NCC-WCH

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Gastro-oesophageal reflux disease in children and young people

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

Methods, evidence and recommendations

Draft for Consultation

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Contents

1 Guideline Summary

2 Guideline development group membership, NCC-WCH staff 3 and acknowledgements

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2 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, and it is noticeable 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 alike. 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 commonly seek advice from primary, secondary or tertiary care. As a result, it constitutes a major health burden for the NHS.

Generally, experts that the groups of children most affected by GORD are otherwise normal infants, children with identifiable risk factors or the pubescent young person who acquires the problem similar to adult patients. The two other specific populations of children affected by GORD are premature infants and children with complex, severe neurodisabilities. In this 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 e.g. 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 health 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 throughout 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. Despite this, it is anticipated that some colleagues from the health care community may be disappointed that their particular area of specialist interest is not covered in the way they may have hoped. In answer to this potential complaint it is highlighted that this is a guideline on 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. Finally, 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 is made to make detailed and prescriptive research recommendations.

2.1 Aim of the guideline

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

2.2 Definitions used in this guideline

When developing this guideline the following definitions were used for Gastro-oesophageal reflux (GOR) and Gastro-oesophageal reflux disease (GORD).

2.2.1 Gastro-oesophageal reflux (GOR)

Gastro-oesophageal reflux (GOR) refers to 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.

2.2.2 Gastro-oesophageal reflux disease (GORD)

In this guideline the term "gastro-oesophageal reflux disease" 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.

2.3 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 GDG 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 an ambitious 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.

2.4 Areas outside the remit of the guideline

The remit is limited to people aged under 18 years, therefore those aged more than this are not covered in this guideline. However, guidance for management of reflux in adults is being produced concurrently with this guideline.

Within the population of those aged under 18 years, two 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. Whilst 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 it impractical to assess these.

2.5 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.

2.6 Who has developed the guideline

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) 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, health economics modelling.

All GDG 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 GDG members' declarations of interests see Appendix D.

2.7 Related NICE guidelines

Details are correct at the time of consultation on the guideline (July 2014). Further information is available on the NICE website.

2.7.1 Published

2.7.1.1 General

- Medicines adherence. NICE clinical guidance 76 (2009).

2.7.1 Condition-specific

- Autism – management of autism in children and young people. NICE clinical guideline 170 (2013).
- Feverish illness in children. NICE clinical guideline 160 (2013).
- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease. NICE interventional procedure guidance 461 (2013).
- Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease. NICE interventional procedure guidance 431 (2012).
- Spasticity in children and young people. NICE clinical guideline 145 (2012).
- Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedure guidance 404 (2011).
- Food allergy in children and young people. NICE clinical guideline 116 (2011).
- Barrett's oesophagus – ablative therapy. NICE clinical guideline 106 (2010).
- Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 (2010)
- Constipation in children and young people. NICE clinical guideline 99 (2010).
- Diarrhoea and vomiting in children under 5. NICE clinical guideline 84 (2009).
- Surgical management of otitis media with effusion in children. NICE clinical guideline 60 (2008).
- Urinary tract infection in children. NICE clinical guideline 54 (2007).
- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatments of gastro-oesophageal reflux disease. NICE interventional procedure guideline 222 (2007).
- Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006).
- Obesity. NICE clinical guideline 43 (2006).
- Dyspepsia. NICE clinical guideline 17 (2004).
- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedure guidance 55 (2004).

2.7.2 Under development

NICE is developing the following guidance (details available from the NICE website):

- Dyspepsia and gastro-oesophageal reflux disease (update). NICE clinical guideline. Publication expected September 2014.
- Obesity (update). NICE clinical guideline. Publication expected October 2014.

3 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 (GDG) throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available from: www.nice.org.uk/aboutnice/howwework/NICEEquality

3.1 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 GDG 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 four 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). Searches in Medline and Embase were limited to English language and studies in humans. None of the other searches were limited by language of publication (although publications 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.

3.2 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 GDG was asked to predefine minimally important differences (the smallest difference between

treatments that health professionals or patients think is clinically beneficial). However, the GDG was unable to agree these so imprecision was graded based on statistical differences.

- 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 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 evidence 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 GDG:

- 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 GDG:

- 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 GDG (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 odds ratios (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)

3.3 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 GDG. Outcomes include 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. When assessing the accuracy of a test or the effectiveness of a particular treatment, appropriate information about the effect on one or more primary outcomes was sought.

3.4 Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG 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 GDG 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

3.5 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 GDG to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. Statements summarising the GDG'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 GDG 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 GDG identified 10 'key priorities for implementation' (key recommendations) and five 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 guidelines manual). The priority research recommendations were selected in a similar way.

3.6 Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. The GDG 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.

4 Recommendations and care pathway

4.1 Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation. The full list of recommendations is in section 4.2.

- 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 following '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 one 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.
- Refer infants, children and young people to a specialist for a possible upper GI endoscopy with biopsies if there is:
  - any haematemesis (blood-stained vomit)
  - any melaena (black, foul-smelling stool)
  - dysphagia
  - 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 referral for fundoplication
  - back arching or features of Sandifer's syndrome.
- In formula-fed infants with frequent regurgitation associated with marked distress:
  - review the feeding history **and**
  - reduce the feed volumes only if excessive for the infant's weight, **then**
  - give a trial of either:
    - smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk) **or**

  - thickened formula (for example, containing rice starch, cornstarch, locust bean gum or carob bean gum).

- In formula-fed infants, if small, frequent feeds and thickening the formula are unsuccessful, try stopping the thickening agent 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

Symptom or sign	Possible diagnostic implication	Suggested action
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)	Suggests upper gastrointestinal ulceration, including erosive oesophagitis	Specialist referral for investigation
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 Urinary tract infection in children. NICE clinical guideline 54 [2007]). Persistence suggests an alternative diagnosis	Urine microbiology investigation
Blood in stool	May suggest a variety of conditions, including bacterial gastroenteritis or an acute surgical condition	Specialist referral
Abdominal distension, tenderness or palpable mass.	May suggest intestinal obstruction or another acute surgical condition	Stool microbiology investigation
Systemic		
Appearing unwell	May suggest infection (also see Feverish illness in children. NICE clinical guideline 160 [2013])	Clinical assessment and urine microbiology investigation Specialist referral
Fever	May suggest infection (also see Feverish illness in children. NICE clinical guideline 160 [2013])	Clinical assessment and urine microbiology investigation Specialist referral
Dysuria	May suggest urinary tract infection (also see Urinary tract infection in children. NICE clinical guideline 54 [2007])	Clinical assessment and urine microbiology investigation Specialist referral
Bulging fontanelle	May suggest raised intracranial pressure, for example due to	Specialist referral

Symptom or sign	Possible diagnostic implication	Suggested action
	meningitis (Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 [2010])	
Rapidly increasing head circumference (more than 1 cm per week)	May suggest raised intracranial pressure, for example due to hydrocephalus or a brain tumour	Specialist referral
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 raised intracranial pressure, for example due to meningitis (Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 [2010])	Specialist referral
Eczema	May suggest gastrointestinal cow's milk protein allergy (also see Food allergy in children and young people. NICE clinical guideline 116 [2011])	Trial of cow's milk exclusion Specialist referral

1

4.2 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 require 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 green-yellow) 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 following '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 one 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. Think about referring infant and children with persistent back arching or features of Sandifer's syndrome (episodic torticollis with neck extension and rotation) for specialist assessment (and possible endoscopy and pH–impedance monitoring).
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. Take into account that the following are associated with an increased prevalence of GORD when deciding whether to investigate or treat:
    - 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.
12. GOR only rarely causes episodes of apnoea or apparent life-threatening events (ALTEs), but think about referral for specialist investigations if it is suspected as a possible factor following a general paediatric assessment.
13. 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 Obesity [NICE clinical guideline 43])
14. Do not offer an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of GORD in infants, children and young people.
15. Offer an urgent (same day) upper GI contrast study for infants with unexplained bile-stained vomiting.
16. Think about an upper GI contrast study for children and young people with a history of bile-stained vomiting, particularly if it is persistent or recurrent.
17. Offer an upper GI contrast study for children and young people with a history of GORD presenting with dysphagia.

18. Urgently refer (on the same day) infants younger than 2 months with progressively worsening or forceful vomiting of feeds for investigation for possible hypertrophic pyloric stenosis.
19. Refer infants, children and young people to a specialist for a possible upper GI endoscopy with biopsies if there is:
    - any haematemesis (blood-stained vomit)
    - any melaena (black, foul-smelling stool)
    - dysphagia
    - 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 referral for fundoplication
    - back arching or features of Sandifer's syndrome.
20. Think about performing a pH study, ideally with impedance monitoring, in children and young people with unexplained:
    - recurrent aspiration pneumonia
    - apnoea
    - non-epileptic seizure-like events
    - Sandifer's syndrome
    - unexplained upper airway inflammation
    - dental erosion in children and young people with a neurodisability
    - frequent otitis media.
21. Think about performing a pH study without impedance monitoring:
    - to ensure adequate acid suppression during treatment
    - if symptoms continue during medical management
    - if there is a clinical suspicion of GORD but no regurgitation
    - when thinking about fundoplication.
22. 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.
23. Do not use positional management to treat GOR in sleeping infants. In line with Department of Health advice, infants should be placed on their back when sleeping.
24. In formula-fed infants with frequent regurgitation associated with marked distress:

- review the feeding history **and**
- reduce the feed volumes only if excessive for the infant's weight, **then**
- give a trial of either:
  - smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk) **or**
  - thickened formula (for example, containing rice starch, cornstarch, locust bean gum or carob bean gum).

25. In breast-fed infants with frequent regurgitation associated with marked distress, 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.
26. In formula-fed infants, if small, frequent feeds and thickening the formula are unsuccessful, try stopping the thickening agent 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.
27. 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.
28. Consider a 4-week trial of an H_2RA or a PPI for infants, young children who are unable to verbally express their symptoms and those with a neurodisability and/or communication difficulties who have overt regurgitation with one or more of the following:
    - unexplained feeding difficulties (for example, refusing feeds, gagging or choking)
    - distressed behaviour
    - faltering growth.
29. Consider a 4-week trial of a PPI for children and young people with persistent heartburn, retrosternal or epigastric pain.
30. Assess the response to PPI or H_2RA treatment at 4 weeks, and think about referral for specialist assessment and possible endoscopy if the symptoms:
    - do not resolve **or**
    - recur when treatment is stopped.
31. When choosing between H2RAs and PPIs 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.
32. Treat endoscopically determined oesophagitis with an H_2RA or PPI.
33. Repeat endoscopy may be needed after PPI or H_2RA therapy to guide treatment and confirm mucosal healing.
34. 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.

35. 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
36. 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.
37. 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.
38. Offer an upper GI endoscopy with oesophageal biopsies for infants, children and young people before deciding whether to offer fundoplication for presumed GORD.
39. Think about performing other investigations such as pH–impedance monitoring for infants, children and young people before deciding whether to offer fundoplication.
40. 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

Symptom or sign	Possible diagnostic implication	Suggested action
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)	Suggests upper gastrointestinal ulceration, including erosive oesophagitis	Specialist referral for investigation
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 Urinary tract infection in children. NICE clinical guideline 54 [2007]). Persistence	Urine microbiology investigation

Symptom or sign	Possible diagnostic implication	Suggested action
	suggests an alternative diagnosis	
Blood in stool	May suggest a variety of conditions, including bacterial gastroenteritis or an acute surgical condition	Specialist referral
Abdominal distension, tenderness or palpable mass.	May suggest intestinal obstruction or another acute surgical condition	Stool microbiology investigation
Systemic		
Appearing unwell	May suggest infection (also see Feverish illness in children. NICE clinical guideline 160 [2013])	Clinical assessment and urine microbiology investigation Specialist referral
Fever	May suggest infection (also see Feverish illness in children. NICE clinical guideline 160 [2013])	Clinical assessment and urine microbiology investigation Specialist referral
Dysuria	May suggest urinary tract infection (also see Urinary tract infection in children. NICE clinical guideline 54 [2007])	Clinical assessment and urine microbiology investigation Specialist referral
Bulging fontanelle	May suggest raised intracranial pressure, for example due to meningitis (Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 [2010])	Specialist referral
Rapidly increasing head circumference (more than 1 cm per week)	May suggest raised intracranial pressure, for example due to hydrocephalus or a brain tumour	Specialist referral
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 raised intracranial pressure, for example due to meningitis (Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 [2010])	Specialist referral
Eczema	May suggest gastrointestinal cow's milk protein allergy (also see Food allergy in children and young people. NICE clinical guideline 116 [2011])	Trial of cow's milk exclusion Specialist referral

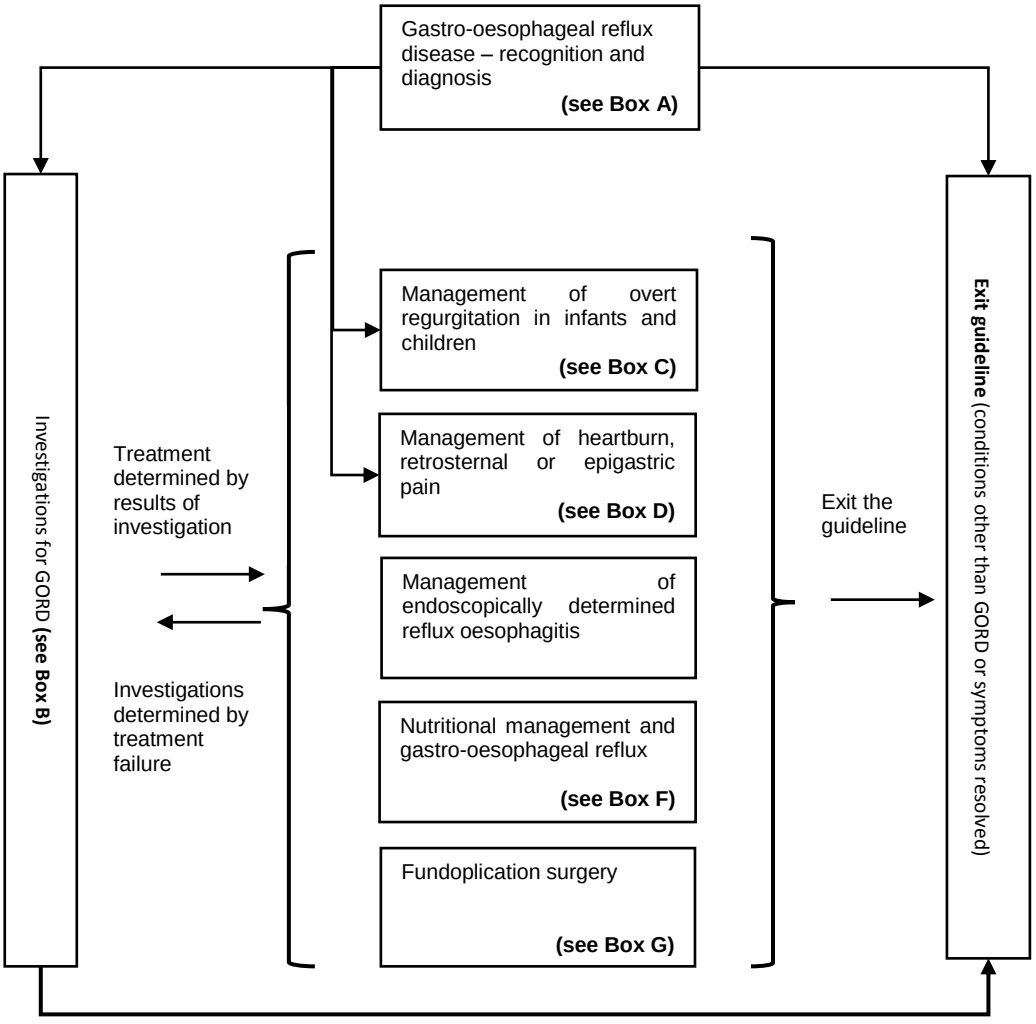
1

4.3 Research Recommendations

1. What are the symptoms associated with GOR and/or GORD in children and young people with a neurodisability?
2. What is the efficacy of cow's milk protein elimination in GOR and/or GORD?
3. What are the effects on pH monitoring results before and after fundoplication?

4.4 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. The care pathway reflects this complexity.



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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 require 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 green-yellow) 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 following 'red flags' in table R1, which may suggest disorders other than GOR. Investigate or refer using clinical judgement.

2

3

4

1 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)	Suggests upper gastrointestinal ulceration, including erosive oesophagitis	Specialist referral for investigation
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 Urinary tract infection in children [NICE clinical guideline 54]) Persistence suggests an alternative diagnosis	Urine microbiology investigation Specialist referral
Blood in stool	May suggest a variety of conditions, including bacterial gastroenteritis 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
Systemic		
Appearing unwell	May suggest infection (also see Feverish illness in children [NICE clinical guideline 160])	Clinical assessment and urine microbiology investigation Specialist referral
Fever	May suggest infection (also see Feverish illness in children [NICE clinical guideline 160])	Clinical assessment and urine microbiology investigation Specialist referral
Dysuria	May suggest urinary tract infection (also see Urinary tract infection in children [NICE clinical guideline 54])	Clinical assessment and urine microbiology investigation Specialist referral
Bulging fontanelle	May suggest raised intracranial pressure, for example due to meningitis (also see Bacterial meningitis and meningococcal septicaemia [NICE clinical guideline 102])	Specialist referral
Rapidly increasing head circumference (more than 1 cm per week)	May suggest raised intracranial pressure, for example due to hydrocephalus or a brain tumour	Specialist referral
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 Bacterial meningitis and meningococcal septicaemia [NICE clinical guideline 102])	Specialist referral
Eczema	May suggest gastrointestinal cow's milk protein allergy (also see Food	Trial of cow's milk exclusion

Symptoms and signs	Possible diagnostic implications	Suggested actions
	allergy in children and young people [NICE clinical guideline 116])	Specialist referral

1

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 one 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.

Think about referring infant and children with persistent back arching or features of Sandifer's syndrome (episodic torticollis with neck extension and rotation) for specialist assessment (and possible endoscopy and pH–impedance monitoring).

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.

Take into account that the following are associated with an increased prevalence of GORD when deciding whether to investigate or treat:

- 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 think about referral for specialist investigations if it is suspected as a possible factor following a general paediatric assessment.

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.

Urgently refer (on the same day) infants younger than 2 months with progressively worsening or forceful vomiting of feeds for investigation for possible hypertrophic pyloric stenosis.

2

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.

Offer an urgent (same day) upper GI contrast study for infants with unexplained bile-stained vomiting.

Think about 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.

Refer infants, children and young people to a specialist for a possible upper GI endoscopy with biopsies if there is:

- any haematemesis (blood-stained vomit)
- any melaena (black, foul-smelling stool)
- dysphagia
- 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 referral for fundoplication
- back arching or features of Sandifer's syndrome.

Think about performing a pH study, ideally with impedance monitoring, in children and young people with unexplained:

- recurrent aspiration pneumonia
- apnoea
- non-epileptic seizure-like events
- Sandifer's syndrome
- unexplained upper airway inflammation
- dental erosion in children and young people with a neurodisability
- frequent otitis media.

Think about performing a pH study without impedance monitoring:

- to ensure adequate acid suppression during treatment
- if symptoms continue during medical management
- if there is a clinical suspicion of GORD but no regurgitation
- when thinking about fundoplication.

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.

1

Box C - Management of overt regurgitation in infants and children

Do not use positional management to treat GOR in sleeping infants. In line with Department of Health advice, infants should be placed on their back when sleeping.

In breast-fed infants with frequent regurgitation associated with marked distress, 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:

- review the feeding history **and**
- reduce the feed volumes only if excessive for the infant's weight, **then**
- give a trial of either:
    - smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk) **or**
    - thickened formula (for example, containing rice starch, cornstarch, locust bean gum or carob bean gum).

