipitated by inhalation of liquid or food either on swallowing or due to a reflux episode entering the lungs.
Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at various stages in the research process, such as in the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounder or confounding factor, publication bias.
Biopsy	A piece of tissue removed for analysis by microscope to determine the presence of any inflammation or other abnormality.
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also double-blind study, single-blind study, triple-blind study.
Bulging fontanelle	The fontanelle is a 'soft spot' palpable on the top of the head in the gap between the skull bones in infants and young children. This gap normally closes before a child is 18 months. If this soft spot is 'bulging' (protruding abnormally), this may indicate a rise in pressure inside the skull. This sometimes happens in infants and young children with meningitis.
Case–control study	A study that starts with the identification of a group of individuals sharing the same characteristics (for example people with a particular disease) and a suitable comparison (control) group (such as people without the disease). All subjects are then assessed with respect to things that happened to them in the past, for example things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.
Causal relationship	Describes the relationship between two variables when it can be established that one causes the other. For example, there is a causal relationship between a treatment and a disease if it can be shown that the treatment changes the course or outcome of the disease. Usually randomised controlled trials are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association

Term	Description
	between two variables. For example, if it happened that everyone who had eaten a particular food became sick and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food caused the sickness – unless all other possible causes (such as environmental factors) had been ruled out.
Child	A person aged 1 year to 11 years.
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy.
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus, within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, for example comparing mortality between one group that received a specific treatment and one group that did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Combined oesophageal pH and impedance monitoring	A technique in which a thin tube is placed via the nose into the oesophagus, allowing simultaneous measurement in real time of acid reflux (by measuring of acid/neutral/alkaline by the pH part of the tube) and volume reflux, whether acid or not (by the impedance part of the tube which works on the principle of conduction of electricity differing between gas, liquid and solid and can thus detect reflux of liquid regardless of its pH). Usually occurs over 24 hours and allows association between reflux and symptoms in real time.
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95% confidence interval' as the range of effects within which we are 95% confident that the true effect lies.
Confounder or confounding factor	Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Contrast study	X-rays are performed while the patient ingests a substance, such as barium, which will show up on X-ray, to highlight certain aspects of the anatomy. The gastrointestinal tract and elements of its function can be visualised by this method.

Term	Description
Cost effectiveness	Value for money. A specific healthcare treatment is said to be 'cost effective' if it gives a greater health gain than could be achieved by using the resources in other ways.
Cost effectiveness analysis	A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units'; for example the cost of preventing one additional heart attack.
Cows' milk protein	One or more of the several proteins present in cows' milk.
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.
Diaphragmatic hernia	When a congenital defect, or hole, occurs in the diaphragm (the muscles separating the abdominal contents from the chest) which may allow contents of the abdomen to pass into the chest.
Distressed behaviour	An observed manifestation of pain or discomfort in infants or children, or young people with a neurodisability who are unable to communicate clearly. Examples include crying, grimacing, other objective clinical signs of pain or inconsolability.
Dyspepsia	Pain in the upper abdomen originating from the oesophagus, stomach or upper part of the intestine – also known by terms such as 'indigestion'.
Dysphagia	Difficulty swallowing either liquids or solids.
Dysuria	Pain on, or difficulty in, passing urine.
Endoscopy	The passage of a flexible instrument with a camera on its tip into a body area (such as the stomach or intestine) in order to obtain images or video, and allow the operator to obtain biopsies or to conduct minimally invasive procedures from within the body cavity or organ entered.
Enteral feeding	Nutrition administered using the gastrointestinal tract – this usually involves access by a tube via the nose or through the abdominal wall.
Epigastric pain	Pain located in the area centrally where the rib cage meets just below the breastbone.
Fundoplication	An operation that involves wrapping the upper part of stomach around the oesophagus. The aim is to improve the function of the junction between the oesophagus and stomach in order to prevent or minimise GOR or GORD. A variety of techniques are used.
Fundoplication – open and laparoscopic	Open fundoplication refers to a surgical approach in which the surgeon opens the abdominal cavity with a surgical incision. Laparoscopic fundoplication is performed using a 'keyhole' approach, the surgical instruments being inserted into the abdominal cavity through small incisions thus avoiding the need to open the abdominal cavity.
Gastro-oesophageal reflux	Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus. It is a common physiological event at all ages from infancy to old age, and is often asymptomatic. It occurs more frequently after feeds/meals. In many infants, GOR is associated with a tendency to 'overt regurgitation' - the visible regurgitation of feeds.
Gastro-oesophageal reflux disease	Gastro-oesophageal reflux disease (GORD) refers to gastro-oesophageal reflux that causes symptoms (for example discomfort or pain) severe enough to merit medical treatment, or to gastro-oesophageal reflux-associated complications (such as oesophagitis or pulmonary aspiration). In adults the term GORD is often used more narrowly, referring specifically to reflux oesophagitis.
H_2 receptor antagonists	Drugs which decrease the acid production of the stomach and act on the mechanism which triggers cells to produce acid rather than neutralising acid once it has been produced and released by the cells into the stomach.
Hematemesis	Blood in vomit.