In formula-fed infants, if small, frequent feeds and thickening the formula are unsuccessful, try stopping the thickening agent 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 an H_2RA or a PPI for infants, young children who are unable to verbally express their symptoms and those with a neurodisability and/or communication difficulties who have overt regurgitation with one or more of the following:

- unexplained feeding difficulties (for example, refusing feeds, gagging or choking)
- distressed behaviour
- faltering growth.

When choosing between H_2RAs and PPIs take into account:

- the availability of age-appropriate preparations
- the preference of the parent (or carer), child or young person (as appropriate)
- local procurement costs.

1 Do not offer metoclopramide, domperidone or erythromycin to treat GOR or GORD without seeking
2 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 Obesity [NICE clinical guideline 43])

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

Assess the response to PPI or H_2RA treatment at 4 weeks, and think about referral for specialist assessment and possible endoscopy if the symptoms:

- do not resolve or
- recur when treatment is stopped.

When choosing between H_2RAs and PPIs 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.

3

Box E - Management of endoscopically determined reflux oesophagitis

Treat endoscopically determined oesophagitis with an H_2RA or PPI.

Repeat endoscopy may be needed after PPI or H_2RA therapy to guide treatment and confirm mucosal healing.

When choosing between H_2RAs and PPIs take into account:

- the availability of age-appropriate preparations
- the preference of the parent, 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.

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.

Think about performing other investigations such as pH–impedance monitoring 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.

5 Diagnosing and investigating GORD

5.1 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 which 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.

5.1.1 Review question

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?

5.1.2 Description of included studies

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) five cross-sectional studies (De et al, 2001; Hegar et al, 2004; Gunasekaran et al, 2008; Miyazawa et al, 2002; Nelson et al, 1997) two case-control studies (Nelson et al, 1998; Orenstein et al, 1996) and one 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), three in Indonesia (Hegar et al, 2004; Hegar et al, 2009; Hegar et al., 2013), two in Italy (Campanozzi et al, 2009; Iacono et al, 2005), one in Australia (Martin et al, 2002) one in Japan (Miyazawa et al, 2002) one in Thailand (Osatakul et al, 2002) one in India (De et al, 2001) and one 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 between 10 days and 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 aged 1 to 17 years in one study (Ruigomez et al., 2010) and a mean (SD) of 15.7 ± 1.3 years in the other (Gunasekaran et al, 2008). 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 varied (e.g. 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 GERD (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, three studies used a diary (Hegar et al, 2009; Martin et al, 2002; Osatakul et al, 2002), one study a standard clinical chart (Iacono et al, 2005), and one study computerised medical records (Ruigomez et al., 2010).

No evidence was identified on premature babies or children with neurodisabilities. However, two studies (Campanozzi et al, 2009; Orenstein et al, 1996) included a small proportion of preterm infants.

Whilst 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 GDG prioritised prospective longitudinal cohort studies, but downgraded cross-sectional or retrospective studies as they did not allow a suitable comparison by age.

More details on each individual study can be found in the evidence tables.

5.153 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. However, the evidence identified was not in a suitable format to be put into standard GRADE tables. Therefore, a narrative description of the evidence for each outcome is provided below the GRADE table. 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[a]	None	None	None	Some[b]	Moderate
1 (De et al, 2001)	Cross-sectional	Serious[c]	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[d]	None	None	None	None	Moderate
1 (Hegar et al, 2013)	Prospective cohort	Serious[e]	None	None	None	None	Moderate
1 (Lacono et al, 2005)	Prospective cohort	No serious	None	None	None	None	High

Quality assessment							
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
1 (Martin et al, 2002)	Prospective cohort	Serious[a]	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[c]	None	None	None	None	Moderate
1 (Nelson et al, 1998)	Case-control	Very serious[a,c]	None	None	None	None	Low
1 (Orenstein et al, 1996)	Case-control	Serious[c]	None	None	None	Some[f]	Moderate
1 (Osatakul et al, 2002)	Prospective cohort	Serious[c]	None	None	None	None	Moderate
1 (Ruigomez et al, 2010)	Retrospective cohort	Very serious[g]	None	Some[h]	None	None	Very low
1 (Van Howe et al, 2010)	Prospective cohort	Very serious [a,c]	None	None	None	None	Low

[a] *Unclear whether loss to follow-up is unrelated to key characteristics*
[b] *Prematurity: 8.6% premature at entry to study*
[c] *Outcome is not clearly defined: definition of regurgitation not reported*
[d] *All dropouts because of excessive symptoms were in the partially breastfed group*
[e] *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.*
[f] *Prematurity: 26% of those attending well-baby clinic and 14% of those referred to gastroenterology department premature at entry to study*
[g] *Retrospective study design, based on electronic medical records across a number of GP practices, so variation in tests and treatments, only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken, none of the children in the control cohort had been tested for GER.*
[h] *This study examines GERD not regurgitation.*

5.14 Evidence statements (see Table 5)

5.14.1 Average age at which overt reflux was first reported

Two studies were identified for this 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.

5.14.2 Average age at which overt reflux was most frequent

No evidence was identified for this outcome.

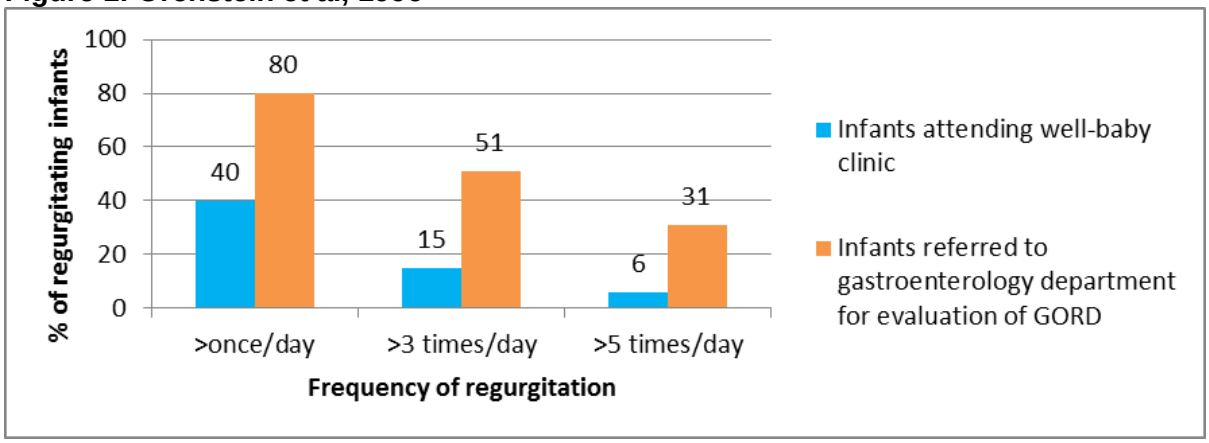
5.1.413 The reported maximum daily frequency of reflux

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.

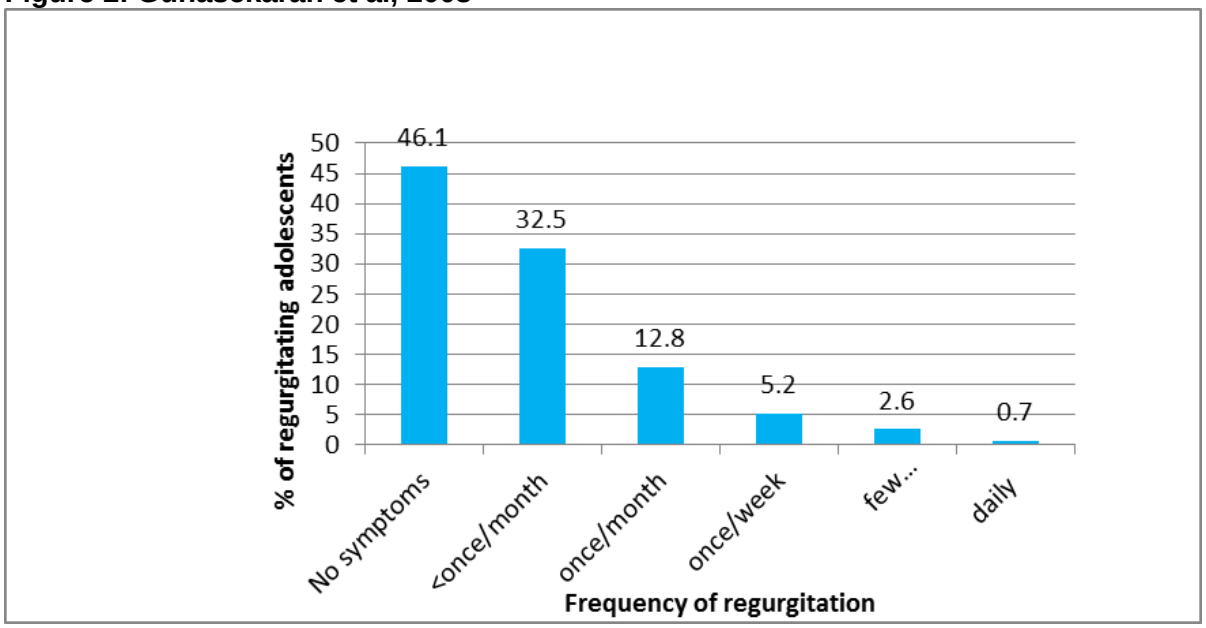
The second study (Orenstein et al, 1996) reported the percentage of infants with regurgitation greater than once a day, greater than 3 times a day and greater than 5 times a day in infants attending a well-baby clinic (median age: 19 weeks, range: 3 to 60 weeks) compared to infants referred to the gastroenterology department (median age: 15 weeks, range: 4 to 56 weeks) for the evaluation of GORD **(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: Orenstein et al, 1996



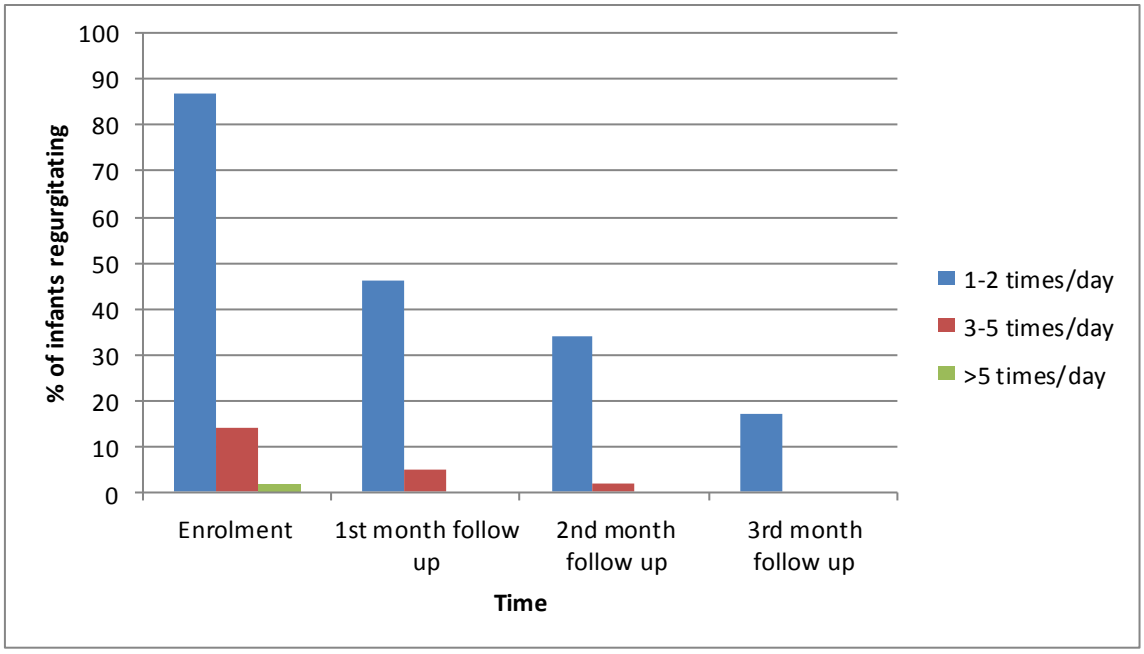
The third study (Gunasekaran et al, 2008) reported the percentage of adolescents (mean age: 15.7 years, range: 14 to 18 years) with no regurgitation, regurgitation less than once a month, regurgitation once a month, once a week, few times a week and daily (**Figure 2**). The evidence was of high quality.

Figure 2: 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/day, 3-5 times/day and >5 times/day at enrolment, 1st month of follow up, 2nd month of follow up and 3rd month of follow up (**Figure 3**). The evidence was of moderate quality.

Figure 3: Hegar et al, 2013

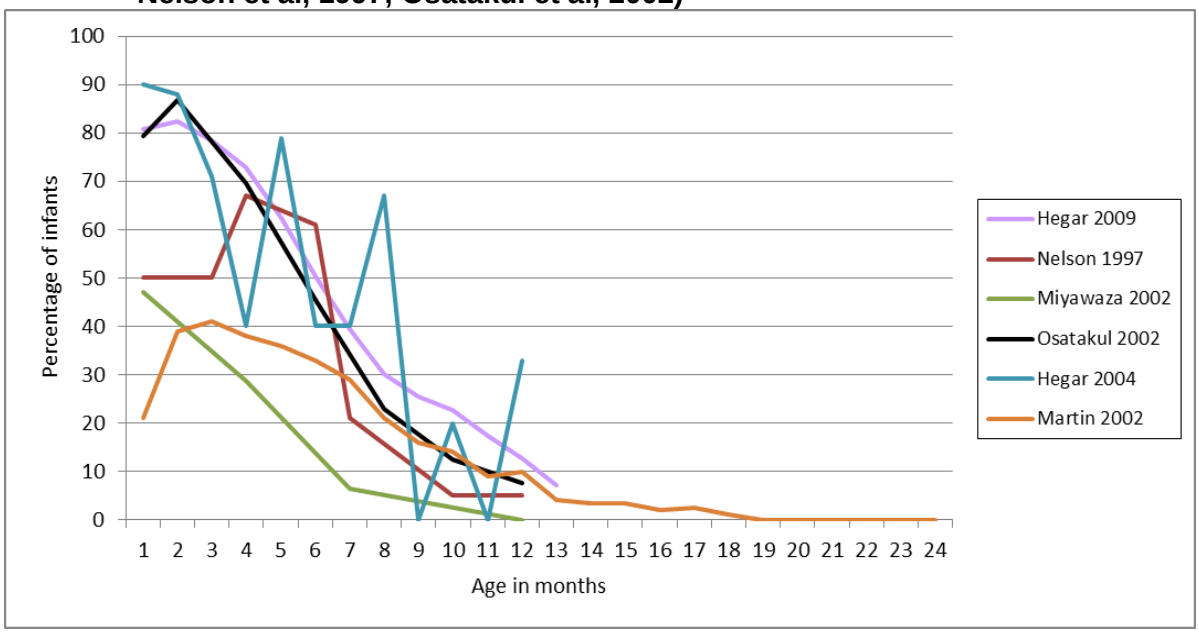


5.1.454 Average frequency of overt reflux at specific ages

5.1.4.461 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 (**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) all showed a decreasing incidence of regurgitation from the age of 4 months onwards. The evidence was of moderate to high quality.

Figure 4: Hegar et al, 2004; Hegar et al, 2009; Martin et al, 2002; Miyawaza et al, 2002; Nelson et al, 1997; Osatakul et al, 2002)



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

Four of the above 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 two of these four studies (Hegar et al, 2004; Hegar et al, 2009) reported the proportion of infants with less than one episode per day, 1 to 4 episodes per day and greater than 4 episodes per day in each age group (**Figure 5a and 5b**). The evidence was of high and moderate quality, respectively.

Figure 5a: Hegar et al, 2004

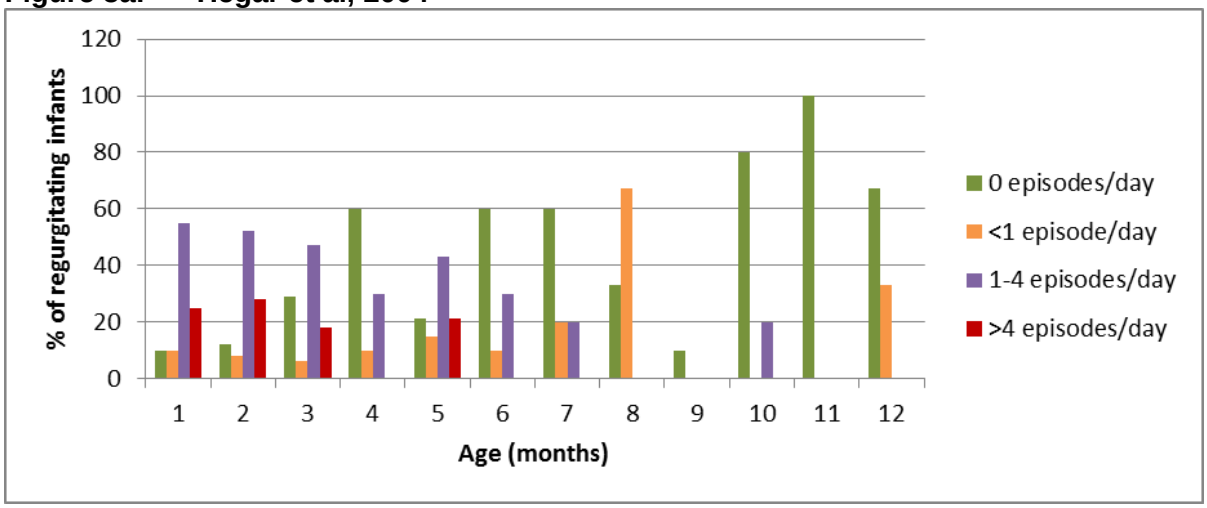
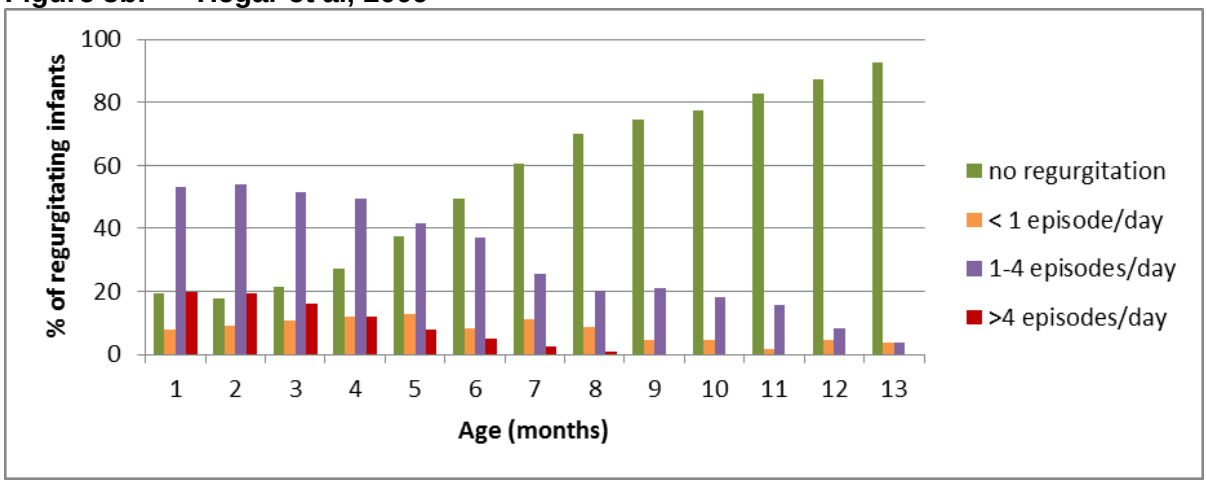
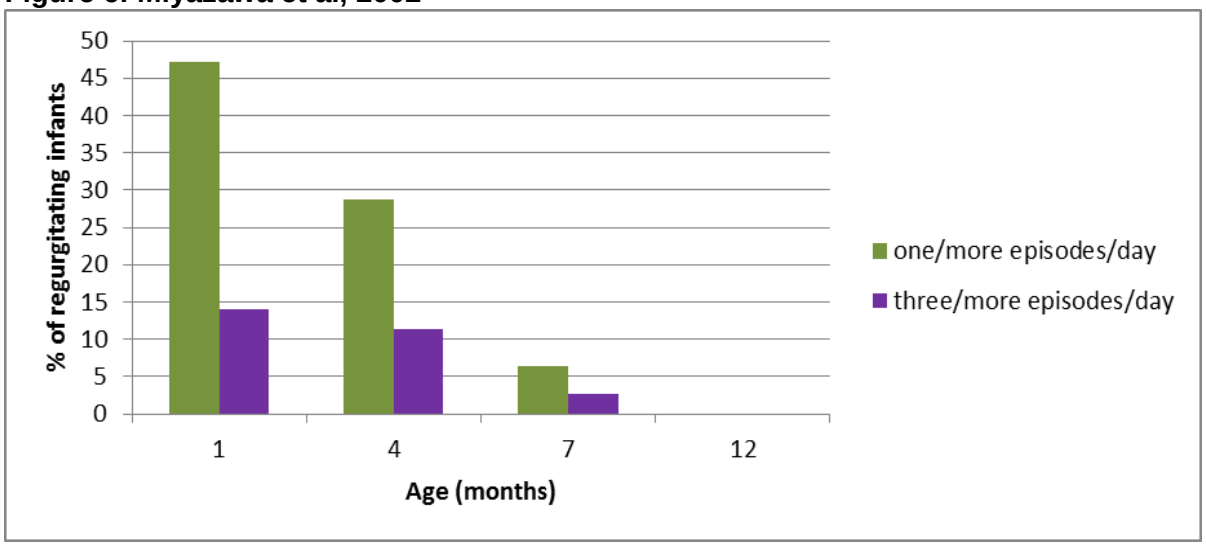


Figure 5b: Hegar et al, 2009



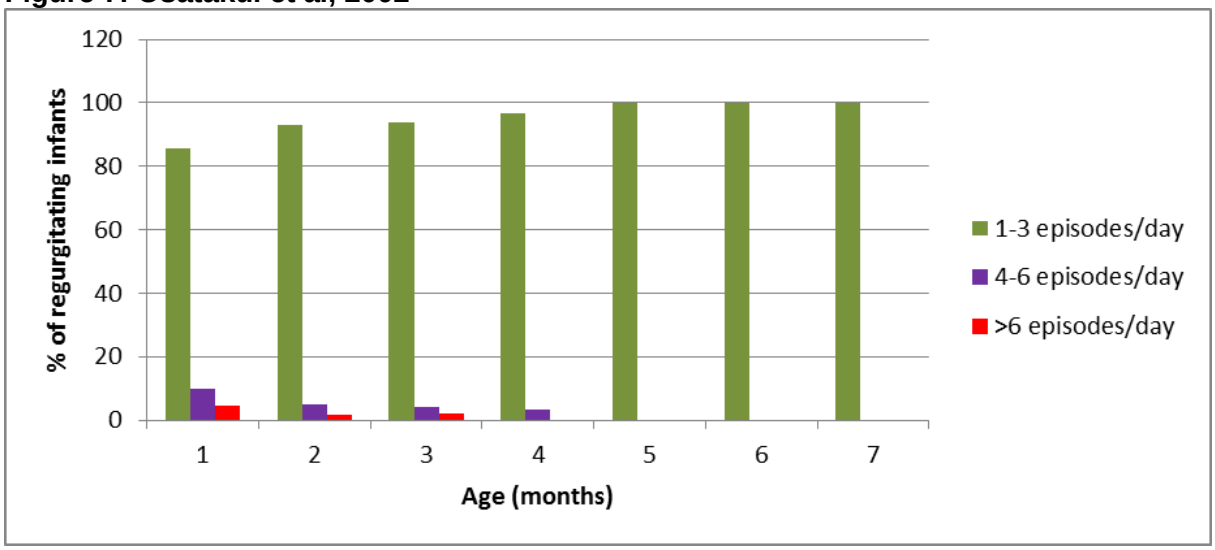
The third study (Miyawaza et al, 2002) reported the proportion of infants with one or more episodes per day and three or more episodes per day at specific ages (**Figure 6**). The evidence was of high quality.

Figure 6: Miyazawa et al, 2002



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

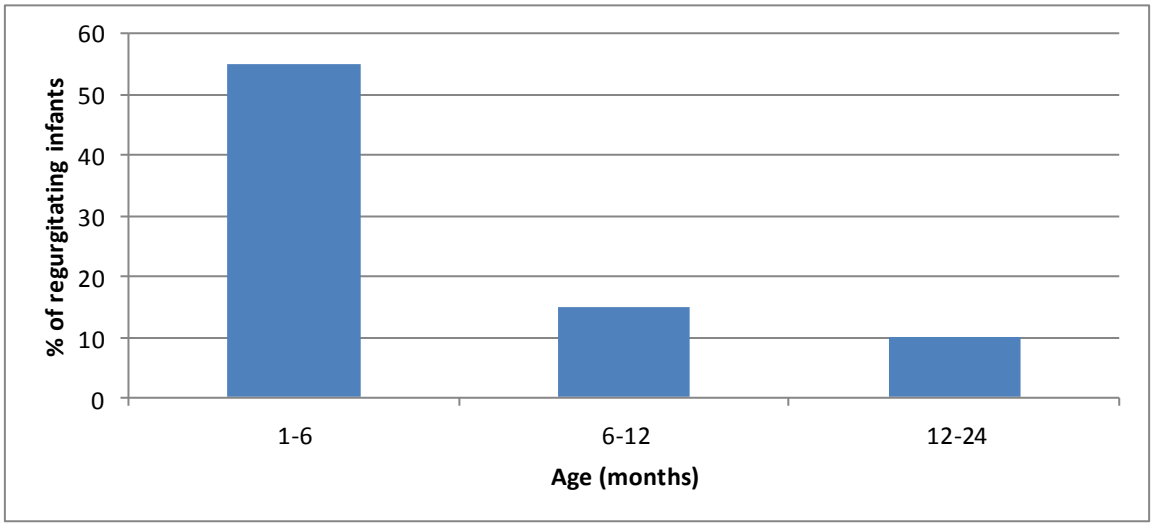
Figure 7: Osatakul et al, 2002



5.1.4.413 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 (**Figure 8**). The evidence was of moderate quality.

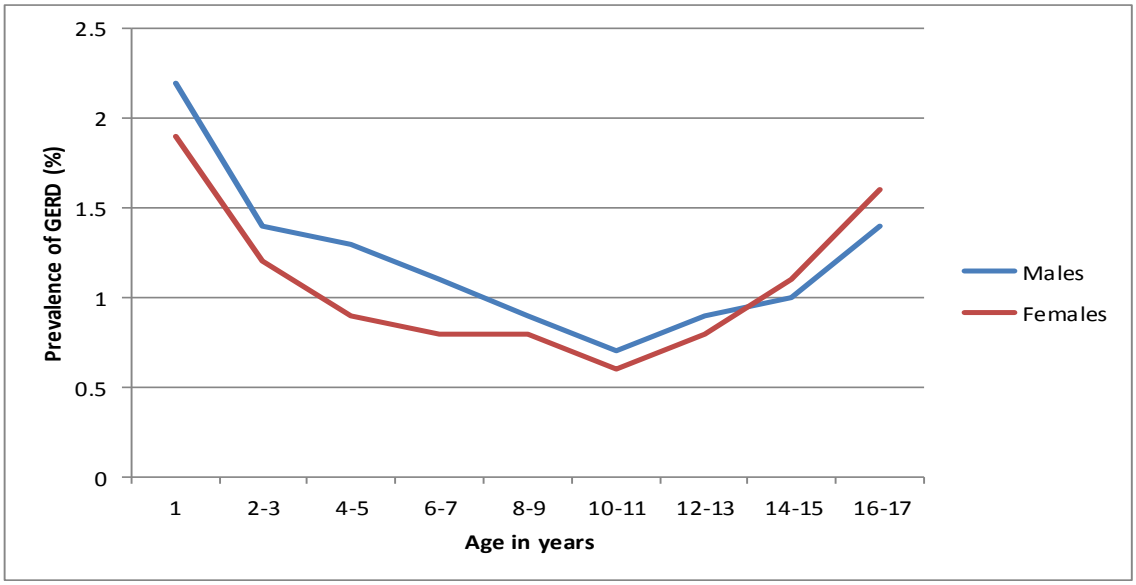
Figure 8: De et al, 2001



5.1.4.464 Reported as the prevalence (%) of GERD during the study period (2000-2005) at specific ages

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

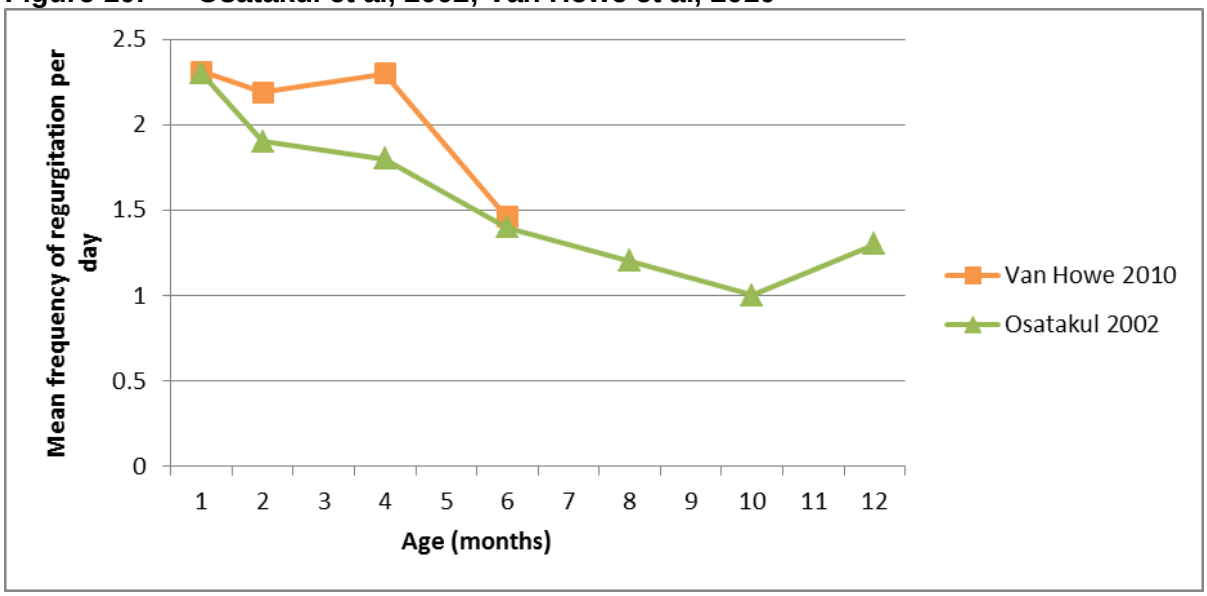
Figure 9: Ruigomez et al., 2010



5.1.4.4 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 (**Figure 10**). The evidence was of moderate and low quality, respectively.

Figure 10: Osatakul et al, 2002; Van Howe et al, 2010



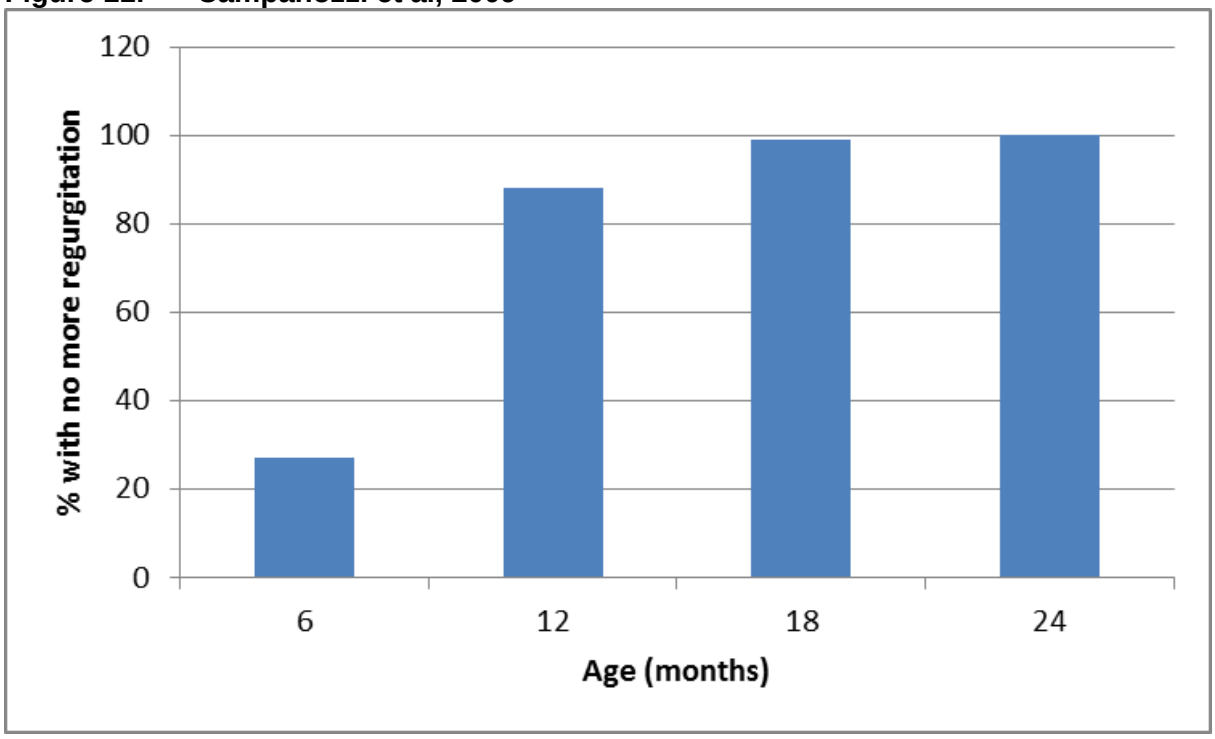
5.1.4.5 Age of cessation of overt reflux

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 19 months of age (**Figure 4**). The evidence was of moderate quality.

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

Figure 11: Campanozzi et al, 2009



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

5.13 Health economics profile

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

5.14 Evidence to recommendations

5.14.1 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 so as to be able 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.

5.14.2 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 to be 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 that this treatment is unnecessary as the reflux is not causing 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 from a review on symptoms and signs, and the clinical knowledge of the GDG, to make recommendations on when GOR becomes problematic and requires investigation and treatment.

5.1.6.271 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 at 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 GDG 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, the GDG, based on their own experience, 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 of age 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.

5.1.6.2232 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 of age. In these studies the proportion of infants with overt reflux during the first 6 months of life ranged from 20%-80%, and based on these studies the GDG concluded that at least 40% are affected by this condition. By 12 months of age most studies reported that fewer than 10% of the infants had overt reflux. The GDG believed that health care professionals should be aware of this, because unusually persistent regurgitation might require careful consideration with regard to the need for investigation.

5.1.6.2333 Frequency of reflux

In one population based study the frequency of regurgitation episodes was reported in a cohort of 100 infants. Based on this study the GDG included in their 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.

5.1.6.3433 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 resource significant resource implications.

5.1.614 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 an RCT as outlined in the GRADE methodology (see chapter 3).

The GDG noted that no studies were based within 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 new born 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 GDG 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" or not would vary depending on that study's definition. In addition to this, the way data was obtained varied. The GDG prioritised those studies that measured reflux using accredited diagnostic tools (for example 24-hour pH monitoring or an endoscopic investigation) in preference to those that defined outcomes and populations using questionnaires.

Finally, the GDG had concerns about study populations being small and the study setting not being representative of the normal situation found in the UK. The GDG found most of the studies cohorts were underpowered and therefore could not be used in isolation to support a recommendation. Furthermore, the GDG 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).

5.1.675 Other considerations

5.1.6.581 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 exists 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 – in reality the GDG were aware that in isolation this is rarely the case. However, certain associated clinical manifestations might indicate the presence of an alternative condition to gastro-oesophageal reflux or a reflux associated condition.

5.1.6.502 Appearance of regurgitation associated GORD

The GDG 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 GDG's clinical experience regarding the expected trend to resolution of regurgitation in simple gastro-oesophageal reflux. It was uncommon for regurgitation to persist after the age of one year; they therefore 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.

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.

Premature infants

The GDG discussed the course of overt regurgitation in premature infants. The GDGs experience was that regurgitation was frequent in this group, 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 GDG made no specific recommendation describing the course of regurgitation in premature infants.

Neurodevelopment

The GDG were 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 GDG made no specific recommendation describing the course of regurgitation in this group.

Recommendations

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 require 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.

Research recommendations

No research recommendations in this area.

5.2 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 is believed to indicate alternative important diagnosis 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 GDG considered that it was important to examine the evidence in this regard 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 utilizing the expert knowledge and experience of the GDG members. The GDG carefully prioritized 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 GDG and where appropriate, recommendations were made.

A general concern with the evidence was that it relied on surrogate markers of GORD such as pH study analysis of acid reflux which is not necessarily indicative of the full spectrum of complications recognised within GORD

5.2.1 Identifying symptoms and signs of GORD

5.2.1.1 Description of included studies

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[a,b]	None	None	None	None	Low
1 Tolia et al, 2009	Systematic Review	Serious[a]	None	None	None	None	Moderate
1 Sherman et al, 2009	Systematic Review & consensus	Serious[a]	None	None	None	None	Moderate

[a] *Search strategy not presented*
[b] *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

Study	Symptoms, signs and other associations identified by review
	•
Tolia et al, 2009	• Asthma • Pneumonia • ALTE • Bronchiectasis • ENT symptoms • Dental erosion
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 • Serous otitis media • Apnoea • Bradycardia

5.2.112 Prioritisation of symptoms and signs

The GDG discussed the list of symptoms and signs included in the above 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 GDG prioritised likelihood ratios as 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 – > 10
- Moderately useful – > 5 to 10
- Not useful – < 5

Negative likelihood ratio:

- Very useful – 0 to 0.1
- Moderately useful – > 0.1 to 0.5
- Not useful – > 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 results of individual reviews are reported below.

5.2.2 Distressed behaviour

5.2.2.1 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 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 suggested possible distress to the observer and the reporting of disturbed sleep in the infant.

5.2.232 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), two in Australia (Ghaem et al, 1998; Mathisen et al, 1999), one in Brazil (Costa et al, 2004) and one 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.

5.2.243 Evidence profile

Study quality was assessed using the GRADE methodology. The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

- Distress in children and young adults for identifying the presence of GORD
  - 'infant colic'/excessive crying
  - posturing
  - disturbed sleep

Table 8: GRADE findings 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[a]	None	None	Serious[b]	None	135	0.54 [0.37, 0.71]	0.86 [0.76, 0.92]	-*	-*	3.88 [2.19, 6.88]	0.53 [0.37, 0.77]	Low
1 (Salvatore et al, 2005)	Prospective Cohort	None	None	None	Serious[b]	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														

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 (Orenstein et al, 1996)	Prospective Case-control	Serious[a]	None	None	Serious[b]	None	135	0.54 [0.37, 0.71]	0.83 [0.75, 0.9]	-*	-*	3.19 [1.88, 5.42]	0.55 [0.38, 0.8]	Low
1 (Salvatore et al, 2005)	Prospective Cohort	None	None	None	Serious[b]	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[c]	None	None	Serious[b]	None	135	0.29 [0.15, 0.46]	0.97 [0.71, 0.99]	-*	-*	9.52 [2.78, 32.63]	0.74 [0.6, 0.91]	Low
1 (Salvatore et al, 2005)	Prospective Cohort	None	None	None	Serious[b]	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[a]	None	None	Serious[b]	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[b]	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

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 (Mathisen et al, 1999)	Prospective cohort	Serious[c]	None	None	Serious[b]	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[a]	None	None	Serious[b]	None	135	0.6 [0.42, 0.76]	0.9 [0.78, 0.95]	-*	-*	6 [3.14, 11.46]	0.44 [0.29, 0.67]	Low
1 (Carret al, 2000)	Retrospective cohort	Very Serious[d]	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
1 (Deal et al, 2005) (1 - 11 months)	Prospective Case-control	Serious[e]	None	None	Serious[b]	None	67	0.66 [0.49, 0.8]	0.78 [0.56, 0.93]	-*	-*	3.03 [1.35, 6.78]	0.44 [0.27, 0.7]	Low
1 (Costa et al, 2004)	Cross-sectional survey	Very serious[f]	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[b]	None	102	0.55 [0.43, 0.67]	0.73 [0.52, 0.88]	-*	-*	2.05 [1.06, 3.99]	0.61 [0.43, 0.86]	Moderate

[a] *Classification of control group was based on not being treated for GORD. The GORD group was based on pH monitoring*
[b] *Wide confidence intervals covering categories from low to high.*
[c] *Children in the control group were not tested for GOR. Small sample size*
[d] *Retrospective chart review based on diagnosis of GERD*
[e] *Presence of GORD was based on clinical judgement, which would include items contained in questionnaire*
[f] *Definition of GORD based on Rome II criteria, no objective measure undertaken*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.204 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 disturb 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 useful” 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.