Term	Description
Hiatus hernia	An abnormal formation at the junction between the oesophagus and stomach, in which part of the stomach enters into the chest with the effect of compromising the function of this area in preventing GOR or GORD.
Hydrolysed formula	A milk which has the protein artificially broken down into smaller molecules called peptides which are less likely to cause an allergic reaction.
Hypertrophic pyloric stenosis	A condition in the first 6 to 10 weeks of life in which the exit point of the stomach is progressively blocked due to the increase in size and contraction of the muscle surrounding this area, with consequent vomiting and need for corrective surgery.
Infant	A person older than 28 days but younger than 1 year.
Likelihood ratio	Used to assess the benefit of undertaking a diagnostic test. It is based on sensitivity and specificity.
Marked distress	There is very limited evidence, and no objective or widely accepted clinical definition, for what constitutes 'marked distress' in infants and children who are unable to adequately communicate (expressively) their sensory emotions. In this guideline, 'marked distress' refers to an outward demonstration of pain or unhappiness that is outside what is considered to be the normal range by an appropriately trained, competent healthcare professional, based on a thorough assessment. This assessment should include a careful analysis of the description offered by the parents or carers in the clinical context of the individual child.
Medical management	Any intervention aimed at alleviating a disease or condition when instigated by a medical practitioner or team.
Melaena	Black, foul-smelling stool which is suggestive of a major haemorrhage from the upper gastrointestinal tract. The appearance is due to alteration of the blood as it passes through the gastrointestinal tract.
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, for example because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also systematic review and heterogeneity.
Negative predictive value	The proportion of people with a negative test result who do not have the disease (where not having the disease is indicated by the gold standard test being negative).
Neurodisability	Neurodevelopmental disabilities (neurodisabilities) are a diverse group of chronic disorders that can begin during the development process (including conception, birth and periods of growth). They last throughout an individual's lifetime. Cerebral palsy is the most common cause of physical disability in childhood.
Obese/obesity	Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Weight in kilograms is divided by the square of height in metres, giving body mass index (BMI) as a measurement in kg/m^2. Age and gender specific charts are used to determine the BMI centile. A BMI above the 98th centile indicates obesity in a child or young person.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (such as whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (such as whether or not they died), without the

Term	Description
	intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
Occult reflux	The movement of part or all of the stomach contents up the oesophagus, but not to the extent that it enters the mouth or is obvious to the child, parents or carers, or observing healthcare professional. There is no obvious, visible regurgitation or vomiting. It is sometimes referred to as silent reflux.
Odds ratio	Odds are a way of representing probability, especially familiar for betting. In recent years, odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk', so an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also relative risk, risk ratio.
Oesophageal atresia	A birth defect in which the oesophagus develops abnormally during pregnancy, resulting in a blind ended tube with no passage to the stomach.
Oesophageal pH monitoring	A technique in which a thin tube is placed via the nose into the oesophagus. This allows measurement in real time of acid reflux (by measuring of acid/neutral/alkaline).
Otitis media	Inflammation of the middle ear.
Outcome	The end result of care and treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.
Overt regurgitation	The voluntary or involuntary movement of part or all of the stomach contents up the oesophagus at least as far as the mouth, and often emerging from the mouth. Regurgitation is in principle clinically observable, so is an overt phenomenon, although lesser degrees of regurgitation into the mouth might be overlooked.
p value	If a study is done to compare two treatments then the p value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the p value was 0.03. What this means is that if there really was no difference between treatments, then there would only be a 3% chance of getting the results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of p is below 0.05 (less than 5%) the result is seen as statistically significant. Where the value of p is 0.001 or less, the result is seen as highly significant. p values just tell us whether an effect can be regarded as statistically significant or not: they do not relate to how big the effect might be (see instead 'confidence interval').
Paediatric specialist	A healthcare professional who has had specific training or has recognised expertise in the management of children and their illnesses. Examples include paediatricians and healthcare professionals working in children's emergency departments.
Physiological reflux	Reflux which occurs in all infants and children to a lesser or greater extent due to immature anatomy and function at the junction between the oesophagus and stomach.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial that are indistinguishable

Term	Description
	from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any effect that is simply due to receiving care or attention.
Positive predictive value	The proportion of people with a positive test result who have the disease (where having the disease is indicated by the 'gold' standard test being positive).
Premature birth	Any pregnancy which leads to birth before 37 weeks' gestation.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Premature infant	A baby born before 37 completed weeks of gestation.
Prokinetic agents	Drugs which help the stomach to empty faster by increasing the speed at which contents are passed through the stomach.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Protocol	A plan or set of steps that defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.
Proton pump inhibitors	Drugs which reduce the amount of acid produced by inhibiting an enzyme that triggers the cells in the stomach to make acid.
Random allocation or randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups, with one (the experimental group) receiving the treatment that is being tested and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Read codes	A taxonomy that attributes a unique code to a hierarchical thesaurus of clinical tems. Read codes are used in the NHS to encode patient findings and procedures in electronic recording systems to support reporting (for example for audit, activity or financial reporting).
Reflux oesophagitis	Inflammation of the lining of the oesophagus due to gastro-oesophageal reflux. This can often be seen using endoscopy, but when mild the inflammatory changes may only be detected when biopsies taken at endoscopy are examined under a microscope.
Refractory	A situation in which an intervention is unsuccessful in its intended aim, or when a medical condition does not respond to treatment as planned.
Regurgitation	The voluntary or involuntary movement of stomach contents up the oesophagus at least as far as the mouth, and often emerging from the mouth. (See also overt regurgitation).
Relative risk	A summary measure that represents the ratio of the risk of a given event or outcome (such as an adverse reaction to the drug being tested) in

Term	Description
	one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.
Retrospective study	A retrospective study deals with past events and does not involve studying future events. This contrasts with studies that are prospective.
Retrosternal	Behind the breastbone.
Sandifer's syndrome	A condition in which abnormal posturing of an infant or child's head and neck, usually to one side or another, occur due to GOR or GORD. It should resolve with correct treatment of GOR or GORD.
Secondary care	Care provided in district general hospitals, generally led by paediatricians and a multidisciplinary team.
Sensitivity	In diagnostic testing, sensitivity refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its negative predictive value (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To fully judge the accuracy of a test, its specificity must also be considered.
Silent reflux	See occult reflux.
Specialist	A paediatrician with the skills, experience and competency necessary to deal with the particular clinical concern that has been identified by the referring healthcare professional. In this guideline this is most likely to be a consultant general paediatrician. Depending on the clinical circumstances, 'specialist' may also refer to a paediatric surgeon, paediatric gastroenterologist or a doctor with the equivalent skills and competency.
Specificity	In diagnostic testing, specificity refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its positive predictive value (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its sensitivity must also be considered.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.
Tertiary care	Care provided in university ('teaching') hospitals, generally led by paediatric gastroenterologists and a multidisciplinary team.
Treatment failure	When a medical intervention has failed to relieve or resolve the problem or condition.
Urgent	Requiring same day care.
Young person	A person aged 12 years to 17 years.