5.2.255 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.276 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.28 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.

5.2.391 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, 2014)).

Four studies were undertaken in the USA (Carr et al, 2000; Tolia et al , 2003; Orenstein et al, 1996; Mousa et al, 2005), one in Thailand (Assadamongkol et al, 1993) three in Brazil (Costa et al, 2004; Koda et al, 2010; Mezzacappa et al, 2008), one in Malaysia (Mazliah et al, 2000), two in Belgium (Sacre et al, 1989; Salvatore et al, 2005), one in Turkey (Yuksel et al, 2014) and one from Germany (Peters et al, 2002).

Two studies examined the temporal relationship between apnoea and GER (Mousa et al, 2005; Peters et al, 2002). Ten studies examined the relationship between reported presence of apnoea and GERD (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, 2014). Sample sizes ranged from 798 to 19.

5.2.322 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

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

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

Quality assessment							Number of children	Temporal association	Quality
Number. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Temporal link between apnoea and reflux in infants									
1 (Mousa et al, 2005)	Cohort	Serious[a]	None	Serious[b]	None	Yes	25	6173 5-minute time events were recorded across the 25 children. 4706 (76.2%) of the time events had no GER or apnoea. 89 had apnoea with GER. 439 apnoea events alone. 939 reflux alone. In 2 of 25 children apnoea and GER 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 (Peters et al, 2002)	Cohort	Serious[c]	None	Serious[d]	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

[a] *Small sample size*
[b] *11 of 25 children were premature*
[c] *Small sample size*
[d] *Examining a specific group of AOP*

1 **Table 10: GRADE findings for evaluation of apnoea for identifying 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	
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]	-*	-*	4.92 [3.17, 7.62]	0.63 [0.51, 0.79]	High
1 (Tolia et al, 2003)	Retrospective chart review	Very Serious[b]	None	None	Serious[c]	Yes[d]	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[e]	None	None	Serious[c]	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[f]	None	None	Serious[c]	None	135	0.43 [0.26, 0.61]	0.98 [0.93, 1]	-*	-*	21.43 [5.16, 89.04]	0.58 [0.44, 0.78]	Low
Apnoea with cyanosis used to identify presence of GOR/D														
1 (Orenstein et al, 1996)	Case-control	Serious[f]	None	None	Serious[c]	None	135	0.17 [0.07, 0.34]	1 [0.96, 1]	-*	-*	∞	0.83 [0.71, 0.96]	Low

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	
1 (Salvatore et al, 2005)	Cohort	None	None	None	Serious[c]	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[g]	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[h]	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 (Carret et al, 2000)	Retrospective cohort	Very Serious[i]	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[j,l]	None	None	Very Serious[c]	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, 2014)	Case-control	Serious[l]	None	Serious[m]	None	None	71	0.05 [0.01, 0.17]	1 [0.89, 1]	-[*]	-[*]	∞	0.95 [0.88, 1.02]	Low
Apnoea in preterm infants only used to identify presence of GOR/D														

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	
1 (Mezzacappa et al, 2008)	Retrospective case-control	Very Serious [k]	None	None	None	None	194	0.94 [0.87, 0.98]	0.13 [0.06, 0.21]	-*	-*	1.08 [0.98, 1.19]	0.45 [0.16, 1.25]	Low

1 [a] *Children admitted due to ALTE*
2 [b] *Retrospective chart review based on diagnosis of GERD*
3 [c] *Wide confidence intervals covering categories from low to high.*
4 [d] *ALTE as a presenting symptom. ALTE not defined*
5 [e] *Method of confirming GORD varied between children.*
6 [f] *Classification of control group was based on not being treated for GORD.*
7 [g] *Retrospective chart review*
8 [h] *Definition of GERD included having apnoea*
9 [i] *Retrospective chart review*
10 [j] *Retrospective chart review*
11 [k] *Retrospective chart review*
12 [l] *Small sample size*
13 [m] *All children had otitis media*
14 [*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
15 [**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.363 Evidence statements (see Table 9 and Table 10)

17 Evidence from 2 studies showed there was no temporal association between apnoea events
18 and GER. The evidence was of moderate to low quality.

19 Six of ten studies found that apnoea was not a useful marker for the presence of GOR/D, but
20 four studies showed it was a moderately or very useful marker. All ten studies found that
21 absence of apnoea was not useful for identifying the absence of GOR/D. The quality of
22 evidence ranged from high to very low quality.

5.2.334 Evidence to recommendations

24 The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.345 Recommendations

26 The recommendations covering risk-factors can be found in section 5.2.15

5.2.74 Epigastric or chest pain

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

5.2.41 Description of included studies

Four studies on abdominal or chest pain were included in the review.

Two studies were undertaken in the USA (Deal et al, 2005; Carr et al, 2000), one study was undertaken in Norway (Stordal et al, 2005) and one from Turkey (Uzun et al, 2012). Samples sizes ranged from 321 to 67 children. Prevalence of GORD ranged from 73% to 12%. 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).

5.2.42 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

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

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

Quality assessment							Number of patients	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	
Chest pain (including heartburn) used to identify presence of GOR/D														
1 (Stordal et al, 2005)	Cohort	None	None	None	Serious[a]	Some[b]	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[c]	None	None	Serious[a]	Some[b]	321	0.27 [0.14, 0.44]	0.96 [0.93, 0.98]	-[*]	-[*]	6.98 [3.18, 15.3]	0.76 [0.62, 0.92]	Low
1 Carr et al, 2000	Retrospective case-control	Very Serious[d]	None	None	Very serious[a]	Some[e]	295	0.12 [0.08, 0.17]	0.79 [0.69, 0.87]	-[*]	-[*]	0.58 [0.33, 1.01]	1.11 [0.98, 1.26]	Very low

Quality assessment							Number of patients	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	
Abdominal pain or "stomach ache" used to identify presence of GOR/D														
1 (Stordal et al, 2005)	Cohort	None	None	None	Very serious[a]	Some[b]	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[c]	None	None	Very serious[a]	Some[b]	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 (Carret et al, 2000)	Retrospective cohort	Very serious[d]	None	None	Very serious[a]	Some[e]	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[f]	None	None	Very serious[a]	None	67	0.43 [0.27, 0.59]	0.96 [0.81, 1]	-[*]	-[*]	11.48 [1.62, 81.21]	0.6 [0.45, 0.79]	Very low
1 (Uzun et al, 2012)	Retrospective cohort	Very serious[d]	None	None	Very serious[a]	Some[g]	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[a]	Some[b]	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

Quality assessment							Number of patients	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 (Stordal et al, 2005)	Case-control	Serious[c]	None	None	Serious[a]	Some[b]	321	0.27 [0.14, 0.44]	0.93 [0.89, 0.96]	-*	-*	3.84 [1.95, 7.56]	0.79 [0.64, 0.96]	Low

a Wide confidence intervals covering categories from low to high.
b Based on children referred for pH assessment
c Unknown if control group had abnormal pH as not tested.
d Based on retrospective review of medical notes. Based on recorded symptoms rather than questionnaire.
e Mean average age was 4.4 years so accuracy of symptoms reporting is unclear.
f Presence of GORD was based on clinical judgement rather than a diagnostic test.
g Children aged 2 to 17 years – so reliability of reporting across the group is unclear.
** Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
*** Calculated by the NCC technical team based on figures presented within the studies*

5.2.4.3 Evidence statements (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 GDG outlined three specific types of pain based on location within the body: chest (heartburn), abdominal (including stomach ache) and epigastric.

5.2.4.3.1 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 two 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.

5.2.4.3.2 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 three found it was not useful. One study of abdominal pain generally found a moderately useful negative likelihood ratio the other three 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.

5.2.4.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.415 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.235 Hoarseness

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

5.2.581 Description of included studies

Two studies were included in this review (Carr et al, 2000; Yuksel et al, 2014). 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.

5.2.522 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

- Association between hoarseness (and associated conditions) and GER in children.

Table 12: GRADE findings for evaluation of hoarseness 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
Hoarseness														
1 (Carr et al, 2000)	Retrospective cohort	Very serious[a]	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, 2014)	Case-control	Serious[b]	None	Serious[c]	Very serious[d]	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

[a] *Retrospective chart review*
[b] *Retrospective chart review*
[c] *All children had Otitis Media*
[d] *Confidence intervals cover several categories of usefullness*
** *Calculated by the NCC technical team based on figures presented within the studies*

5.2.51 Evidence statements (see Table 12)

One study suggests that hoarseness is not useful for identifying GORD. The quality of evidence was low.

5.2.54 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.55 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.6 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 which prevents a subsequent enjoyable feeding experience. Studies looking at this association may be hampered by the longitudinal timeline of such a process i.e. looking for GOR/D 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.

5.2.61 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). Four studies were undertaken in the USA (Deal et al, 2005; Orenstein et al, 1996; Salvatore et al, 2005; Carr et al, 2000), one from Australia (Heine et al, 2006), one from Malaysia (Mazliah et al, 2000), one from Turkey (Yuksel et al, 2014) and one from 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). One reported on crying when feeding (Salvatore et al, 2005). One study reported on feeding problems (Mazliah et al, 2000). One reported on feeding intolerance (Mezzacappa et al, 2008). One study on feeding complex (Yuksel et al, 2014).

5.2.62 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

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

1 **Table 13: GRADE findings for evaluation of feeding difficulties to identify GORD**

Quality assessment							Number of patients	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	
Feeding refusal used to identify presence of GOR/D														
1 (Deal et al, 2005) (1 - 11 months	Case-control	Serious[a]	None	None	Very serious[b]	None	67	0.41 [0.26, 0.58]	0.83 [0.61, 0.95]	-*	-*	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[a]	None	None	Very serious[b]	None	67	0.65 [0.48, 0.79]	0.76 [0.56, 0.9]	-*	-*	2.69 [1.36, 5.34]	0.46 [0.29, 0.74]	Very low
1 (Heine et al, 2006)	Cohort	None	None	Serious[c]	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[c]	None	None	Serious[b]	None	135	0.31 [0.17, 0.49]	0.96 [0.9, 0.99]	-*	-*	7.86 [2.67, 23.08]	0.71 [0.57, 0.9]	Low
1 (Salvatore et al, 2005)	Cohort	None	None	None	Serious[b]	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

Quality assessment							Number of patients	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 (Carr et al, 2000)	Retrospective cohort	Very Serious[d]	None	None	Very serious[b]	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[c]	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[d]	None	None	Very serious[b]	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[b]	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[b]	None	40	0.85 [0.62, 0.97]	0.8 [0.56, 0.94]	-*	-*	4.25 [1.74, 10.41]	0.19 [0.06, 0.54]	Low
Feeding problems used to identify presence of GOR/D														

Quality assessment							Number of patients	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 (Mazliah et al, 2000)	Cross-sectional survey	None	None	None	Very serious[b]	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
Feeding intolerance used to identify presence of GOR/D														
1 (Mezzacappa et al, 2008)	Retrospective Case-control	Very Serious[d]	None	None	Serious[b]	None	174	0.71 [0.61, 0.8]	0.4 [0.3, 0.51]	-*	-*	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[b]	None	40	0.2 [0.06, 0.44]	0.9 [0.68, 0.99]	-*	-*	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[b]	None	40	0.35 [0.15, 0.59]	0.8 [0.56, 0.94]	-*	-*	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[b]	None	40	0.2 [0.06, 0.44]	0.95 [0.75, 1]	-*	-*	4 [0.49, 32.73]	0.84 [0.66, 1.07]	Low
Feeding complex														

Quality assessment							Number of patients	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 (Yuksel et al, 2014)	Case-control	Serious[e]	None	Serious[f]	Serious[b]	None	71	0.44 [0.28, 0.6]	0.66 [0.47, 0.81]	-*	-*	1.27 [0.7, 2.3]	0.86 [0.59, 1.25]	Very Low

[a] *Presence of GORD based on clinical judgement*
[b] *Wide confidence intervals covering categories from low to high.*
[c] *Control group not tested for reflux symptoms*
[d] *Based on retrospective review of medical notes. Based on recorded symptoms rather than all symptoms that were present.*
[e] *Retrospective chart review*
[f] *All children had Otitis Media*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.6.3 Evidence statements (see Table 13)

5.2.6.4 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 this finding was of moderate to very low quality.

5.2.6.5 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.

5.2.6.6 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, but absence of choking or gagging was "moderate useful" for identifying those without GORD. The evidence for this finding was of very low quality.

5.2.6.7 Crying when feeding

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 moderate quality.

5.2.6.8 Feeding problems

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

5.2.6.316 Feeding intolerance

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

5.2.654 Evidence to recommendations

6 The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.675 Recommendations

8 The recommendations covering risk-factors can be found in section 5.2.15

5.297 Otitis media

10 At first assessment it is not intuitive to invoke reflux as a cause of otitis media. Alternatively,
11 there could be a common cause for both pathologies, but to examine the question of whether
12 GOR/D causes otitis media is important. Of course both conditions are very common and
13 therefore this was examined with the available evidence in the literature. Episodes of acute
14 otitis media were looked at and serious otitis media (‘glue ear’) was also the subject of this
15 particular review area.

5.2.761 Description of included studies

17 Four observational studies were included in this review (El-Serag et al, 2001; Kotsis et al,
18 2009; Aydin et al, 2011; O'Reilly et al, 2008). Two studies examined otitis media as a risk-
19 factor for presence of GORD (El-Serag et al, 2001; Kotsis et al, 2009). Two studies
20 examined GORD as a risk-factor for otitis media (Aydin et al, 2011; O'Reilly et al, 2008).
21 Sample size range from 9900 to 40.

5.2.722 Evidence profile

23 The GRADE profiles in the tables that follow show results of included studies for the
24 symptoms and signs selected for review by the GDG:
25 • Association between Otitis media and GER in children

26 **Table 14: GRADE findings for evaluation of otitis media for identifying 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	
Presence of otitis media for identifying GORD														
1 (El-Serag et al, 2001)	Retrospective case-control	Very serious[a]	None	None	None	None	9900	0.1 [0.07, 0.13]	0.8 [0.79, 0.8]	-*	-*	0.49 [0.37, 0.66]	1.13 [1.09, 1.17]	Low

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	
1 (Kotsis et al, 2009) – Serious OM vs None	Prospective cohort	None	None	None	Serious[b]	None[c]	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[b]	None[d]	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[e]	None	Serious[f]	Very serious[b]	None	40	0.3 [0.12, 0.54]	0.85 [0.62, 0.97]	-*	-*	2 [0.58, 6.91]	0.82 [0.59, 1.16]	Very low
1 (O'Reilly et al, 2008)	Case-control	Very serious[g]	None	None	None	None	509	0.2 [0.17, 0.24]	0.98 [0.92, 1]	-*	-*	12.95 [1.84, 91.23]	0.81 [0.77, 0.85]	Low

[a] *Retrospective and based on computer records*
[b] *Outcome cover several categories for several items*
[c] *Serious OM vs None*
[d] *Any OM vs none*
[e] *Small sample size*
[f] *adenoid hypertrophy*
[g] *Identification of GORD based on medical records*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.713 Evidence statements (see Table 14)

Evidence from one study showed the presence of GORD (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. Three other studies showed that found no useful relationship between GOR and otitis media. The evidence for this finding was of moderate to very low quality.

5.2.774 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.795 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.218 Lower respiratory tract infection

Both GOR/D and respiratory infections are relatively common in infants, children, and young people and the question as to whether an association or causal link exists requires an answer. Postulation that when an increased work of breathing is necessary during a lower respiratory infection the increased negative pressure in the thorax which is generated may predispose to greater GOR, is countered by the opposite argument that reflux may cause micro-aspiration and therefore respiratory vulnerability to infection. While in the neurologically compromised child reflux can lead to aspiration and chest problems where airway protective mechanisms are absent or compromised but this is different to saying that reflux leads to lower respiratory chest infection per se. The area is poorly understood and often confused because many of the children with severe, complex neurology have both problems. For these reasons the GDG decided that this area required examination.

5.2.831 Description of included studies

Six 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), one Thailand (Assadamongkol et al, 1993), one Malaysia (Mazliah et al, 2000), one Belgium (Salvatore et al, 2005), and one in Australia (El-Serag et al, 2001). Six studies examined the association between pneumonia and GORD (El-Serag et al, 2001; Mazliah et al, 2000; Assadamongkol et al, 1993; Salvatore et al, 2005; Orenstein et al, 1996). One study examined bronchiectasis and GORD (El-Serag et al, 2001). Sample size ranged from 9900 to 44.

5.2.822 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

- Association between pneumonia and GER in children

1 **Table 15: GRADE findings for evaluation of pneumonia**

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	
Ever had pneumonia used to identify presence of GOR/D														
1 (El-Serag et al, 2001)	Retrospective cohort	Very serious[a]	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[b]	None	None	None	None	135	0.09 [0.02, 0.23]	1 [0.96, 1]	-*	-*	-	0.91 [0.83, 1.01]	Moderate
1 (Salvatore et al, 2005)	Cohort	None	None	None	Serious[c]	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[d]	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[d]	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

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	
1 (Mazliah et al, 2000)	Cross-sectional survey	Serious [e]	None	None	Serious [c]	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 [a]	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

[a] *Retrospective and based on computer records*
[b] *Classification of control group was based on not being treated for GORD.*
[c] *Wide confidence intervals covering categories from low to high.*
[d] *Retrospective chart review*
[e] *Method of confirming GORD varied between children*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*

5.2.8 Evidence statements (see Table 15)

5.2.8.1 Pneumonia

Three studies showed results from not useful to moderately useful for using ever having 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 a not a useful marker for GORD. Study quality was of moderate to low quality.

5.2.8.2 Bronchiectasis

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

5.2.9 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.10 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.9 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 cow's milk protein allergy, small bowel enteropathy and absorption issues; and the increased energy required to feed frequently. This area required objective interrogation of the literature it was felt by the GDG.

5.2.941 Description of included studies

Five 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). One from Belgium (Orenstein et al, 1996), one from Brazil (Costa et al, 2004), three from USA (Orenstein et al, 1996; Carr et al, 200; Tolia et al, 2003). Sample size ranged from 99 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).

5.2.942 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

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

Table 16: GRADE findings for evaluation of faltering growth.

Quality assessment							Number of patients	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	
Weight gain problems														
1 (Orenstein et al, 1996)	Case-control	Serious[c]	None	None	Serious[b]	None	135	0.26 [0.12, 0.43]	1 [0.96, 1]	-*	-*	∞	0.74 [0.61, 0.9]	Low
1 (Salvatore et al, 2005)	Cohort	None	None	None	Serious[b]	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[a]	None	None	Very serious[b]	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

Quality assessment							Number of patients	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 (Tolia et al, 2003)	Retrospective cohort	Very serious[a]	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[d]	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, 2014)	Case-control	Serious[e]	None	Serious[f]	Serious[g]	None	71	0.44 [0.28, 0.6]	0.66 [0.47, 0.81]	-*	-*	1.27 [0.7, 2.3]	0.86 [0.59, 1.25]	

[a] *Based on retrospective review of medical notes.*
[b] *Wide confidence intervals covering categories from low to high.*
[c] *Control group not tested for reflux symptoms.*
[d] *Classification of cases and controls based on Rome II criteria for adults and not diagnostic tests.*
[e] *Retrospective chart review*
[f] *All children had Otitis Media*
[g] *Wide confidence intervals covering categories from low to moderate.*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.9.3 Evidence statements (see Table 16)

5.2.9.3.1 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.

Three 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.

5.2.9.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.9 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.10 Asthma

As for lower respiratory infections, the increased work of breathing induced by asthma have been assumed to increase reflux, and conversely the GOR/D 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 GDG believed this was an important area which needed to be assessed.

5.2.10.1 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 five examined if 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 as a symptom.

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

5.2.10.2 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

- Association between asthma and GER in children

Table 17: GRADE findings for evaluation of diagnostic value of asthma 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	
Using presence of asthma to identify GORD														
1 (El-Serag et al, 2001)	Retrospective cohort	Very serious[a]	None	None	None	None	9900	0.13 [0.12, 0.15]	0.93 [0.93, 0.94]	-*	-*	1.95 [1.7, 2.24]	0.93 [0.91, 0.95]	Low

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	
1 (Ruigomez et al, 2010)	Retrospective cohort	Very serious[b]	None	None	None	None	6677	0.25 [0.23, 0.27]	0.81 [0.8, 0.82]	-*	-*	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[c]	None	None	Very serious[d]	None	39	0.33 [0.16, 0.55]	0.93 [0.68, 1]	-*	-*	5 [0.69, 36.08]	0.71 [0.52, 0.98]	Very Low
1 (Debley et al, 2006)	Case-control	Serious[e]	None	None	None	None	2397	0.19 [0.15, 0.24]	0.97 [0.97, 0.98]	-*	-*	7.65 [5.18, 11.31]	0.83 [0.78, 0.88]	Moderate
1 (Stordal et al, 2006)	Case-control	Serious[f]	None	None	None	None	1136	0.2 [0.17, 0.23]	0.92 [0.88, 0.95]	-*	-*	2.37 [1.55, 3.61]	0.88 [0.83, 0.92]	Moderate
1 (Chopra et al, 1995)	Case-control	Serious[g]	None	None	Very serious[d]	None	90	0.39 [0.28, 0.5]	1 [0.69, 1]	-*	-*	∞	0.61 [0.51, 0.73]	Very Low
1 (Gustafsson et al, 1990)	Case-control	Very Serious[h]	None	None	Serious[d]	None	69	0.5 [0.34, 0.66]	0.85 [0.66, 0.96]	-*	-*	3.38 [1.3, 8.76]	0.59 [0.42, 0.83]	Very Low

[a] *Retrospective and based on computer records*
[b] *Retrospective and based on computer records. On 15.7% of GORD group had formal test.*

[c] *Definition of GORD was based on barium meal only.*
[d] *Wide confidence intervals means results cover several categories*
[e] *Definition of GORD was based on a questionnaire.*
[f] *Definition of GORD was based on a questionnaire.*
[g] *GORD based on scintiscan. Control group was very small sample size.*
[h] *Results are based on two separate studies using the same methodology. Cases include people age 18 and over.*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.10.3 Evidence statements (see Table 17)

5.2.10.3.1 Asthma

Evidence from two studies found that asthma is not a useful diagnostic marker for identifying GORD, with both positive and negative likelihood ratios being low. Evidence from two of five studies suggests that the presence of GOR is a moderately useful diagnostic marker for children having asthma. The other three studies could not find a definitive effect.

5.2.10.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.10.5 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.11 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 – 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 GDG.

5.2.11.1 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, 2014). One study was undertaken in Australia (Chang et al, 2006), one in the USA (Carr et al, 2000), one in Belgium (Salvatore et al, 2005) and two in Turkey (Uzun et al, 2012; Yuksel et al, 2014). Sample size range from 214 to 70.

5.2.11.2 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

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

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

Quality assessment	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[a]	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[b]	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[c]	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, 2014)	Case-control	Serious[d]	None	Serious[e]	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

[a] *Based on presenting symptoms rather than questionnaire, so not all children will have been asked about same symptoms*
[b] *Retrospective chart review*
[c] *Chronic cough based on a single question involving parental assessment*
[d] *Retrospective chart review*
[e] *All children had Otitis Media*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.11.13 Evidence statements (see Table 18)

5.2.11.321 Chronic cough

Evidence from four 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.

5.2.11.64 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.11.85 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.12 Dental erosion

It was the experience of several expert members of the GDG 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/D and hence this was a condition that the GDG thought should be examined.

5.2.12.61 Description of included studies

Six 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). Five studies used the presence of dental erosion in children with and without GORD and one examined the presence of GERD in children as a risk factor for dental erosion.

One study was undertaken in Brazil (Guare et al, 2012), one in Australia (Linnett et al, 2002), two in Turkey (Ersin et al, 2006; Polat et al, 2013), one in UK (Shaw et al, 1998, and one from the USA (Wild et al, 2011). Three of the studies examined only children with cerebral palsy (Guare et al, 2012; Polat et al, 2013; Wild et al, 2011). Sample size ranged from 104 to 37 children.

5.2.12.72 Evidence profile

The GRADE profiles in the tables that follow show results of included studies for the symptoms and signs selected for review by the GDG.

- Association between dental erosion and GER in children

Table 19: GRADE findings for evaluation of dental erosion 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	
Presence of any type of dental erosion compared to no dental erosion used to identify presence of GOR/D														

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	
1 (Linnett et al, 2002)	Case-control	Serious[a]	None	None	None	None	104	0.46 [0.32, 0.61]	0.6 [0.39, 0.73]	-*	-*	1.14 [0.73, 1.78]	0.9 [0.65, 1.26]	Moderate
1 (Ersin et al, 2006)	Case-control	Serious[b]	None	None	Serious[c]	None	80	0.76 [0.6, 0.89]	0.76 [0.62, 0.88]	-*	-*	3.21 [1.81, 5.66]	0.31 [0.17, 0.56]	Low
1 (Shaw et al, 1998)	Case-control	Serious[d]	None	None	Very serious[c]	None	41	0.81 [0.58, 0.95]	0.85 [0.58, 0.97]	-*	-*	5.4 [1.86, 15.64]	0.22 [0.09, 0.55]	Very low
1 (Wild et al, 2011)	Case-control	Serious[e]	None	None	Serious[c]	None	72	0.76 [0.63, 0.86]	0.43 [0.12, 0.71]	-*	-*	1.33 [0.82, 2.14]	0.56 [0.26, 1.2]	Low
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]	-*	-*	2.53 [1.58, 4.06]	0.45 [0.3, 0.67]	High
1 (Farahmand et al,	Case-control	Very serious[i]	None	None	Very serious[c]	None	64	0.98 [0.9, 1]	0.81 [0.69, 0.9]	-*	-*	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														

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	
1 (Guare et al, 2012)	Case-control	Serious[f]	None	None	Very serious[c]	None	46	0.9 [0.68, 0.99]	0.81 [0.72, 0.93]	-*	-*	4.68 [2.1, 10.43]	0.12 [0.03, 0.47]	Very low
1 (Shaw et al, 1998)	Case-control	Very serious[g]	None	None	Very serious[c]	None	21	0.75 [0.43, 0.95]	0.67 [0.3, 0.93]	-*	-*	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 used to identify presence of GOR/D														
1 (Polat et al, 2013)	Case-control	Very serious[h]	None	None	Very serious[c]	None	37	0.84 [0.6, 0.97]	0.72 [0.54, 0.9]	-*	-*	3.03 [1.4, 6.55]	0.22 [0.07, 0.64]	Very low
Localised vs generalised erosions														
1 (Farahmand et al,	Case-control	Very serious[i]	None	None	Very serious[c]	None	64	0.34 [0.22, 0.48]	0.55 [0.23, 0.83]	-*	-*	0.75 [0.35, 1.58]	1.21 [0.68, 2.15]	Very low

[a] *Control group were not assessed for GORD*
[b] *Unclear how presence of GER was determined in case and control groups*
[c] *Outcome cover several categories for several items*
[d] *Unclear how GER was determined in all children. Children referred to a tertiary dental unit.*
[e] *Unclear if analysis was undertaken on all children or only those who had pH monitoring*
[f] *Small sample size*
[g] *Unclear how GER was determined in all children. Small sample size.*
[h] *Analysis relates to GORD as a risk-factor for dental erosion rather than dental erosion as a marker of GORD*
[i] *excluded children where other sources of erosion were identified*
[*] *Predicative values cannot be calculated from case-control studies as the true prevalence cannot be calculated.*
[**] *Calculated by the NCC technical team based on figures presented within the studies*

5.2.12.13 Evidence statements (see Table 19)

5.2.12.32 Dental erosion

Results from 4 case-control studies comparing prevalence of dental erosion in children with and without GOR show range from not useful to moderately useful for identifying children with and without GORD (positive and negative likelihood ratios) but it was useful for identifying children without GER. The quality of the evidence was moderate to very low.

Results from 2 studies involving children with cerebral palsy show 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. The quality of the evidence for this was very low.

5.2.12.14 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.2.14

5.2.12.15 Recommendations

The recommendations covering risk-factors can be found in section 5.2.15

5.2.13 Health economics profile

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

5.2.14 Evidence to recommendations

The aims of these questions were to determine the usefulness of individual symptoms and signs as pointers to a diagnosis of GORD (observed distress, epigastric or chest pain, hoarseness) 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.

5.2.14.1 Consideration of clinical benefits and harms

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

5.2.14.3 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 GDG noted that one observational study of moderate quality showed that excessive crying alone was of no diagnostic use, whilst a second low quality study found that prolonged crying was associated with and increased likelihood of the child having gastro-oesophageal reflux. The GDG noted that in this study the presence of GORD (i.e. 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 GDG agreed that that this symptom was actually common and had many potential explanations.

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

Results from four low or very low quality observational studies showed that abnormal posturing was a potentially useful sign of GORD. The GDG 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 GDG 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. They made a specific recommendation to this effect.

5.2.14.12 Apnoea

Evidence from 12 observational studies was examined by the GDG. The GDG focused on the results of two studies that examined the temporal link between apnoea and reflux. The GDG believed these were the best-designed studies for confirming a link between apnoea and reflux. The GDG noted that the other 10 studies reported variable diagnostic usefulness of apnoea for identifying GOR/D.

The GDG 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 apnoea before contemplating investigation for occult reflux. The GDG 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 that consideration should be given to possibly doing a combined intraluminal oesophageal pH and impedance study.

5.2.14.13 Epigastric or chest pain

Evidence from four 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 GDG 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 GDG was aware of published studies in adults showing that epigastric pain and heartburn are reduced by the use of acid suppressing drugs. Therefore, the GDG concluded that in children who are able to express their symptoms that heartburn was a useful indicator of GORD. The GDG was sufficiently convinced of the importance of these symptoms that they recommended that if there was persistent heartburn, retrosternal or epigastric pain then a four week trial of treatment with a PPI be considered. If this was ineffective or if the symptom returned on discontinuing the treatment they recommended that consideration be given to referring the patient for an upper gastrointestinal endoscopy. It

would be important to rule out other explanations for the symptom and to look for evidence of gastro-oesophageal reflux oesophagitis.

5.2.14.13 Hoarseness

Evidence from two observational studies did not finding diagnostic value for hoarseness as a pointer to GORD. While the GDG 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 GDG recommended that in the absence of overt regurgitation, hoarseness occurring as the sole symptoms did not indicate a need to either investigate or treat for GORD.

5.2.14.15 Feeding difficulties

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

The GDG reflected on the fact that feeding difficulties were very common concern in infants and while 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 GDG 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.

5.2.14.16 Otitis media

The results of four observational studies showed varying degrees of usefulness for otitis media being a marker for GORD. The GDG debated the plausibility of a physiological link 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 GDG focused on the moderate quality evidence, and based on this the GDG concluded that in situations where an infant presented with recurrent otitis media that reflux could be a potential cause, and therefore that health care professionals should be aware that frequently recurring otitis media is a potential complication of gastro-oesophageal reflux.

5.2.14.17 Lower respiratory tract infection

Evidence from seven observational studies showed that previous episodes of pneumonia were a potentially useful marker for GORD. The GDG 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 GDG believed that a single episode of pneumonia was a common phenomenon, but if repeated that reflux aspiration should be considered as a possible explanation.

5.2.14.18 Faltering growth

Evidence from five observational studies showed varied results on the usefulness in terms of likelihood ratios of faltering growth to identify GOR/D. The concluded that whilst presence of faltering growth could be a marker of GORD they were concerned that it could lead to inappropriate treatment and other potential serious causes remaining uninvestigated. The GDG concluded that in isolation faltering growth should not be used as a symptom of problematic reflux or GORD.

5.2.14.119 Asthma

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

The GDG concluded that while 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 at least 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 the patients' 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 GDG was aware that some studies had been performed to see if reflux treatment improved asthma control but the results were inconclusive to date. The GDG recommended that health care professionals should be aware of the association between reflux and asthma but that reflux had not been shown to cause or worsen asthma.

5.2.14.1110 Chronic cough

Evidence from five observational studies showed that chronic cough was of no diagnostic value in identifying GORD. The GDG argued that in a similar way to pneumonia and otitis media that 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 GDG 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.

5.2.14.1211 Dental

The evidence from eight observational studies showed mixed results for the association between dental erosion and reflux. The GDG 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 GDG concluded that the evidence was convincing enough to recommend that dental erosion could due to gastro-oesophageal reflux in children with neurodisabilities.

5.2.14.1312 Appearance of regurgitation associated with conditions other than GORD

Based on their clinical knowledge the GDG highlighted a number of clinical manifestations and features which they considered should be recognised as "red flags" suggesting possible disorders other than gastro-oesophageal reflux in infants presenting with vomiting or regurgitation.

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 GDG 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 GDG recommended that frequent forceful (projectile) vomits should be considered as possible "red flags". Likewise, bile-stained (green) vomits strongly suggest possible intestinal obstruction and this also would be a red flag suggesting a disorder other than GOR.

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 GDG 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, there are some symptoms that, in combination with regular reflux, are symptomatic of familiar conditions other than GORD. When reflux is found in children and young people in combination with one or more additional gastrointestinal symptom(s) (for example diarrhoea or a tender/distended abdomen), the Diarrhoea and vomiting NICE clinical guideline (CG84) should be referred too. Similarly when an infant is vomiting in addition to symptoms associated with fever (for example the infant in lethargic and/or irritable) the Feverish illness in children NICE clinical guideline (CG160) should be referred to. Finally, although relatively rare, vomiting in relation or combination with symptoms that could also be associated with meningitis should be referred to the Bacterial meningitis and meningococcal septicaemia NICE clinical guideline (CG102).

5.2.146 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 in order to identify condition, and differentiate serious from non-serious cases.

The GDG stated that having evidence based 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 GDG highlighted that symptoms and signs are a rapid and non-invasive method of identifying children and young people with problematic reflux or GOR, as they form part of a standard consultation there would be no additional costs associated.

5.2.147 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, overt reflux and those where there was no clear indication of reflux of any form. This prevented the GDG from making recommendations for those children individually and, instead the GDG would only recommend signs and symptoms that would require investigation/treatment 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, the definition of the GORD between papers varied to the extent that it would not be appropriate to group outcomes between different papers. The GDG therefore examined the definition of GORD, the validity of that definition and made their decision accordingly. For example, those studies where children underwent endoscopic investigation to ascertain if they had erosive esophagitis were looked on more favourably than children that 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 for example.

The third source of bias was heterogeneity between the results of studies. The GDG 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 GDG 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 GDG was often unable to interpret the results.

5.2.14 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.

5.2.15 Recommendations

5.2.15.1 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 green-yellow) 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 following '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

Symptom or sign	Possible diagnostic implication	Suggested action
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)	Suggests upper gastrointestinal ulceration, including erosive oesophagitis	Specialist referral for investigation
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 Urinary tract infection in children. NICE clinical guideline 54 [2007]). Persistence	Urine microbiology investigation

Symptom or sign	Possible diagnostic implication	Suggested action
	suggests an alternative diagnosis	
Blood in stool	May suggest a variety of conditions, including bacterial gastroenteritis or an acute surgical condition	Specialist referral
Abdominal distension, tenderness or palpable mass.	May suggest intestinal obstruction or another acute surgical condition	Stool microbiology investigation
Systemic		
Appearing unwell	May suggest infection (also see Feverish illness in children. NICE clinical guideline 160 [2013])	Clinical assessment and urine microbiology investigation Specialist referral
Fever	May suggest infection (also see Feverish illness in children. NICE clinical guideline 160 [2013])	Clinical assessment and urine microbiology investigation Specialist referral
Dysuria	May suggest urinary tract infection (also see Urinary tract infection in children. NICE clinical guideline 54 [2007])	Clinical assessment and urine microbiology investigation Specialist referral
Bulging fontanelle	May suggest raised intracranial pressure, for example due to meningitis (Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 [2010])	Specialist referral
Rapidly increasing head circumference (more than 1 cm per week)	May suggest raised intracranial pressure, for example due to hydrocephalus or a brain tumour	Specialist referral
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 raised intracranial pressure, for example due to meningitis (Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 [2010])	Specialist referral
Eczema	May suggest gastrointestinal cow's milk protein allergy (also see Food allergy in children and young people. NICE clinical guideline 116 [2011])	Trial of cow's milk exclusion Specialist referral

6. Do not routinely investigate or treat for GOR if an infant or child without overt regurgitation presents with only one 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. **Think about referring infant and children with persistent back arching or features of Sandifer's syndrome (episodic torticollis with neck extension and rotation) for specialist assessment (and possible endoscopy and pH–impedance monitoring).**

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.**

5.2.15 Research recommendations

1. **What are the symptoms associated with GOR and/or GORD in children and young people with a neurodisability?**

Why this is important

The available evidence on the symptoms associated with GOR and/or GORD in children and young people with a neurodisability is limited and of poor quality. The lack of a set of clearly defined features makes GOR and/or GORD difficult to recognise and differentiate from other vomiting problems. The proposed study would use objective measures of reflux (such as pH monitoring) to assess the GOR and/or GORD symptoms in children and young people with neurodisability.

5.3 Risk Factors

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

5.3.1 Review question

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

It was not practical or useful to assess all possible risk-factors; therefore the GDG 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.

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, say 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.

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.

5.3.2 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 e.g. Bronchopulmonary dysplasia / chronic lung disease of prematurity.

The main two areas identified for further scrutiny were the chronic suppurative lung conditions i.e. bronchiectasis or cystic fibrosis and the 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 post natal chronological age. In both cases a potential mechanism for increasing tendency to GOR / 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 e.g. most babies with chronic lung disease have been or still are premature. Finally, Asthma although strictly speaking also a chronic lung disease was investigated separately.

5.3.251 Description of included studies

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 and Fuloria et al, 2000). Two were retrospective cohort studies (Akinola et al, 2004 and Ruigomez et al, 2010) and three were case-control studies (Mezzacappa et al, 2008; El-Serag et al, 2001; Fuloria et al, 2000). Three studies were undertaken in USA (Akinola et al, 2004; El-Serag et al, 2001 and Fuloria et al, 2000), one in UK (Ruigomez et al, 2010) and one 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 three studies (Akinola et al, 2004; Mezzacappa et al, 2008; Fuloria et al, 2000) to children aged 1 to 17 years in one 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 two studies (Akinola et al, 2004; Mezzacappa et al, 2008), cystic fibrosis in one 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 four 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 GER in two studies (Akinola et al, 2004; Fuloria et al, 2000) and GERD in three studies (Mezzacappa et al, 2008; El-Serag et al, 2001 and Ruigomez et al, 2010). The settings of the studies included neonatal intensive care units, hospitals and primary care practices.