9.2 Abbreviations

Abbreviation	Description
BMI	body mass index
CF	cystic fibrosis
ALTE	apparent life threatening event
CI	confidence interval
CMA	cows' milk allergy
CNS	central nervous system
EEG	electroencephalogram
GER	gastro-esophageal reflux
GERD	gastro-esophageal reflux
GI	gastrointestinal
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H_2RA	H_2 receptor antagonist
LNF	Laparoscopic Nissen Fundoplication
LR+/LR−	positive likelihood ratio/negative likelihood ratio
LRTI	lower respiratory tract infection
MD	mean difference
NA	not applicable
NGT	nasogastric tube
NICU	neonatal intensive care unit
NJY	naso jejunal tube
NPV	negative predictive value
NR	not reported
ONF	Open Nissen Fundoplication
OR	odds ratio
PPI	proton pump inhibitors
PPV	positive predictive value
QALY	quality adjusted life year
RCT	randomised controlled trial
RR	risk ratio
SCBU	special care baby unit
SD	standard deviation
SIDS	sudden infant death syndrome
URI	upper respiratory infection

References

Abrahams & Burkitt, 1970

Abrahams,P., Burkitt,B.F., Hiatus hernia and gastro-oesophageal reflux in children and adolescents with cerebral palsy, Australian Paediatric Journal, 6, 41-46, 1970

Akinola et al., 2004

Akinola,E., Rosenkrantz,T.S., Pappagallo,M., McKay,K., Hussain,N., Gastroesophageal reflux in infants < 32 weeks gestational age at birth: lack of relationship to chronic lung disease, American Journal of Perinatology, 21, 57-62, 2004

Ammari et al., 2012

Ammari,M., Djeddi,D., Leke,A., Delanaud,S., Stephan-Blanchard,E., Bach,V., Telliez,F., Relationship between sleep and acid gastro-oesophageal reflux in neonates, Journal of Sleep Research, 21, 80-86, 2012

Assadamongkol et al., 1993

Assadamongkol,K., Phuapradit,P., Petsrikun,K., Viravithya,W., Gastroesophageal reflux in children: correlation of symptoms with 24-hour esophageal pH monitoring, Journal of the Medical Association of Thailand Chotmaihet thangphaet, 76 Suppl 2, 49-54, 1993

Aydin et al., 2011

Aydin,E., Tastan,E., Aydogan,F., Arslan,N., Karaca,G., Role of nasopharyngeal reflux in the etiology of otitis media with effusion, Journal of Otolaryngology - Head and Neck Surgery, 40, 499-503, 2011

Bagucka, 1999

Bagucka,B., Acid gastroesophageal reflux in the 10 degrees reversed Trendelenburg position in supine sleeping infants, Acta Paediatrica Taiwanica, 40, 298-301, 1999

Baker et al., 2013

Baker,L., Emil,S., Baird,R., A comparison of techniques for laparoscopic gastrostomy placement in children, Journal of Surgical Research, 184, 392-396, 2013

Bellissant et al., 1997

Bellissant,E., Duhamel,J.F., Guillot,M., Pariente-Khayat,A., Olive,G., Pons,G., The triangular test to assess the efficacy of metoclopramide in gastroesophageal reflux, Clinical Pharmacology and Therapeutics, 61, 377-384, 1997

Bhat et al., 2007

Bhat,R.Y., Rafferty,G.F., Hannam,S., Greenough,A., Acid gastroesophageal reflux in convalescent preterm infants: effect of posture and relationship to apnea, Pediatric Research, 62, 620-623, 2007

Bibi et al., 2001

Bibi,H., Khvolis,E., Shoseyov,D., Ohaly,M., Ben,Dor D., London,D., Ater,D., The prevalence of gastroesophageal reflux in children with tracheomalacia and laryngomalacia, Chest, 119, 409-413, 2001

Bines et al., 1992

Bines,J.E., Quinlan,J.E., Treves,S., Kleinman,R.E., Winter,H.S., Efficacy of domperidone in infants and children with gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 14, 400-405, 1992

Blewett et al., 2002

Blewett,C.J., Hollenbeak,C.S., Cilley,R.E., Dillon,P.W., Economic implications of current surgical management of gastroesophageal reflux disease, Journal of Pediatric Surgery, 37, 427-430, 2002

Boccia et al., 2007

Boccia,G., Manguso,F., Miele,E., Buonavolonta,R., Staiano,A., Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable?, American Journal of Gastroenterology, , 1291-1297, 2007

Bojke et al., 2007

Bojke,L., Hornby,E., Sculpher,M., REFLUX Trial Team., A comparison of the cost effectiveness of pharmacotherapy or surgery (laparoscopic fundoplication) in the treatment of GORD, Pharmacoeconomics, 25, 829-841, 2007

Borrelli et al., 2012

Borrelli,O., Mancini,V., Thapar,N., Giorgio,V., Elawad,M., Hill,S., Shah,N., Lindley,K.J., Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease, Journal of Pediatrics, 161, 476-481, 2012

Buts et al., 1987

Buts,J.P., Barudi,C., Otte,J.B., Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children, European Journal of Pediatrics, 146, 156-158, 1987

Campanozzi et al., 2009

Campanozzi,A., Boccia,G., Pensabene,L., Panetta,F., Marseglia,A., Strisciuglio,P., Barbera,C., Magazzu,G., Pettoello-Mantovani,M., Staiano,A., Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey, Pediatrics, 123, 779-783, 2009

Carr et al., 2000

Carr,M.M., Nguyen,A., Nagy,M., Poje,C., Pizzuto,M., Brodsky,L., Clinical presentation as a guide to the identification of GERD in children, International Journal of Pediatric Otorhinolaryngology, 54, 27-32, 2000

Carr et al., 2001

Carr,M.M., Nagy,M.L., Pizzuto,M.P., Poje,C.P., Brodsky,L.S., Correlation of findings at direct laryngoscopy and bronchoscopy with gastroesophageal reflux disease in children: a prospective study, Archives of Otolaryngology -- Head and Neck Surgery, 127, 369-374, 2001