More details on each individual study can be found in the evidence tables.

5.3.282 Evidence profile

Table 20: GRADE findings 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 GER[a]/GERD[b]											
1 (Akinola, 2004)	Retrospective cohort	Very serious[c,d]	None	Serious[e]	Very serious[f]	None	64/87 (74%)	38/50 (76%)	OR: 0.88 (0.39 to 1.97)[g]	-	Very low
1 (Mezzacappa, 2008)	Retrospective case-control	Very serious[c,h,i]	None	Serious[j]	Very serious[f]	None	33/87 (38%)	44/87 (51%)	Adjusted OR: 0.89 (0.46 to	-	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
									1.75)[k]		
Cystic Fibrosis											
Prevalence and odds ratio for cystic fibrosis in children with and without GERD[l,m]											
1 (El-Serag, 2001)	Retrospective case-control	Very serious[c,n]	None	No serious	No serious	None	NR/1980	NR/7920	Adjusted OR: 2.89 (1.97 to 4.25)[o]	-	Low
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[c,p]	None	No serious	Very serious[f]	None	5/1700 (0.3%)	2/4977 (0.04%)	Adjusted OR: 3.3 (0.6 to 18.1)[q]	-	Very low
Bronchiectasis											
Prevalence and odds ratio for bronchiectasis (with or without collapse) in children with and without GERD[l]											
1 (El-Serag, 2001)	Retrospectivecase-control	Very serious[c,n]	None	No serious	Serious[f]	None	NR/1980	NR/7920	Adjusted OR: 2.28 (1.14 to 4.57)[o]	-	Very low
Chronic Lung Disease											
Prevalence and odds ratio for chronic lung disease of prematurity in children with and without GER[r]											
1 (Fuloria, 2000)	Retrospective case-control	Serious[c]	None	Serious[s]	Serious[f]	None	NR	NR	Adjusted OR: 2.1 (1.1 to 3.5)[t]	-	Very low
Severe Chronic Lung Disease											
Prevalence and odds ratio for severe chronic lung disease in children with and without GER[a]											
1 (Akinola, 2004)	Retrospective cohort	Very serious[c,d]	None	Serious[e]	Very serious[f]	None	46/87 (53%)	30/49 (61%)	OR: 0.71 (0.35 to 1.45)[g]	-	Very low

[a] *Akinola 2004: diagnostic criteria for GER - 18 to 24 hour esophageal pH monitoring, infants were identified as positive for GER 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 GERD - prolonged distal intra-esophageal pH monitoring, reflux index ≥10%*
[c] *Retrospective study design*
[d] *Unadjusted ORs*
[e] *Infants less than 32 weeks gestational age admitted to the neonatal intensive care unit*
[f] *Confidence interval spans multiple interpretations*
[g] *NCC-WCH calculation*
[h] *No details of how bronchopulmonary dysplasia was defined/diagnosed*

[i] *Not explained which pH test was selected for inclusion as there seems to be more than one per child (235pH studies in 193 infants)*
[j] *Birthweight <2000g and gestational age ≤37 weeks*
[k] *OR adjusted for birthweight and postconceptional age at time of pH study*
[l] *El-Serag 2001: diagnostic criteria for GERD – subjects identified from electronic medical records, based on ICD-9 coding of GERD (530.81, 530.10, 530.11, 530.19, 530.3)*
[m] *Ruigomez 2010: diagnostic criteria for GERD - 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.*
[n] *Both the risk factor and outcome based on reliability of coding in medical records*
[o] *OR adjusted for age, gender and ethnicity*
[p] *Only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control cohort had been tested for GER*
[q] *OR adjusted for age, sex, year of diagnosis, visits to primary care physician in the previous year*
[r] *Fuloria 2000: diagnostic criteria for GER - defined as either treatment with anti-reflux medications (metaclopramide, bethanecol, cisparide, cimetidine or ranitidine) or a positive test for GER. Tests for GER included esophageal pH probe, upper gastrointestinal contrast studies and microscopic examination of tracheal aspirates for lipid laden macrophages. Tests for GER were performed and treatment was initiated at the discretion of the attending neonatologist.*
[s] *Very low birth weight premature infants*
[t] *OR adjusted for gestational age, gender, race, days on assisted ventilation and days of hospitalisation*

5.3.23 Evidence statements (see Table 20)

5.3.2.31 Bronchopulmonary dysplasia

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

5.3.2.32 Cystic fibrosis

Two studies evaluated the odds of developing GERD 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.

5.3.2.33 Bronchiectasis (with or without collapse)

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

5.3.2.34 Chronic lung disease

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

5.3.2.35 Severe chronic lung disease

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

5.3.24 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.3.9

5.3.25 Recommendations

The recommendations covering risk-factors can be found in section 5.3.10

5.3.13 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 are 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 GI motility and intra-abdominal pressure making GOR / GORD more likely via a whole variety of potentially important mechanisms.

5.3.3.1 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), one a retrospective cohort (Ruigomez et al, 2010) and one a retrospective review (Halpern et al., 1991). Two studies were undertaken in USA (Fuloria et al, 2000; Halpern et al., 1991) and the other in 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 one study (Fuloria et al, 2000) and children aged 1 to 17 years in the 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), one 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 one on CNS disease which also included a wide range of conditions (Halpern et al., 1991). The studies reported different outcomes such as GER (Fuloria et al, 2000; Halpern et al., 1991) in two studies and GERD 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.

5.3.3.2 Evidence profile

Table 21: GRADE findings 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 GER[a]											
1 (Fuloria, 2000)	Retrospective case-control	Very serious[b,c]	None	Serious[d]	Very serious[e]	None	15/111 (14%)	31/235 (13%)	OR: 1.03 (0.53 to 1.99)[f]	-	Very low
Prevalence and odds ratio for neurological disabilities[g] in children with and without GERD[h]											
1 (Ruigo	Retrospectiv	Very serio	None	None	None	None	107/1700	72/4977	Adjusted	-	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
mez, 2010)	e cohort	us[b,i]					(6.3%)	(1.4%)	OR: 3.40 (2.50 to 4.70)[j]		
Prevalence and odds ratio for CNS disease[k] in children with and without GER[l] – total population											
1 (Halpern et al., 1991)	Retrospective review	Very serious[b,c]	None	None	Very serious[e]	None	101/463 (21.8%)	31/149 (20.8%)	OR: 1.06 (0.68 to 1.67)[c]	-	Very low
Prevalence and odds ratio for CNS disease[k] in children with and without GERl – subjects > 1 year of age											
1 (Halpern et al., 1991)	Retrospective review	Very serious[b,c]	None	None	Serious[e]	None	31/69 (44.9%)	14/57 (24.6%)	OR: 2.51 (1.16 to 5.4)[c]	-	Very low
Prevalence and odds ratio for CNS disease[k] in children with and without GER[l] – subjects < 1 year of age											
1 (Halpern et al., 1991)	Retrospective review	Very serious[b,c]	None	None	Very serious[e]	None	70/394 (17.8%)	17/92 (18.5%)	OR: 0.95 (0.53 to 1.71)[c]	-	Very low

[a] *Fuloria 2000: diagnostic criteria for GER - defined as either treatment with anti-reflux medications (metaclopramide, bethanecol, cisparide, cimetidine or ranitidine) or a positive test for GER. Tests for GER included esophageal pH probe, upper gastrointestinal contrast studies and microscopic examination of tracheal aspirates for lipid laden macrophages. Tests for GER were performed and treatment was initiated at the discretion of the attending neonatologist.*
[b] *Retrospective study design*
[c] *Calculated by NCC-WCH, therefore unadjusted odds ratios*
[d] *Very low birth weight premature infants with chronic lung disease*
[e] *Confidence interval spans three possible interpretations*
[f] *Calculated by NCC-WCH technical team based on data reported in the article*
[g] *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*
[h] *Ruigomez 2010: diagnostic criteria for GERD - 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.*
[i] *Only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control group had been tested for GERD*
[j] *OR adjusted for age, sex, year of diagnosis, visits to primary care physician in the previous year*
[k] *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.*
[l] *Halpern 1991: diagnostic criteria for GER: initial evaluation included an extensive history and physical examination, barium oesophagram, upper gastrointestinal series and 18 to 24 hour esophageal pH monitoring. Documentation of GER by an abnormal pH score derived from 18 to 24 hour esophageal pH monitoring.*

5.3.3 Evidence statements (see Table 21)

5.3.3.1 Neurodisabilities

Three studies evaluated the odds of developing GORD in children with neurodisabilities. 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 GERD (evidence of low quality). The second study did not find a statistically significant association between cerebral palsy and GER (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 GER in children greater than 1 year of age but not for the total population or for children less than 1 year of age (very low quality evidence).

5.3.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.3.9

5.3.5 Recommendations

The recommendations covering risk-factors can be found in section 5.3.10

5.4 Prematurity

Extremely premature / 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 require a combination of enteral and parenteral feeding in the early stages of their post-natal 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 post natal ages during infancy and their subsequent childhood.

5.4.1 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 one was a case-control study (Forssell et al, 2012). One study was undertaken in the Netherlands (Deurloo et al, 2004), one in Sweden (Forssell et al, 2012), and one in Israel (Kohelet et al, 2004). Sample sizes ranged from 134 to 10715. The age of the subjects varied including newborns in two studies (Kohelet et al, 2004; Deurloo et al, 2004) children up to the age of 19 years in the third study (Forssell et al, 2012).

The definition of prematurity was reported in three studies (Deurloo et al., 2004; Forssell et al., 2012; Kohelet et al., 2004) and varied. One study (Forssell et al, 2012) examined both prematurity and extreme prematurity defined as 33 to 36 weeks gestation and ≤32 weeks gestation respectively. This study examined the association between prematurity and

esophagitis at different ages. The studies reported different outcomes including esophagitis in one study (Forssell et al, 2012), and GOR in two studies (Deurloo et al, 2004; Kohelet et al, 2004). The settings of the studies varied including a paediatric surgical centre, medical centre and hospital.

More details on each individual study can be found in the evidence tables.

5.3.462 Evidence profile

Table 22: GRADE findings 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**
Prematurity											
Prevalence and odds ratio for gestational age ≤32 weeks (versus 37 to 41 weeks) in children with and without subsequent oesophagitis[a] at the following ages:											
≤9 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[b,c]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 6.82 (4.65 to 10.03)[d]	-	Moderate
10 to 19 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[b,c]	No serious	No serious	Serious[e]	None	NR	NR	Adjusted OR: 2.09 (1.18 to 3.70)[d]	-	Low
Prevalence and odds ratio for gestational age 33 to 36 weeks (versus 37 to 41 weeks) in children with and without oesophagitis[a] at the following ages:											
≤9 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[b,c]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.75 (1.42 to 2.14)[d]	-	Moderate
10 to 19 years											
1 (Forssell, 2012)	Retrospective case-control	Serious[b,c]	No serious	No serious	Serious[e]	None	NR	NR	Adjusted OR: 1.41 (1.10 to 1.80)[d]	-	Low
Prevalence and odds ratio for prematurity (25 to 36 weeks of gestation) in children with and without											

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
GER[f]											
1 (Kohelet, 2004)	Retrospective cohort	Very serious[b,g]	No serious	No serious	Very serious[e]	None	18/62 (29%)	27/72 (38%)	OR: 0.68 (0.33 to 1.41)[h]	-	Very low
Prevalence and odds ratio for prematurity (<37weeks gestation) in children with and without GOR[i]											
1 (Deurloo, 2004)	Retrospective cohort	Very serious[b,g]	No serious	Serious[j]	Serious[e]	None	32/73 (44%)	44/124 (35%)	OR: 1.42 (0.79 to 2.56)[h]	-	Very low

[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] *Retrospective study design*
[c] *Oesophagitis based on unverified clinical coding criteria*
[d] *OR adjusted for birth weight for gestational age, maternal age and birth order*
[e] *Confidence interval spans multiple interpretations*
[f] *Kohelet 2004: diagnostic criteria for GER - 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%.*
[g] *Unadjusted odds ratios*
[h] *Calculated by NCC-WCH technical team based on data reported in the article*
[i] *Deurloo 2004: diagnostic criteria for GOR - Diagnosed either by clinical symptoms (n=30) or by 24 hour pH measurement (n=43).*
[j] *Infants with oesophageal atresia*

5.3.13 Evidence statements (see Table 22)

5.3.13.1 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 and 10 to 19 years). This study also reported a statistically significant association between extreme prematurity (gestational age of ≤32 weeks) and esophagitis at ≤9 years and at 10 to 19 years.

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

The fourth study did not find a statistically significant association between preterm delivery (not defined) and eosinophilic esophagitis.

The evidence ranged from very low to moderate quality.

5.3.14 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.3.9

5.3.4 Recommendations

The recommendations covering risk-factors can be found in section 5.3.10

5.3 Surgical or congenital disorders

This section describes the available evidence in respect of structural or anatomical problems of the oesophagus / upper gastrointestinal system. The conditions that were targeted by the GDG were hiatus hernia (where there is a telescoping effect / invagination of the stomach back through the gastro-oesophageal junction), diaphragmatic hernia (where there is an abnormal weakness / discontinuity in the tissue plane between the thorax and abdomen which can result in the herniation of part of the gastro-intestinal tract in to 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 three 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.

5.3.5 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), one a retrospective cohort (Ruigomez et al, 2010) and one a case control study (Abrahams et al, 1970). One study was undertaken in UK (Ruigomez et al, 2010), one in Australia (Abrahams et al, 1970) and one 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 one 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), one study on hiatal hernia alone (Steward et al, 1993) and one study 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 one study (Steward et al, 1993), GERD in one study (Ruigomez et al, 2010) and gastrointestinal symptoms in another study (Abrahams et al, 1970). The settings of the studies varied including a spastic centre, hospitals and primary care.

More details on each individual study can be found in the evidence tables.

5.3.512 Evidence profile

Table 23: GRADE findings 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[b]	None	Serious[c]	None	None	8/16 (50%)	5/63 (8%)	OR: 11.6 (3.04 to 44.29)[d]	-	Low
Hiatal Hernia											
Prevalence and odds ratio for hiatal hernia in children with and without erosive oesophagitis[e]											
1 (Steward, 1993)	Prospective cohort	Serious[b]	None	No serious	Serious[f]	None	12/20 (60%)	25/75 (33%)	OR: 3.00 (1.09 to 8.28)[d]	-	Low
Hiatal And Diaphragmatic Hernia											
Prevalence and odds ratio for hiatus hernia (congenital and acquired hiatus and diaphragmatic hernia) in children with and without GERD[g]											
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[h,i]	None	None	None	None	13/1700 (0.8%)	6/4977 (0.1%)	Adjusted OR: 7.4 (2.7 to 20.3)[j]	-	Low
Oesophageal Atresia											
Prevalence and odds ratio for congenital oesophageal disorders (oesophageal atresia, stenosis and traque-oesophageal fistula) in children with and without GERD[g]											
1 (Ruigomez, 2010)	Retrospective cohort	Very serious[h,i]	None	None	None	None	8/1700 (0.5%)	5/4977 (0.1%)	Adjusted OR: 4.3 (1.3 to 14.1)[j]	-	Low

[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] *Unadjusted odds ratios*
[c] *All children with severe physical disability (cerebral palsy)*
[d] *Calculated by NCC-WCH technical team based on data reported in the article*
[e] *Steward 1993: diagnostic criteria for erosive oesophagitis – endoscopy, oesophagitis was defined by the demonstration of friability, erosions or ulceration of the mucosa*
[f] *Confidence interval spans multiple interpretations*

[g] *Ruigomez 2010: diagnostic criteria for GERD - 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.*
[h] *Retrospective study design*
[i] *Only 15.3% of GERD cohort had a record of a formal diagnostic test being undertaken and none of the children in the control cohort had been tested for GER*
[j] *OR adjusted for age, sex, year of diagnosis and visits to primary care physician in the previous year*

5.3.5 Evidence statements (see Table 23)

5.3.5.1 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.

5.3.5.2 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.

5.3.5.3 Hiatal and diaphragmatic hernia

One study evaluated the odds of developing GERD 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.

5.3.5.4 Oesophageal atresia

One study evaluated the odds of developing GERD 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.

5.3.6 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.3.9

5.3.7 Recommendations

The recommendations covering risk-factors can be found in section 5.3.10

5.3.6 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.

5.3.8.1 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.

5.3.612 Evidence profile

Table 24: GRADE findings 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
Family History of GORD											
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[b]	None	14/52 (26.9 %)	189/963 (19.6 %)	Adjusted OR: 1.74 (0.82 to 3.69)c	-	Moderate
Both mother and father have epigastric pain											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[b]	None	4/52 (7.7%)	13/963 (1.3 %)	Adjusted OR: 4.15 (0.78 to 22.2)c	-	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[b]	None	13/32 (40.6 %)	226/988 (22.9 %)	Adjusted OR: 2.47 (0.99 to 6.16)[c]	-	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)[c]	-	High
Prevalence and odds ratio for a family history of acid regurgitation in adolescents with and without acid regurgitationa in the following categories:											
Either mother or father has acid regurgitation											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[b]	None	15/49 (30.6 %)	147/965 (15.2 %)	Adjusted OR: 2.54 (1.16 to	-	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
									5.60)[c]		
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)[c]	-	High

[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] *Confidence interval spans multiple interpretations*
[c] *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.*

5.3.6.3 Evidence statements (see Table 24)

5.3.6.3.1 Family history of epigastric pain

One study evaluated the 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.

5.3.6.3.2 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; however, 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.

5.3.6.3.3 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.

5.3.6.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.3.9

5.3.6.5 Recommendations

The recommendations covering risk-factors can be found in section 5.3.10

5.317 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 both boys and girls. In this section the evidence in relation to obesity as an isolated risk factor GORD is explored.

5.3.781 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), three 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 USA (Koebnick et al, 2011; Elitsur et al, 2009; El-Serag et al, 2001; Pashankar et al, 2009), one study in Norway (Stordal et al, 2006), one study in Northern Ireland (Murray et al, 2007), and one study in Italy (Quitadamo et al, 2012). Sample sizes for the analysis of this risk factor were reported in three studies and ranged from 153 to 9900. The age of the subjects varied including 7 to 16 year olds in two studies (Stordal et al, 2006; Pashankar et al, 2009), 2 to 18 year olds in two studies (Quitadamo et al, 2012; El-Serag et al, 2001), 2 to 19 year olds in one study (Koebnick et al, 2011), 13 to 17 year olds in one study (Murray et al, 2007) and children with a mean age of 10.6 years in one study (Elitsur et al, 2009).

One study reported on overweight alone (Stordal et al, 2006), two studies on overweight or obesity (Quitadamo et al, 2012; Elitsur et al, 2009), one study on overweight and obesity separately (Murray et al, 2007), one study on obesity (Pashankar et al, 2009), one study on morbid obesity (El-Serag et al, 2001) and one study on overweight, moderate obesity and extreme obesity separately (Koebnick et al, 2011). The studies reported different outcomes including GERD in three studies (Koebnick et al, 2011; Elitsur et al, 2009; El-Serag et al, 2001), a positive reflux symptom score in two studies (Quitadamo et al, 2012; Pashankar et al, 2009), a positive GERD symptom score in one study (Stordal et al, 2006) and epigastric pain, heartburn and acid regurgitation in one study (Murray et al, 2007) defined in various ways. The settings of the studies varied including 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.

5.3.852 Evidence profile

Table 25: GRADE findings 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 GERD[a]											
1 (Stordal, 2006)	Prospective case contro	Serious[b]	No serious	Serious[c]	Serious[d]	None	NR	NR	Adjusted OR: 1.6	-	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
	l								(1.1 to 2.4)[e]		
Prevalence and odds ratio for overweight in children with and without epigastric pain[f]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[d]	None	NR	NR	Adjusted OR: 1.09 (0.49 to 2.40)[g]	-	Low
Prevalence and odds ratio for overweight in children with and without heartburn[f]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[d]	None	NR	NR	Adjusted OR: 1.06 (0.35 to 3.21)[g]	-	Low
Prevalence and odds ratio for overweight in children with and without acid regurgitation[f]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[d]	None	NR	NR	Adjusted OR: 1.64 (0.72 to 3.72)[g]	-	Low
Prevalence and odds ratio for overweight in children with and without GERD[h] at the following ages:											
2 to 5 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 0.95 (0.85 to 1.07)[j]	-	Moderate
6 to 11 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 0.99 (0.87 to 1.12)[j]	-	Moderate
12 to 19 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.08 (1.01 to 1.15)[j]	-	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**
Overweight/Obesity											
Prevalence and odds ratio for overweight/obesity in children with and without a positive reflux score[k]											
1 (Quitadamo, 2012)	Prospective cohort	Serious[l]	No serious	No serious	No serious	None	29/49 (59%)	30/104 (29%)	OR: 3.58 (1.76 to 7.28)[m]	-	Moderate
Prevalence and odds ratio for overweight/obesity in children with and without GERD[n]											
1 (Elitsur, 2009)	Retrospective chart review	Very serious[i,o]	No serious	No serious	Serious[d]	None	237/491 (48%)	108/247 (44%)	OR: 1.2 (0.88 to 1.63)[m]	-	Very low
Obesity											
Prevalence and odds ratio for obesity in children with and without a positive reflux symptom score[p]											
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)[q]	-	High
Prevalence and odds ratio for obesity in children with and without epigastric pain[f]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[d]	None	NR	NR	Adjusted OR: 0.84 (0.20 to 3.65)[g]	-	Low
Prevalence and odds ratio for obesity in children with and without heartburn[f]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Very serious[d]	None	NR	NR	Adjusted OR: 0.84 (0.11 to 6.60)[g]	-	Low
Prevalence and odds ratio for obesity in children with and without acid regurgitation[f]											
1 (Murray, 2007)	Prospective cross-sectional	No serious	No serious	No serious	Serious[d]	None	NR	NR	Adjusted OR: 3.46 (1.24 to 9.69)[g]	-	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 GERD[h] at the following ages:											
2 to 5 years											

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
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 0.92 (0.80 to 1.06)[j]	-	Moderate
6 to 11 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	Serious[d]	None	NR	NR	Adjusted OR: 1.16 (1.02 to 1.32)[j]	-	Low
12 to 19 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.16 (1.07 to 1.25)[j]	-	Moderate
Extreme/Morbid Obesity											
Prevalence and odds ratio for extreme obesity in children with and without GERD[h] at the following ages:											
2 to 5 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	Serious[d]	None	NR	NR	Adjusted OR: 1.26 (0.95 to 1.68)[j]	-	Low
6 to 11 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	Serious[d]	None	NR	NR	Adjusted OR: 1.32 (1.13 to 1.56)[j]	-	Low
12 to 19 years											
1 (Koebnick, 2011)	Retrospective cross sectional	Serious[i]	No serious	No serious	No serious	None	NR	NR	Adjusted OR: 1.40 (1.28 to 1.52)[j]	-	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 GERD[r]											
1 (El-Serag, 2001)	Retrospective case-control	Very serious[i,s]	No serious	No serious	Serious[d]	None	NR/1980	NR/7920	Adjusted OR: 1.90 (1.17 to 3.02)[t]	-	Very low

[a] *Stordal 2007: diagnostic criteria for GERD - 7-item GERD questionnaire developed and validated by the author. GERD if 3 or more points on a questionnaire. A score of 3 or more points (positive symptom score) has a 75% sensitivity and 96% specificity for GERD defined by an abnormal pH monitoring. Overweight: BMI calculated as weight divided by height² and compared to international age-adjusted percentiles. Overweight and obesity were defined as BMI corresponding to an adult BMI above 25 and 30, respectively.*

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

[c] *Population included children with asthma*

[d] *Confidence interval spans multiple interpretations*

[e] *Odds ratio adjusted for age, gender and asthma*

[f] *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).

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

[h] *Koebnick 2011: diagnostic criteria - International Classification of Disease codes (ICD-9 code 530.81). GERD diagnosis was validated in a random subsample of about 5% of cases (n=480) by confirming diagnosis codes for GERD 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*

[i] *Retrospective study design*

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

[k] *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*

[l] *Positive reflux score not defined*

[m] *NCC-WCH calculation*

[n] *Elitsur 2009: diagnostic criteria for GERD – 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*

[o] *Unadjusted odds ratios*

[p] *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*

[q] *Odds ratio was adjusted for age, sex, race and caffeine exposure.*
[r] *El-Serag 2001: diagnostic criteria for GERD - based on ICD-9 coding of GERD (530.81, 530.10, 530.11, 530.19, 530.3). Morbid obesity diagnosed according to ICD-9 codes.*
[s] *Both the risk factor and outcome based on reliability of coding in medical records*
[t] *Odds ratio adjusted for age, gender and ethnicity*

5.3.7.3 Evidence statements (see Table 25)

5.3.7.3.1 Overweight

Three studies evaluated the odds of developing symptoms of GER in children and young people who were overweight. One study reported a statistically significant association between being overweight and a positive GERD symptom score. A second study did not find a statistically significant association between overweight and the risk of developing epigastric pain, heartburn or acid regurgitation. A third study which looked at the association between being overweight and GERD 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.

5.3.7.3.2 Overweight/obesity

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

5.3.7.3.3 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.

5.3.7.3.4 Moderate obesity (BMI for age ≥95th percentile or a BMI ≥30kg/m²)

One study evaluated the risk of developing GERD at different ages (three 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 and. 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.

5.3.7.3.5 Extreme/morbid obesity

Two studies evaluated the association between extreme or morbid obesity and the risk of developing GERD. One study reported a statistically significant association between morbid obesity and GERD. The other study which looked at the association between extreme obesity and the risk of developing GERD (three 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.

5.3.7.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 5.3.9

5.3.7 Recommendations

The recommendations covering risk-factors can be found in section 5.3.10

5.3 Health economics profile

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

5.3 Evidence to recommendations

5.3.9 Relative value placed on the risk-factors considered

The GDG 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.

5.3.9 Consideration of clinical usefulness of risk-factor

No criteria were pre-specified for judging the usefulness of a risk-factor. The GDG focused their 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, therefore, the GDG relied on their clinical experience when making recommendations.

5.3.9.1 Chronic lung disease

Whilst five studies were available on chronic lung disease, 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, however, the GDG was concerned about the quality of the included studies and inconsistency between them. Interestingly, the GDG are 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 GDG 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.

5.3.9.2 Congenital heart disease

Although the GDG 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.

5.3.9.3 Neurodisabilities

The GDG was 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 three studies were identified that measured this risk-factor, and of these only one presented adjusted odds-ratios. This supported the GDGs experience that neurodisability was a risk-factor for developing GORD, therefore it was recommended that this be included as a risk-factor.

As was highlighted earlier in this chapter, the GDG recognise that the literature is hampered by vague generalizations and a failure to look at specific diagnosis in assessing the problem. Similarly, children with these problems are often suffering a variety of problems that may all

be contributing to complex feeding problems, chest disease, pain, faltering growth and emesis. This makes the description of the problem as GOR / GORD of debatable value.

5.3.9.234 Prematurity

The GDG 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 three available studies, two did not find that premature infants were subsequently at greater risk of developing GER, 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 GDG 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 GDG recommended that prematurity be listed as a risk-factor for subsequently developing GORD.

However, the GDG was unsure if this conclusion should covered 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 GDG discussed their experience, which suggested that there were higher rates of overt reflux in premature infants for the reasons outlined in the section introduction i.e. 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 GDG debated if 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.

5.3.9.235 Surgical or congenital disorders

Evidence from three observational studies showed an association between congenital disorders and reflux symptoms. The evidence, though limited, matched the GDGs experience that congenital disorders were risk-factors for developing GORD. Furthermore, the GDG 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 GDG felt it was appropriate to recommend that congenital disorders are a risk-factor for GORD.

5.3.9.236 Family history of GORD

Only one 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 GDGs own experience of family history of GORD. The GDG 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 GDG 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 GDG 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 GDG concluded that a family history of GOR could be a useful risk-factor and that a recommendation could be made on this.

Obesity

Results from seven 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 GDGs experience that excess weight was associated with GORD. The GDG 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 it was still a useful risk-factor, and a recommendation could be made on obesity as a risk-factor for GORD.

The GDG did not discuss what affect weight reduction would have on GORD although the GDG agreed that healthy eating, regular exercise and where necessary safe weight loss programs are likely to be beneficial for all obese children and adults including the reduction of a whole number of potentially serious co-morbidities.

Consideration of health benefits and resource uses

Discussion within the GDG 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, but especially in primary care. The cost of equipment, training and time required would be prohibitive. Therefore, initial diagnosis had to be based on risk-factors, symptoms and signs and examination in the first instance.

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, and imprecision in the results which meant that usefulness of a risk-factor was uncertain. The evidence was of very low to high quality.

Other issues

No equality issues were specified for this question.

Recommendations

Recommendations

11. Take into account that the following are associated with an increased prevalence of GORD when deciding whether to investigate or treat:

- 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.

12. **GOR only rarely causes episodes of apnoea or apparent life-threatening events (ALTEs), but think about referral for specialist investigations if it is suspected as a possible factor following a general paediatric assessment.**

13. **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 Obesity [NICE clinical guideline 43])**

5.3.107 Research recommendations

No research recommendations in this area.

5.4 Indications for investigation and treatment

Health 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 a common symptoms in other potentially more serious conditions. The aim of these questions was to help health professionals decide which symptoms, signs and risk-factors indicated the need for which tests and treatments, if any.

5.4.1 Review question

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

5.4.2 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 GDG used the result of the reviews on natural history of reflux, symptoms and sign, and risk-factors in conjunction with their clinical experience to address these questions.

5.4.3 Evidence profile

None

5.4.4 Evidence statements

None

5.4.5 Health economics profile

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

5.4.6 Evidence to recommendations

The GDG listed a number of diagnostic tests that are commonly used to investigate the potential effect of reflux, these being: gastrointestinal contrast studies, upper gastrointestinal endoscopy with biopsy, and pH monitoring with or without impedance monitoring. To undertake and interpret the results of these tests requires specialist training, which is beyond the remit of this guideline. The GDG therefore limited their discussion to the indications for undertaking investigations. There were four main areas for investigations: where a condition other than reflux was suspected, where treatment had failed, to monitor the effect of treatment, or before deciding to undertake surgery. The GDG concluded that GI contrast studies were only indicated when conditions other than reflux are suspected, for example hypertrophic pyloric stenosis, and that undertaking this test to identify GORD had no clinical value and exposed the infant, child or young person to an unnecessary dose of radiation. The GDG agreed that GI endoscopy should be the main test used to investigate reflux related symptoms and was indicated in situations where reflux symptoms had not improved, oesophagitis was suspected, to monitor healing of oesophagitis or if other conditions were suspected. In comparison pH and impedance monitoring should only be considered in more specific situations related to concerns about the level of acid suppression being achieved by pharmaceutical treatment or where reflux was suspected of being related to a specific symptom, such as apnoea. Further explanation for these recommendations can be found in

the evidence to recommendation sections of symptoms and signs review, and within individual treatment chapters.

5.437 Recommendations

5.4.741 Recommendations

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

15. Offer an urgent (same day) upper GI contrast study for infants with unexplained bile-stained vomiting.

16. Think about an upper GI contrast study for children and young people with a history of bile-stained vomiting, particularly if it is persistent or recurrent.

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

18. Urgently refer (on the same day) infants younger than 2 months with progressively worsening or forceful vomiting of feeds for investigation for possible hypertrophic pyloric stenosis.

19. Refer infants, children and young people to a specialist for a possible upper GI endoscopy with biopsies if there is:

- any haematemesis (blood-stained vomit)
- any melaena (black, foul-smelling stool)
- dysphagia
- 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 referral for fundoplication
- back arching or features of Sandifer's syndrome.

20. Think about performing a pH study, ideally with impedance monitoring, in children and young people with unexplained:

- recurrent aspiration pneumonia
- apnoea
- non-epileptic seizure-like events
- Sandifer's syndrome
- unexplained upper airway inflammation
- dental erosion in children and young people with a neurodisability
- frequent otitis media.

21. **Think about performing a pH study without impedance monitoring:**
    - to ensure adequate acid suppression during treatment
    - if symptoms continue during medical management
    - if there is a clinical suspicion of GORD but no regurgitation
    - when thinking about fundoplication.

22. **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.

5.4.12 Research recommendations

No research recommendations in this area.

6 Initial management of GOR and GORD

6.1 Infant Positioning

Positional management involves assessing if altering the position an infant is placed 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 SIDS and placing infants to sleep on their fronts has become clear this advice has been withdrawn. However, interest has remain in altering the angle at which infants may be positioned while still in the back (supine) position.

6.1.1 Review question

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

6.1.2 Description of included studies

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), two from the UK (Bhat et al, 2007; Ewer et al, 1999) one from Australia (Tobin et al, 1997) and one from Belgium (Bagucka et al, 1999).

Sample sizes ranged from 9 to 90 infants. The age of the subjects varied including infants born prematurely in two studies (Bhat et al, 2007; Ewer et al, 1999) and infants less than 6 months old 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 varied including medical centres, an asthma centre, paediatric gastroenterology units, 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 four studies (Orenstein et al, 1983a; Orenstein et al, 1983b; Orenstein et al, 1990; Tobin et al, 1997) and sleeping position in two 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.

6.1.3 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.

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 findings 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[a, b, c,d]	NA	Serious	Non[e]	Yes[f]	n=21 Median (range): 0 (0 to 11.4)	n=21 Median (range): 3 (0 to 15.4)	NA	p=0.002	Very low
1 (Tobin et al 1997)	RCT – crossover	Serious[c,d]	NA	Non[e]	Non[e]	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)[g]	p <0.05	Moderate

[a] *Method of randomisation not reported*
[b] *Unclear whether there was adequate concealment of allocation*
[c] *Unclear whether investigators were blinded to intervention*
[d] *Unclear whether investigators were blinded to confounding factors*
[e] *12/21 subjects were oxygen dependent and had or subsequently fulfilled the diagnosis of BPD (oxygen dependency beyond 36 weeks postmenstrual age)*
[f] *Infants born premature*
[g] *Calculated by NCC-WCH technical team based on data reported in the article*

Table 27: GRADE findings 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[a])	RCT – crossover	Serious[a,b,c]	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)[d]	p <0.001	Moderate
Number of episodes with pH <4.0											
1 (Orenstein et al 1983[a])	RCT – crossover	Serious[a,b,c]	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)[d]	p < 0.001	Moderate
Number of such episodes lasting longer than 5 minutes											
1 (Orenstein et al 1983[a])	RCT – crossover	Serious[a,b,c]	None	None	Serious[e]	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)[d]	p<0.05	Low
Duration of the longest episode in each 2 hour postprandial period											
1 (Orenstein et al 1983[a])	RCT – crossover	Serious[a,b,c]	None	None	Serious[e]	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)[d]	p<0.05	Low

[a] *Unclear whether there was adequate concealment of allocation*
[b] *Unclear whether investigators were blinded to intervention*
[c] *Unclear whether investigators were blinded to confounding factors*
[d] *Calculated by NCC-WCH technical team based on data reported in the article*
[e] *Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)*

Table 28: GRADE findings 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[a,b]	None	None	Serious[c]	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)[d]	p= NS[e]	Low
Number of episodes with pH <4.0											
1 (Orenstein et al 1990)	RCT – crossover	Serious[a,b]	None	None	Serious[c]	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)[d]	p= NS[e]	Low
Mean duration of reflux episodes											
1 (Orenstein et al 1990)	RCT – crossover	Serious[a,b]	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)[d]	p= NS[e]	Moderate
Number of reflux episodes lasting longer than 5 minutes											
1 (Orenstein et al 1990)	RCT – crossover	Serious[a,b]	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)d	p= NS[e]	Moderate
Duration of the longest reflux episode											
1 (Orenstein et al 1990)	RCT - crossover	Serious[a,b]	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)[d]	p= NS[e]	Moderate

NS – not significant

[a] *Unclear whether there was adequate concealment of allocation*

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

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

[d] *Calculated by NCC-WCH technical team based on data reported in the article*
[e] *Significance defined as p<0.05*

Table 29: GRADE findings 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 1983[b])	RCT – crossover	Serious[a,b,c]	None	None	Serious[d]	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)[e]	p= 0.023	Low
Number of episodes with pH <4.0											
1 (Orenstein et al 1983[b])	RCT – crossover	Serious[a,b,c]	None	None	Serious[d]	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)[e]	p= 0.002	Low
Number of reflux episodes lasting longer than 5 minutes											
1 (Orenstein et al 1983[b])	RCT – crossover	Serious[a,b,c]	None	None	Serious[d]	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)[e]	p= 0.093	Low
Duration of the longest reflux episode in each 2 hour postprandial period											
1 (Orenstein et al 1983[b])	RCT – crossover	Serious[a,b,c]	None	None	Serious[d]	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)[e]	p= 0.079	Low

[a] *Unclear whether there was adequate concealment of allocation*
[b] *Unclear whether investigators were blinded to intervention*
[c] *Unclear whether investigators were blinded to confounding factors*
[d] *Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)*
[e] *Calculated by NCC-WCH technical team based on data reported in the article*

Table 30: GRADE findings 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[a,b,c,d]	None	None	Serious[e]	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)[f]	p=0.08	Very low
Number of episodes with pH <4.0											
1 (Bagucka et al 1999)	RCT – crossover	Very serious[a,b,c,d]	None	None	Very serious[g]	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)[f]	p=0.95	Very low
Duration of the longest reflux episode											
1 (Bagucka et al 1999)	RCT – crossover	Very serious[a,b,c,d]	None	None	Serious[e]	None	n= 10 Mean (SD): 38.9 (46.81)	n= 10 Mean (SD): 17 (6.34)	MD: 22.00 (-7.37 to 51.37)[f]	p=0.16	Very low

[a] *Method of randomisation not reported*
[b] *Unclear whether there was adequate concealment of allocation*
[c] *Unclear whether investigators were blinded to intervention*
[d] *Unclear whether investigators were blinded to confounding factors*
[e] *Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)*
[f] *Calculated by NCC-WCH technical team based on data reported in the article*
[g] *Confidence interval of standardised mean difference crosses 3 zones (very wide confidence interval)*

Table 31: GRADE findings 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[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 6.3 (7.2)	n=18 Mean (SD): 29.4 (13.6)	MD: -23.10 (-30.20 to -16.00)[d]	p<0.05	Moderate
1 (Tobin et al 1997)	RCT – crossover	Serious[a,b]	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)[d]	p<0.05	Moderate
Number of episodes with pH <4.0											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 15.4 (11.9)	n=18 Mean (SD): 41.6 (19.5)	MD: -26.20 (-36.75 to -15.65)[d]	p<0.05	Moderate
Number of reflux episodes lasting longer than 5 minutes											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 1.1(1.7)	n=18 Mean (SD): 4.5 (3.4)	MD: -3.40 (-5.15 to -1.65)[d]	p<0.05	Moderate
Duration of the longest reflux episode											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 8.6 (9.3)	n=18 Mean (SD): 26 (16.5)	MD: -17.4 (-26.18 to -8.62)[d]	p<0.05	Moderate

[a] *Unclear whether investigators were blinded to intervention*
[b] *Unclear whether investigators were blinded to confounding factors*
[c] *Infants born premature*
[d] *Calculated by NCC-WCH technical team based on data reported in the article*