Carroccio et al., 1994

Carroccio,A., Iacono,G., Montalto,G., Cavataio,F., Soresi,M., Notarbartolo,A., Domperidone plus magnesium hydroxide and aluminum hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus placebo, Scandinavian Journal of Gastroenterology, 29, 300-304, 1994

Chang et al., 2006

Chang,A.B., Cox,N.C., Faoagali,J., Cleghorn,G.J., Beem,C., Ee,L.C., Withers,G.D., Patrick,M.K., Lewindon,P.J., Cough and reflux esophagitis in children: their co-existence and airway cellularity, BMC Pediatrics, 6, 4-, 2006

Chao & Vandenplas, 2007

Chao,H.C., Vandenplas,Y., Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation, Nutrition, 23, 23-28, 2007

Chao & Vandenplas, 2007a

Chao,H.C., Vandenplas,Y., Comparison of the effect of a cornstarch thickened formula and strengthened regular formula on regurgitation, gastric emptying and weight gain in infantile regurgitation, Diseases of the Esophagus, 20, 155-160, 2007

Chen et al., 2014

Chen,J.H., Wang,H.Y., Lin,H.H., Wang,C.C., Wang,L.Y., Prevalence and determinants of gastroesophageal reflux symptoms in adolescents, Journal of Gastroenterology and Hepatology, 29, 269-275, 2014

Chopra et al., 1995

Chopra,K., Matta,S.K., Madan,N., Iyer,S., Association of gastroesophageal reflux (GER) with bronchial asthma, Indian Pediatrics, 32, 1083-1086, 1995

Contencin & Narcy, 1992

Contencin,P., Narcy,P., Gastropharyngeal reflux in infants and children. A pharyngeal pH monitoring study, Archives of Otolaryngology -- Head and Neck Surgery, 118, 1028-1030, 1992

Costa et al., 2004

Costa,A.J.F., Silva,G.A.P., Gouveia,P.A.C., Pereira,FilhoE, Prevalence of pathologic gastroesophageal reflux in regurgitant infants, Jornal de Pediatria, 80, 291-295, 2004

Cresi et al., 2008

Cresi,F., Marinaccio,C., Russo,M.C., Miniero,R., Silvestro,L., Short-term effect of domperidone on gastroesophageal reflux in newborns assessed by combined intraluminal impedance and pH monitoring, Journal of Perinatology, 28, 766-770, 2008

Cucchiara et al., 1989

Cucchiara,S., Gobio-Casali,L., Balli,F., Magazzu,G., Staiano,A., Astolfi,R., Amarri,S., Conti-Nibali,S., Guandalini,S., Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study, Journal of Pediatric Gastroenterology and Nutrition, 8, 150-156, 1989

Cucchiara et al., 1993

Cucchiara,S., Minella,R., Iervolino,C., Franco,M.T., Campanozzi,A., Franceschi,M., D'Armiento,F., Auricchio,S., Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis, Archives of Disease in Childhood, 69, 655-659, 1993

Davidson et al., 2013

Davidson,G, Wenzl,TG, Thomson,M, Omari,T, Barker,P, Lundborg,P, Illueca,M, Efficacy and Safety of Once-Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease in Neonatal Patients, Journal of Pediatrics, 163, 692-698.e2, 2013

Davidson et al., 2013a

Davidson,G., Wenzl,T.G., Thomson,M., Omari,T., Barker,P., Lundborg,P., Illueca,M., Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients, Journal of Pediatrics, 163, 692-698, 2013

De et al., 2001

De,S., Rajeshwari,K., Kalra,K.K., Gondal,R., Malhotra,V., Mittal,S.K., Gastrooesophageal reflux in infants and children in north India, Tropical Gastroenterology, 22, 99-102, 2001

Deal et al., 2005

Deal,L., Gold,B.D., Gremse,D.A., Winter,H.S., Peters,S.B., Fraga,P.D., Mack,M.E., Gaylord,S.M., Tolia,V., Fitzgerald,J.F., Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: development and initial validation, Journal of Pediatric Gastroenterology and Nutrition, 41, 178-185, 2005

Debley et al., 2006

Debley,J.S., Carter,E.R., Redding,G.J., Prevalence and impact of gastroesophageal reflux in adolescents with asthma: a population-based study, Pediatric Pulmonology, 41, 475-481, 2006

Del et al., 2005

Del,Buono R., Wenzl,T.G., Ball,G., Keady,S., Thomson,M., Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH, Archives of Disease in Childhood, 90, 460-463, 2005

Deurloo et al., 2004

Deurloo,J.A., Smit,B.J., Ekkelkamp,S., Aronson,D.C., Oesophageal atresia in premature infants: an analysis of morbidity and mortality over a period of 20 years, Acta Paediatrica, 93, 394-399, 2004

Diaz et al., 2005

Diaz,D.M., Gibbons,T.E., Heiss,K., Wulkan,M.L., Ricketts,R.R., Gold,B.D., Antireflux surgery outcomes in pediatric gastroesophageal reflux disease, American Journal of Gastroenterology, 100, 1844-1852, 2005

Elitsur et al., 2009

Elitsur,Y., Dementieva,Y., Elitsur,R., Rewalt,M., Obesity is not a risk factor in children with reflux esophagitis: a retrospective analysis of 738 children, Metabolic Syndrome and Related Disorders, 7, 211-214, 2009

El-Serag et al., 2001

El-Serag,H.B., Gilger,M., Kuebeler,M., Rabeneck,L., Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects, Gastroenterology, 121, 1294-1299, 2001

Ersin et al., 2006

Ersin,N.K., Oncag,O., Tumgor,G., Aydogdu,S., Hilmioglu,S., Oral and dental manifestations of gastroesophageal reflux disease in children: a preliminary study, Pediatric Dentistry, 28, 279-284, 2006

Ewer et al., 1999

Ewer,A.K., James,M.E., Tobin,J.M., Prone and left lateral positioning reduce gastro-oesophageal reflux in preterm infants, Archives of Disease in Childhood Fetal and Neonatal Edition, 81, F201-F205, 1999

Farahmand et al., 2013

Farahmand,F., Sabbaghian,M., Ghodousi,S., Seddighoraee,N., Abbasi,M., Gastroesophageal reflux disease and tooth erosion: a cross-sectional observational study, Gut and Liver, 7, 278-281, 2013

Forbes et al., 1986

Forbes,D., Hodgson,M., Hill,R., The effects of gaviscon and metoclopramide in gastroesophageal reflux in children, Journal of Pediatric Gastroenterology and Nutrition, 5, 556-559, 1986

Forssell et al., 2012

Forssell,L., Cnattingius,S., Bottai,M., Lagergren,J., Ekbom,A., Akre,O., Risk of esophagitis among individuals born preterm or small for gestational age, Clinical Gastroenterology and Hepatology, 10, 1369-1375, 2012

Frakaloss et al., 1998

Frakaloss,G., Burke,G., Sanders,M.R., Impact of gastroesophageal reflux on growth and hospital stay in premature infants, Journal of Pediatric Gastroenterology and Nutrition, 26, 146-150, 1998

Fuloria et al., 2000

Fuloria,M., Hiatt,D., Dillard,R.G., O'Shea,T.M., Gastroesophageal reflux in very low birth weight infants: association with chronic lung disease and outcomes through 1 year of age, Journal of Perinatology, 20, 235-239, 2000

Ghaem et al., 1998

Ghaem,M., Armstrong,K.L., Trocki,O., Cleghorn,G.J., Patrick,M.K., Shepherd,R.W., The sleep patterns of infants and young children with gastro-oesophageal reflux, Journal of Paediatrics and Child Health, 34, 160-163, 1998

Gonda-Domin et al., 2013

Gonda-Domin,M., Lisiecka,K., Rojek,R., Mokrzycka,M., Szymanowicz,J., Glura,B., Dental manifestations of gastroesophageal reflux disease in children, Przeglad Gastroenterologiczny, 8, 180-183, 2013

Guare et al., 2012

Guare,R.O., Ferreira,M.C., Leite,M.F., Rodrigues,J.A., Lussi,A., Santos,M.T., Dental erosion and salivary flow rate in cerebral palsy individuals with gastroesophageal reflux, Journal of Oral Pathology and Medicine, 41, 367-371, 2012

Gunasekaran et al., 2008

Gunasekaran,T.S., Dahlberg,M., Ramesh,P., Namachivayam,G., Prevalence and associated features of gastroesophageal reflux symptoms in a Caucasian-predominant adolescent school population, Digestive Diseases and Sciences, 53, 2373-2379, 2008

Gustafsson et al., 1990

Gustafsson,P.M., Kjellman,N.I., Tibbling,L., Bronchial asthma and acid reflux into the distal and proximal oesophagus, Archives of Disease in Childhood, 65, 1255-1258, 1990

Halpern et al., 1991

Halpern,L.M., Jolley,S.G., Johnson,D.G., Gastroesophageal reflux: a significant association with central nervous system disease in children, Journal of Pediatric Surgery, 26, 171-173, 1991

Hegar et al., 2004

Hegar,B., Boediarso,A., Firmansyah,A., Vandenplas,Y., Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants, World Journal of Gastroenterology, 10, 1795-1797, 2004

Hegar et al., 2009

Hegar,B., Dewanti,N.R., Kadim,M., Alatas,S., Firmansyah,A., Vandenplas,Y., Natural evolution of regurgitation in healthy infants, Acta Paediatrica, 98, 1189-1193, 2009

Hegar et al., 2013

Hegar,B., Satari,D.H., Sjarif,D.R., Vandenplas,Y., Regurgitation and gastroesophageal reflux disease in six to nine months old indonesian infants, Pediatric Gastroenterology Hepatology and Nutrition, 16, 240-247, 2013

Heine et al., 2006

Heine,R.G., Jordan,B., Lubitz,L., Meehan,M., Catto-Smith,A.G., Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress, Journal of Paediatrics and Child Health, 42, 134-139, 2006

Hussain et al., 2014

Hussain,S., Kierkus,J., Hu,P., Hoffman,D., Lekich,R., Sloan,S., Treem,W., Safety and Efficacy of Delayed Release Rabeprazole in 1- to 11-Month-Old Infants With Symptomatic GERD, Journal of Pediatric Gastroenterology and Nutrition, 58, 233-243, 2014

Iacono et al., 2002

Iacono,G., Vetrano,S., Cataldo,F., Ziino,O., Russo,A., Lorello,D., D'amico,D., Di,Rosa C., Le,Moli C., Di,Prima L., Giannitrapani,L., Cavataio,F., Clinical trial with thickened feeding for treatment of regurgitation in infants, Digestive and Liver Disease, 34, 532-533, 2002

Iacono et al., 2005

Iacono,G., Merolla,R., D'Amico,D., Bonci,E., Cavataio,F., Di,Prima L., Scalici,C., Indinnimeo,L., Averna,M.R., Carroccio,A., Paediatric Study Group on Gastrointestinal Symptoms in Infancy., Gastrointestinal symptoms in infancy: a population-based prospective study, Digestive and Liver Disease, 37, 432-438, 2005

Iglesias et al., 1997

Iglesias,J.L., Meier,D.E., Thompson,W.R., Cost analysis of laparoscopic and open fundoplication in children, Pediatric Endosurgery and Innovative Techniques, 1, 15-21, 1997

Knatten et al., 2012

Knatten,C.K., Fyhn,T.J., Edwin,B., Schistad,O., Emblem,R., Bjornland,K., Thirty-day outcome in children randomized to open and laparoscopic Nissen fundoplication, Journal of Pediatric Surgery, 47, 1990-1996, 2012

Koda et al., 2010

Koda,Y.K., Ozaki,M.J., Murasca,K., Vidolin,E., Clinical features and prevalence of gastroesophageal reflux disease in infants attending a pediatric gastroenterology reference service, Arquivos de Gastroenterologia, 47, 66-71, 2010

Koebnick et al., 2011

Koebnick,C., Getahun,D., Smith,N., Porter,A.H., Der-Sarkissian,J.K., Jacobsen,S.J., Extreme childhood obesity is associated with increased risk for gastroesophageal reflux disease in a large population-based study, International Journal of Pediatric Obesity, 6, e257-e263, 2011

Kohelet et al., 2004

Kohelet,D., Boaz,M., Serour,F., Cohen-Adad,N., Arbel,E., Gorenstein,A., Esophageal pH study and symptomatology of gastroesophageal reflux in newborn infants, American Journal of Perinatology, 21, 85-91, 2004

Kotsis et al., 2009

Kotsis,G.P., Nikolopoulos,T.P., Yiotakis,I.E., Papacharalampous,G.X., Kandiloros,D.C., Recurrent acute otitis media and gastroesophageal reflux disease in children. Is there an association?, International Journal of Pediatric Otorhinolaryngology, 73, 1373-1380, 2009

Leung & Lai, 1984

Leung,A.K.C., Lai,P.C.W., Use of metoclopramide for the treatment of gastroesophageal reflux in infants and children, CURR THER RES, CLIN EXP, 36, 911-915, 1984

Linnett et al., 2002

Linnett,V., Seow,W.K., Connor,F., Shepherd,R., Oral health of children with gastro-esophageal reflux disease: a controlled study, Australian Dental Journal, 47, 156-162, 2002

Martin et al., 2002

Martin,A.J., Pratt,N., Kennedy,J.D., Ryan,P., Ruffin,R.E., Miles,H., Marley,J., Natural history and familial relationships of infant spilling to 9 years of age, Pediatrics, 109, 1061-1067, 2002

Mathisen et al., 1999

Mathisen,B., Worrall,L., Masel,J., Wall,C., Shepherd,R.W., Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study, Journal of Paediatrics and Child Health, 35, 163-169, 1999

McHoney et al., 2011

McHoney,M., Wade,A.M., Eaton,S., Howard,R.F., Kiely,E.M., Drake,D.P., Curry,J.I., Pierro,A., Clinical outcome of a randomized controlled blinded trial of open versus laparoscopic Nissen fundoplication in infants and children, Annals of Surgery, 254, 209-216, 2011

Mezzacappa & Rosa, 2008

Mezzacappa,M.A., Rosa,A.C., Clinical predictors of abnormal esophageal pH monitoring in preterm infants, Arquivos de Gastroenterologia, 45, 234-238, 2008

Miller, 1999

Miller,S., Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux, Current Medical Research and Opinion, 15, 160-168, 1999

Miyazawa et al., 2002

Miyazawa,R., Tomomasa,T., Kaneko,H., Tachibana,A., Ogawa,T., Morikawa,A., Prevalence of gastro-esophageal reflux-related symptoms in Japanese infants, Pediatrics International, 44, 513-516, 2002

Miyazawa et al., 2004

Miyazawa,R., Tomomasa,T., Kaneko,H., Morikawa,A., Effect of locust bean gum in anti-regurgitant milk on the regurgitation in uncomplicated gastroesophageal reflux, Journal of Pediatric Gastroenterology and Nutrition, 38, 479-483, 2004

Miyazawa et al., 2006

Miyazawa,R., Tomomasa,T., Kaneko,H., Morikawa,A., Effect of formula thickened with locust bean gum on gastric emptying in infants, Journal of Paediatrics and Child Health, 42, 808-812, 2006

Miyazawa et al., 2007

Miyazawa,R., Tomomasa,T., Kaneko,H., Arakawa,H., Morikawa,A., Effect of formula thickened with reduced concentration of locust bean gum on gastroesophageal reflux, Acta Paediatrica, 96, 910-914, 2007

Miyazawa et al., 2008

Miyazawa,R., Tomomasa,T., Kaneko,H., Arakawa,H., Shimizu,N., Morikawa,A., Effects of pectin liquid on gastroesophageal reflux disease in children with cerebral palsy, BMC Gastroenterology, Vol.8, pp.11, 2008., -, -32676

Moore et al., 2003

Moore,D.J., Tao,B.S., Lines,D.R., Hirte,C., Heddle,M.L., Davidson,G.P., Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux, Journal of Pediatrics, 143, 219-223, 2003

Moukarzel et al., 2007

Moukarzel,A.A., Abdelnour,H., Akatcherian,C., Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER, Journal of Clinical Gastroenterology, 41, 823-829, 2007

Mousa et al., 2005

Mousa,H., Woodley,F.W., Metheney,M., Hayes,J., Testing the association between gastroesophageal reflux and apnea in infants, Journal of Pediatric Gastroenterology and Nutrition, 41, 169-177, 2005

Murray et al., 2007

Murray,L.J., McCarron,P., McCorry,R.B., Boreham,C.A., McGartland,C.P., Johnston,B.T., Prevalence of epigastric pain, heartburn and acid regurgitation in adolescents and their parents: evidence for intergenerational association, European Journal of Gastroenterology and Hepatology, 19, 297-303, 2007

Nelson et al., 1997

Nelson,S.P., Chen,E.H., Syniar,G.M., Christoffel,K.K., Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group, Archives of Pediatrics and Adolescent Medicine, 151, 569-572, 1997

Nelson et al., 1998

Nelson,S.P., Chen,E.H., Syniar,G.M., Christoffel,K.K., One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group, Pediatrics, 102, E67-, 1998

Nielsen et al., 2004

Nielsen,R.G., Bindslev-Jensen,C., Kruse-Andersen,S., Husby,S., Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure, Journal of Pediatric Gastroenterology and Nutrition, 39, 383-391, 2004

Omari et al., 2007

Omari,T.I., Haslam,R.R., Lundborg,P., Davidson,G.P., Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux, Journal of Pediatric Gastroenterology and Nutrition, 44, 41-44, 2007

O'Reilly et al., 2008

O'Reilly,R.C., He,Z., Bloedon,E., Papsin,B., Lundy,L., Bolling,L., Soundar,S., Cook,S., Reilly,J.S., Schmidt,R., Deutsch,E.S., Barth,P., Mehta,D.I., The role of extraesophageal reflux in otitis media in infants and children, Laryngoscope, 118, 1-9, 2008

Orenstein & Whitington, 1983

Orenstein,S.R., Whitington,P.F., Positioning for prevention of infant gastroesophageal reflux, Journal of Pediatrics, 103, 534-537, 1983

Orenstein et al., 1983

Orenstein,S.R., Whitington,P.F., Orenstein,D.M., The infant seat as treatment for gastroesophageal reflux, New England Journal of Medicine, 309, 760-763, 1983

Orenstein et al., 1987

Orenstein,S.R., Magill,H.L., Brooks,P., Thickening of infant feedings for therapy of gastroesophageal reflux, Journal of Pediatrics, 110, 181-186, 1987

Orenstein et al., 1996

Orenstein,S.R., Shalaby,T.M., Cohn,J.F., Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire, Clinical Pediatrics, 35, 607-614, 1996

Orenstein et al., 2009

Orenstein,S.R., Hassall,E., Furmaga-Jablonska,W., Atkinson,S., Raanan,M., Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease, Journal of Pediatrics, 154, 514-520, 2009

Orenstein, 1990

Orenstein,S.R., Prone positioning in infant gastroesophageal reflux: is elevation of the head worth the trouble?, Journal of Pediatrics, 117, 184-187, 1990

Osatakul et al., 2002

Osatakul,S., Sriplung,H., Puetpaiboon,A., Junjana,C.O., Chamnongpakdi,S., Prevalence and natural course of gastroesophageal reflux symptoms: a 1-year cohort study in Thai infants, Journal of Pediatric Gastroenterology and Nutrition, 34, 63-67, 2002

Ostlie et al., 2007

Ostlie,D.J., St Peter,S.D., Snyder,C.L., Sharp,R.J., Andrews,W.S., Holcomb,G.W.,III, A financial analysis of pediatric laparoscopic versus open fundoplication, Journal of Laparoendoscopic and Advanced Surgical Techniques, Part A. 17, 493-496, 2007

Ostrom et al., 2006

Ostrom,K.M., Jacobs,J.R., Merritt,R.J., Murray,R.D., Decreased regurgitation with a soy formula containing added soy fiber, Clinical Pediatrics, 45, 29-36, 2006

Park et al., 2013

Park,J.H., Park,H., Lee,D.H., Sung,I.K., A randomized, double blinded, clinical trial to assess the efficacy and cost effectiveness of omeprazole compared to rabeprazole in the maintenance therapy of patients with gastroesophageal reflux disease, Journal of Neurogastroenterology and Motility, 19, -, 2013

Pashankar et al., 2009

Pashankar,D.S., Corbin,Z., Shah,S.K., Caprio,S., Increased prevalence of gastroesophageal reflux symptoms in obese children evaluated in an academic medical center, Journal of Clinical Gastroenterology, 43, 410-413, 2009

Peter et al., 2002

Peter,C.S., Sprodowski,N., Bohnhorst,B., Silny,J., Poets,C.F., Gastroesophageal reflux and apnea of prematurity: no temporal relationship, Pediatrics, 109, 8-11, 2002

Petersen et al., 1989

Petersen,K.K., Bertelsen,V., Dirdal,M., Funch-Jensen,P., Thommesen,P., The incidence of gastro-oesophageal reflux in children with exogenic and endogenic asthma tested by a new radiological method, Rontgen-Blatter, 42, 527-529, 1989

Polat et al., 2013

Polat,Z., Akgun,O.M., Turan,I., Guven,PolatG, Altun,C., Evaluation of the relationship between dental erosion and scintigraphically detected gastroesophageal reflux in patients with cerebral palsy, Turkish Journal of Medical Sciences, 43, 283-288, 2013

Quitadamo et al., 2012

Quitadamo,P., Buonavolonta,R., Miele,E., Masi,P., Coccorullo,P., Staiano,A., Total and abdominal obesity are risk factors for gastroesophageal reflux symptoms in children, Journal of Pediatric Gastroenterology and Nutrition, 55, 72-75, 2012

Ruigomez et al., 2010

Ruigomez,A., Wallander,M.A., Lundborg,P., Johansson,S., Rodriguez,L.A., Gastroesophageal reflux disease in children and adolescents in primary care, Scandinavian Journal of Gastroenterology, 45, 139-146, 2010

Sacre & Vandenplas, 1989

Sacre,L., Vandenplas,Y., Gastroesophageal reflux associated with respiratory abnormalities during sleep, Journal of Pediatric Gastroenterology and Nutrition, 9, 28-33, 1989

Salvatore et al., 2005

Salvatore,S., Hauser,B., Vandemaele,K., Novario,R., Vandenplas,Y., Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology?, Journal of Pediatric Gastroenterology and Nutrition, 40, 210-215, 2005

Shaw et al., 1998

Shaw,L., Weatherill,S., Smith,A., Tooth wear in children: an investigation of etiological factors in children with cerebral palsy and gastroesophageal reflux, Journal of Dentistry for Children, 65, 484-486, 1998

Sherman et al., 2009

Sherman,P.M., Hassall,E., Fagundes-Neto,U., Gold,B.D., Kato,S., Koletzko,S., Orenstein,S., Rudolph,C., Vakil,N., Vandenplas,Y., A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. [151 refs], American Journal of Gastroenterology, 104, 1278-1295, 2009

Simeone et al., 1997

Simeone,D., Caria,M.C., Miele,E., Staiano,A., Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine, Journal of Pediatric Gastroenterology and Nutrition, 25, 51-55, 1997

Siti et al., 2000

Siti,Mazliah K., Norzila,M.Z., Deng,C.T., Zulfiqar,A., Azizi,B.H., Prevalence, clinical predictors and diagnosis of gastro-oesophageal reflux in children with persistent respiratory symptoms, Medical Journal of Malaysia, 55, 180-187, 2000

Srivastava et al., 2009

Srivastava,R., Downey,E.C., O'Gorman,M., Feola,P., Samore,M., Holubkov,R., Mundorff,M., James,B.C., Rosenbaum,P., Young,P.C., Dean,J.M., Impact of fundoplication versus gastrojejunal feeding tubes on mortality and in preventing aspiration pneumonia in young children with neurologic impairment who have gastroesophageal reflux disease, Pediatrics, 123, 338-345, 2009

Steward et al., 1993

Steward,R.J., Johnston,B.T., Boston,V.E., Dodge,J., Role of hiatal hernia in delaying acid clearance, Archives of Disease in Childhood, 68, 662-664, 1993

Stordal et al., 2005

Stordal,K., Johannesdottir,G.B., Bentsen,B.S., Sandvik,L., Gastroesophageal reflux disease in children: association between symptoms and pH monitoring, Scandinavian Journal of Gastroenterology, 40, 636-640, 2005

Stordal et al., 2006

Stordal,K., Johannesdottir,G.B., Bentsen,B.S., Carlsen,K.C., Sandvik,L., Asthma and overweight are associated with symptoms of gastro-oesophageal reflux, Acta Paediatrica, 95, 1197-1201, 2006

Sutphen & Dillard, 1988

Sutphen,J.L., Dillard,V.L., Effect of feeding volume on early postcibal gastroesophageal reflux in infants, Journal of Pediatric Gastroenterology and Nutrition, 7, 185-188, 1988

Tighe et al., 2010

Tighe M, Afzal N, Bevan A, Higgins B, Beattie RM. Pharmacological treatment for gastro-oesophageal reflux in children. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD008550. DOI: 10.1002/14651858.CD008550

Teixeira et al., 2007

Teixeira,B.C., Norton,R.C., Penna,F.J., Camargos,P.A., Lasmar,L.M., Macedo,A.V., Gastroesophageal reflux and asthma in childhood: a study on their relationship using esophageal PH monitoring, Jornal de Pediatria, 83, 535-540, 2007

Tobin et al., 1997

Tobin,J.M., McCloud,P., Cameron,D.J., Posture and gastro-oesophageal reflux: a case for left lateral positioning, Archives of Disease in Childhood, 76, 254-258, 1997

Tolia & Vandenplas, 2009

Tolia,V., Vandenplas,Y., Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. [68 refs], Alimentary Pharmacology and Therapeutics, 29, 258-272, 2009

Tolia et al., 1989

Tolia,V., Calhoun,J., Kuhns,L., Kauffman,R.E., Randomized, prospective double-blind trial of metoclopramide and placebo for gastroesophageal reflux in infants, Journal of Pediatrics, 115, 141-145, 1989

Tolia et al., 2003

Tolia,V., Wuerth,A., Thomas,R., Gastroesophageal reflux disease: Review of presenting symptoms, evaluation, management, and outcome in infants, Digestive Diseases and Sciences, 48, 1723-1729, 2003

Uzun et al., 2012

Uzun,H., Alagoz,D., Okur,M., Dikici,B., Kocabay,K., Senses,D.A., Ozkan,A., Kaya,M., Do gastrointestinal and respiratory signs and symptoms correlate with the severity of gastroesophageal reflux?, BMC Gastroenterology, 12, 22-, 2012

Van & Storms, 2010

Van,HoweR, Storms,M.R., Gastroesophageal reflux symptoms in infants in a rural population: longitudinal data over the first six months, BMC Pediatrics, 10, 7-, 2010

Vandenplas et al., 1994

Vandenplas,Y., Hachimi-Idrissi,S., Casteels,A., Mahler,T., Loeb,H., A clinical trial with an "anti-regurgitation" formula, European Journal of Pediatrics, 153, 419-423, 1994

Vandenplas et al., 2009

Vandenplas,Y., Rudolph,C.D., Di,Lorenzo C., Hassall,E., Liptak,G., Mazur,L., Sondheimer,J., Staiano,A., Thomson,M., Veereman-Wauters,G., Wenzl,T.G., North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition., Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), Journal of Pediatric Gastroenterology and Nutrition, 49, 498-547, 2009

Vanderhoof et al., 2003

Vanderhoof,J.A., Moran,J.R., Harris,C.L., Merkel,K.L., Orenstein,S.R., Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux, Clinical Pediatrics, 42, 483-495, 2003

Wenzl et al., 2003

Wenzl,T.G., Schneider,S., Scheele,F., Silny,J., Heimann,G., Skopnik,H., Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance, Pediatrics, 111, e355-e359, 2003

Wild et al., 2011

Wild,Y.K., Heyman,M.B., Vittinghoff,E., Dalal,D.H., Wojcicki,J.M., Clark,A.L., Rechmann,B., Rechmann,P., Gastroesophageal reflux is not associated with dental erosion in children, Gastroenterology, 141, 1605-1611, 2011

Winter et al., 2012

Winter,H., Gunasekaran,T., Tolia,V., Gottrand,F., Barker,P.N., Illueca,M., Esomeprazole for the treatment of GERD in infants ages 1-11 months, Journal of Pediatric Gastroenterology and Nutrition, 55, 14-20, 2012

Xinias et al., 2005

Xinias,I., Mouane,N., Le,Luyer B., Spiroglou,K., Demertzidou,V., Hauser,B., Vandenplas,Y., Cornstarch thickened formula reduces oesophageal acid exposure time in infants, Digestive and Liver Disease, 37, 23-27, 2005

Yuksel et al., 2013

Yuksel,F., Dogan,M., Karatas,D., Yuce,S., Senturk,M., Kulahli,I., Gastroesophageal reflux disease in children with chronic otitis media with effusion, Journal of Craniofacial Surgery, 24, 380-383, 2013

Appendices

The appendices are presented in 3 separate documents; Appendices F and I and in individual documents and the third contains all the remaining appendices.