Table 32: GRADE findings 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[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 11 (9.3)	n=18 Mean (SD): 29.4 (13.6)	MD: -18.4 (-26.01 to -10.79)[d]	p<0.05	Moderate
1 (Tobin et al 1997)	RCT – crossover	Serious[a,b]	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)[d]	p<0.05	Moderate
Number of episodes with pH <4.0											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 24.6 (14.8)	n=18 Mean (SD): 41.6 (19.5)	MD: -17.00 (-28.33 to -5.67)[d]	p<0.05	Moderate
Number of reflux episodes lasting longer than 5 minutes											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 1.8 (2.1)	n=18 Mean (SD): 4.5 (3.4)	MD: -2.70 (-4.55 to -0.85)[d]	p<0.05	Moderate
Duration of the longest reflux episode											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	None	Yes[c]	n=18 Mean (SD): 10 (10.2)	n=18 Mean (SD): 26 (16.5)	MD: -16 (-24.98 to -7.02)[d]	p<0.05	Moderate

[a] *Unclear whether investigators were blinded to intervention*
[b] *Unclear whether investigators were blinded to confounding factors*
[c] *Infants born premature*
[d] *Calculated by NCC-WCH technical team based on data reported in the article*

Table 33: GRADE findings 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[a,b]	None	None	Serious[c]	Yes[d]	n=18 Mean (SD): 6.3 (7.2)	n=18 Mean (SD): 11 (9.3)	MD: -4.70 (-10.15 to 0.75)[e]	p<0.05	Low
1 (Tobin et al 1997)	RCT – crossover	Serious[a,b]	None	None	Serious[c]	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)[e]	NS	Low
Number of episodes with pH <4.0											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	Serious[c]	Yes[d]	n=18 Mean (SD): 15.4 (11.9)	n=18 Mean (SD): 24.6 (14.8)	MD: -9.20 (-17.98 to -0.42)[e]	p<0.05	Low
Number of reflux episodes lasting longer than 5 minutes											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	Serious[c]	Yes[d]	n=18 Mean (SD): 1.1 (1.7)	n=18 Mean (SD): 1.8 (2.1)	MD: -0.70 (-1.95 to 0.55)[e]	p>0.05[f]	Low
Duration of the longest reflux episode											
1 (Ewer et al 1999)	RCT – crossover	Serious[a,b]	None	None	Very serious[g]	Yes[d]	n=18 Mean (SD): 8.6 (9.3)	n=18 Mean (SD): 10 (10.2)	MD: -1.40 (-7.78 to 4.98)[e]	p>0.05[f]	Very low

[a] *Unclear whether investigators were blinded to intervention*
[b] *Unclear whether investigators were blinded to confounding factors*
[c] *Confidence interval of standardised mean difference crosses 2 zones (wide confidence interval)*
[d] *Infants born premature*
[e] *Calculated by NCC-WCH technical team based on data reported in the article*
[f] *Unclear reporting but seems as though p >0.05*
[g] *Confidence interval of standardised mean difference crosses 3 zones (very wide confidence interval)*

Table 34: GRADE findings 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[a], b	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)c	p <0.05	Moderate

[a] *Unclear whether investigators were blinded to intervention*
[b] *Unclear whether investigators were blinded to confounding factors*
[c] *Calculated by NCC-WCH technical team based on data reported in the article*

6.1.4 Evidence statements (see Table 26 to Table 34)

6.1.4.1 Prone versus supine positioning

6.1.4.1.1 Reflux index (percent of time with pH <4.0)

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

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

6.1.4.2.1 Reflux index (percent of time with pH <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 to the infant seat elevated at 60 degrees. The evidence for this finding was of moderate quality.

6.1.4.2.2 Number of reflux episodes with pH <4.0

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

6.1.4.2.3 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 to the infant seat elevated at 60 degrees. The evidence for this finding was of low quality.

6.1.4.2.4 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 to the infant seat elevated at 60 degrees. The evidence for this finding was of low quality.

6.1.4.3 Head-elevated prone positioning versus flat prone positioning

6.1.4.3.1 Reflux index (percent of time with pH < 4.0)

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

6.1.4.3.2 Number of episodes with pH < 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 to the flat prone position. The evidence for this finding was of low quality.

6.1.4.3.3 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 to the flat prone position. The evidence for this finding was of moderate quality.

6.1.4.3.4 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 to the flat prone position. The evidence for this finding was of moderate quality.

6.1.4.3.5 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 to the flat prone position. The evidence for this finding was of moderate quality.

6.1.4.4 Infant seat elevated at 60 degrees versus horizontal prone positioning

6.1.4.4.1 Reflux index (percent of time with pH < 4.0)

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

6.1.4.4.2 Number of episodes with pH < 4.0

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

6.1.4.4.3 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 to horizontal prone positioning. The evidence for this finding was of low quality.

6.1.4.4.4 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 to horizontal prone positioning. The evidence for this finding was of low quality.

6.1.4.15 Supine reversed-Trendelenburg position of 10 degrees versus flat supine positioning

6.1.4.21 Reflux index (percent of time with pH <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 to the flat supine position. The evidence for this finding was of very low quality.

6.1.4.22 Number of episodes with pH <4.0

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

6.1.4.23 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 to the flat supine position. The evidence for this finding was of very low quality.

6.1.4.16 Prone versus right lateral

6.1.4.31 Reflux index (percent of time with pH <4.0)

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

6.1.4.32 Number of episodes with pH <4.0

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

6.1.4.33 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 to the right lateral position. The evidence was of moderate quality.

6.1.4.34 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 to the right lateral position. The evidence was of moderate quality.

6.1.4.17 Left lateral versus right lateral

6.1.4.41 Reflux index (percent of time with pH < 4.0)

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

6.1.4.42 Number of episodes with pH < 4.0

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

6.1.4.73 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 to the right lateral position. The evidence was of moderate quality.

6.1.4.74 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 to the right lateral position. The evidence was of moderate quality.

6.1.48 Prone versus left lateral

6.1.4.80 Reflux index (percent of time with pH <4.0)

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

6.1.4.82 Number of episodes with pH <4.0

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

6.1.4.83 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 to the left lateral position. The evidence was of low quality.

6.1.4.84 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 to the left lateral position. The evidence was of very low quality.

6.1.49 Left lateral versus supine positioning

6.1.4.91 Reflux index (percent of time with pH <4.0)

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

6.1.5 Health economics profile

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

6.1.6 Evidence to recommendations

6.1.61 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 GDG had prioritised the outcome of any change in

frequency of overt gastro-oesophageal reflux. The GDG also considered reported changes in oesophageal acid reflux based on oesophageal pH monitoring.

6.1.632 Consideration of clinical benefits and harms

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

The GDG noted that the prone position improved reflux as measured by pH studies in infants when compared with both the supine and right lateral position. 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 GDG 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, 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 GDG discussed at length the Worldwide Public Health and current Department of Health recommendation that infants should be put to sleep on their backs for every sleep in order to reduce the risk of sudden infant death syndrome (SIDS). Further the whole GDG accepted and recognised the dramatic effect this simple message has had over the last 25 years and the many 100,000s of infant lives that have been saved.

As a result the GDG 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. In stating 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 GDG 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 following publication from the Scottish NHS

http://www.scotland.gov.uk/resource/doc/170857/0047857.pdf

The GDG were also aware of situations where infants, particularly premature infants, are placed in a front (prone) position whilst sleeping on the NICU or SCBU in hospital to help relieve GOR, however, 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 GDG 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 individual and would quite possibly pose a risk to the much larger population of well infants with normal regurgitation and mild physiological GOR were this dangerous practice to become widespread once again.

6.1.643 Consideration of health benefits and resource uses

Whilst 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.

6.1.614 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 GDG 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.

6.1.615 Other considerations

6.1.6.511 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. Once a child can move freely during sleep or at rest, there is little application of positional management in GOR.

6.1.6.522 Positional management of children with neurodisability

No evidence was identified for children with neurodisability, therefore the GDG did not make a recommendation for this group.

6.1.6.533 Positional management supports

The GDG were 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 GDG stated 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 GDG concluded that none could demonstrate benefit and therefore should not be recommended or offered in the NHS.

6.1.6.544 Infant sleeping position and risk of SIDS

Public Health advice to always avoid the front (prone) sleeping position in infants started to become widespread practice in many countries and cultures across the world from the late 1980s. By as the early 1992 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). Gilbert in her paper “The changing epidemiology of SIDS” *Archives of Disease in Childhood* 1994;70:445-449 summarises the data for the UK and emphasises in her introduction that for England and Wales the number of SIDS victims fell by nearly **70%** from 1593 in 1988 to 531 in 1992.

Subsequent work has clarified that it is not sufficient for infants to be placed to sleep in the non-front position but that all infants must be placed on their back at all times for sleep. This is because there remains an increased risk of SIDS with the side sleeping position as compared to the back (supine) position. This further change has led to an ongoing fall in the incidence of this devastating mortal condition and the now very simple guidance from the Department of Health in response to infant sleeping positioning:

http://www.nhs.uk/Conditions/Sudden-infant-death-syndrome/Pages/Introduction.aspx

6.17 Recommendations

6.17.1 Recommendations

23. Do not use positional management to treat GOR in sleeping infants. In line with Department of Health advice, infants should be placed on their back when sleeping.

6.17.2 Research recommendations

No research recommendations in this area.

6.2 Feeding changes

This chapter evaluates the evidence in respect of feed changes in relation to regurgitation and GOR for infants, children and young people. It to be 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 & family as well as health professionals at all tiers of care. In respect of the infants who regurgitate advice may include changing the way the feed is administrated by altering the volume together with the frequency of administration or alternatively by altering the content by thickening the milk or even changing the constituent parts e.g. in the case of hydrolysed milk substitutes.

6.2.1 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 cow's milk protein can reduce the frequency of overt reflux in children and young people.
- To determine if a maternal diet free of cow's milk and/or soya protein can reduce the frequency of overt reflux in children who are being breast fed.

6.2.2 Description of included studies

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), one study on elimination of cow's milk from diet (Borrelli et al, 2012) and one on volume of feeds (Sutphen & Dillard, 1988). No comparative studies were found on the effect elimination of Cow's milk from the maternal diet on infant reflux symptoms. The type of thickening agents used varied but includes corn starch, rice starch (Enfamil) and locust bean.

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 one multinational study undertaken in Greece, Morocco, France and Belgium (Xinias et al, 2005).

The most common study design was 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 6 months or less. A study on cow's milk protein elimination included children up to the age of 24 months.

Only one study examined a specific sub-group, this being children with cerebral palsy (Miyazawa et al, 2008).

More details on each individual study can be found in the evidence tables.

6.2.3 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 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 cow's milk elimination diet on the symptoms of GER.
- GRADE findings for comparison of feeding volume on symptoms of GER.

Table 35: GRADE findings 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[a, b]	None	None	None	None	28 of 82	12 of 84	Relative Risk: 2.39 [1.31, 4.37]	N/A	Moderate
Number of episodes of regurgitation (per day or week)											
3 (4 arms) Moukarzel et al, 2007 Xinias et al, 2005 Miyaz	Meta analysis of RCTs	Serious[a, b]	Serious[c]	None	None	Yes[d]	-	-	Mean Difference: -2.00 [-4.65, 0.65]	N/A	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
awa et al, 2006)											
Change in regurgitation frequency from baseline at one week											
1 (Vanderhoof et al, 2003)	RCT	Very Serious[a, e]	None	None	Serious	No	Change -6 (range +/- 1)[g]	Change -6 (range +/- 1)[g]	Non-significant[g]	N/A	Very low
Episodes of emesis over a 90 minute period											
1 (Orenstein et al, 1986)	RCT; crossover	Very Serious[h]	None	None	Serious	No	1.2 (SD +/- 0.7)[g]	3.9 (SD +/- 0.9)[g]	p = 0.015[g]	N/A	Very low
1 (Wenzl et al, 2003)	RCT; crossover	None	None	None	Serious[f]	No	1.07 (SD +/- 1.69)[g]	4.86 (SD +/- 4.05[g]	p < 0.003[g]	N/A	Moderate
Frequency of regurgitation per day, median (IQR)											
1 (Miyazawa et al, 2004)	RCT; crossover within arms	Serious[a]	None	None	Serious[f]	Yes[i]	HL-350 Median 1.6 (IQR 0.8 to 2.0)[g]	HL-00 Median 3.5 (IQR 2.3 to 4.9)[g]	p = 0.021[g]	N/A	Low
1 (Miyazawa et al, 2004)	RCT; crossover within arms	Serious[a]	None	None	Serious[f]	Yes[i]	HL-450 Median 1.3 (IQR 0.6 to 2.3)[g]	HL-00 Median 2.9 (IQR 2.0 to 3.2)[g]	p = 0.0003[g]	N/A	Low
1 (Miyazawa et al, 2007)	RCT;	Serious[a]	None	None	Serious[f]	Yes[i]	HL-350 Median 2.3 (IQR 1.6 to 3.6)[g]	HL-00 Median 5.2 (IQR 3.7 to 7.8)[g]	p < 0.01)[g]	N/A	Low
Number of episodes of vomiting per day											

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
2 (Moukarzel et al, 2007 Xinias et al, 2005)	Meta analysis of RCTs	Serious[a]	None	None	None	Yes	-	-	Mean Difference: -0.97 [-1.54, -0.39]	N/A	Moderate
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[a, b]	None	None	None	Yes[d]	-	-	Mean Difference: -3.38 [-5.28, -1.48]	N/A	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[a]	Serious[c]	None	None	Yes[d]	-	-	Mean Difference: 3.99 [1.66, 6.31]	N/A	Low
Adverse events											
Discontinued due to diarrhoea											
1 (Iacono et al, 2002)	RCT	Serious[a, b]	None	None	None	No	14 of 82	0 of 84	∞	N/A	Moderate
Reported adverse events (not specified)											

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
1 (Vanderhoof et al, 2003)	RCT	Very Serious[a]	None	None	Serious[f]	No	-	-	No difference between groups[g]	N/A	Very Low
1 (Miyazawa et al, 2004)	RCT; crossover within arms	Serious[a]	None	None	Serious[f]	No	-	-	No difference between groups[g]	N/A	Low
1 (Xinias et al, 2005)	RCT;	Serious[a]	None	None	Serious[f]	No	-	-	No difference between groups[g]	N/A	Low

[a] *Method of randomisation not described in detail*
[b] *High discontinuation rate*
[c] *High heterogeneity between studies*
[d] *Variation in viscosity of formulas and nutritional value of formulas*
[e] *Children assessed at one week and some given further treatment*
[f] *Imprecision could not be investigated due to way result have been reported and cross-over design*
[g] *Result as reported in study*
[h] *Study based on response to a single feed; Method of investigation was scintigraphically*
[I] *It is unclear how these studies are linked. Numbers in each arm differ.*
N/A Not Applicable

Table 36: GRADE findings 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[a]	None	None	Serious[b]	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	N/A	Low
1 (Miyazawa et al, 2008)	RCT; crossover within arms	Serious[a]	None	None	Serious[b]	No	Low Pectin median 0.0 (0.0 to 0.5)	Standard feed median 0.0 (0.0 to 0.1)	NS	N/A	Low

[a] *Method of randomisation not described in detail*
[b] *Could not be calculated*
NS Not significant at p < 0.05

Table 37: GRADE findings 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 (Ostorm et al, 2006)	RCT	Very Serious[a, b]	None	Very serious[c]	Serious[d]	No	11 of 67	3 of 66	Relative Risk: 3.61 [1.06, 12.36]	N/A	Very Low
Number of episodes of regurgitation											
1 (Ostorm et al, 2006)	RCT	Very Serious[a, b]	None	Very serious[c]	None	No		-	Mean difference: -0.40 [-0.49, -0.31]	N/A	Very Low

[a] *Effect of cow's milk intolerance not controlled for in analysis*
[b] *25% discontinuation rate across study*
[c] *Wide confidence intervals*
N/A Not Applicable

Table 38: GRADE findings 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[a, b]	None	Serious[c]	Serious[d]		-	-	Mean Difference: -0.77 [-1.16, -0.38]	N/A	Very low

[a] *Randomisation and concealment not described in detail*
[b] *20% discontinuation from study*
[c] *Comparison group had positional management*
[d] *Wide confidence intervals*
N/A Not Applicable

Table 39: GRADE findings 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[a]	None	Serious[b]	None	Yes	-	-	Mean Difference -1.96 [-2.34, -1.58]	N/A	Very low

[a] *Randomisation and concealment not described in detail*
[b] *Comparison group had partially strengthened formula.*
N/A Not Applicable

Table 40: GRADE findings for comparison of cow's milk protein elimination with continued cow's milk diet on the symptoms of GER

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**
Reflux measured using oesophageal pH or impedance monitoring											
Total number of reflux episodes											
1 (Borrelli et al, 2012)	Non-randomised clinical trial	Very serious[a]	None	None	Serious[b]	No	Amino acid formula: Median 65 (range 39 to 87.5)	Standard cow's milk: Median 105 (range 58 to 127.5)	p < 0.001	N/A	Very low
Reflux Index (% of time pH < 4.0)											
1 (Borrelli et al, 2012)	Non-randomised clinical trial	Very serious[a]	None	None	Serious[b]	No	Amino acid formula: Median 3.4 (SD +/- 2.6)	Standard cow's milk: Median 3.6 (SD +/- 2.7)	NS	N/A	Very low

[a] *Non-randomised study design & all children were known to have CMA*
[b] *Could not be calculated*
N/A Not Applicable

Table 41: GRADE findings for comparison of differing feeding volumes on symptoms of GER

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
Reflux measured using oesophageal pH or impedance monitoring											
Total number of reflux episodes											
1 (Sutphen & Dillard, 1988)	Non-randomised crossover clinical trial	Very serious[a, b]	None	None	Serious[c]	No	9 ml/kg mean 8.1 (SD 13.9)	18 ml/kg mean 14.3 (SD 12.5)	p = 0.004	N/A	Very low
1 (Sutphen & Dillard, 1988)	Non-randomised crossover clinical trial	Very serious[a, b]	None	None	Serious[c]	No	9 ml/kg = mean 9.6 (SD 7.2)	27.3 ml/kg = mean 24.4 (SD 20.2)	p = 0.007	N/A	Very low

[a] *Non-randomised study design*
[b] *Variation in how study protocol was applied.*
[c] *Could not be calculated*
N/A Not Applicable

6.2.74 Evidence statements (see Table 35 to Table 41)

6.2.481 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.

6.2.4122 Cow's milk protein diet

One comparative study found that in a group of children age between 6 to 24 months eliminating Cow's milk protein from 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.

6.2.4173 Feeding volumes

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

6.2.15 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).

6.2.16 Evidence to recommendations

6.2.6.21 Relative value placed on the outcomes considered

The GDG confirmed that suggesting to parents and carers that the feed content and administration be changed is very common both primary and secondary care 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.

6.2.6.22 Consideration of clinical benefits and harms

The GDG 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 GDG recommended that before any alterations are made to feed administration by altering the volume and frequency or content of feed that it be first clarified whether the infant or child has a significant problem with regurgitation that is outside what may be expected for the normal population at that particular age. This is information that can be collected relatively easily by health professionals at all levels by taking a history but may be augmented and improved by suggesting that worried parents keep a more detailed diary of regurgitation episodes together with the feed details over several days consecutively. This not only helps the health professional get a clearer idea of what is the range of the problem but can also help clarify to the parents that it is very variable and quite possibly not as serious as they first imagined.

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 breast fed babies essentially feed “on demand” and it is therefore almost impossible to make specific changes to the feed regime of an exclusively breast fed infant. Similarly, no studies comparing breast fed to formula fed infants were identified so although the GDG unanimously advocate exclusive breast feeding for all young infants wherever possible it is impossible to say whether GOR is more likely with either method of feeding.

6.2.6.291 Feed volume

The daily infant requirements for volume of feeds are often discussed on the product packaging but health professionals usually recommend a total volume of around 150 ml / kg per day divided across a number of feeds (e.g. 6 – 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. Corresponding figures for Breast fed infants are understandably impossible to record and breast fed babies basically feed “on demand” sometimes very frequently indeed in the first few weeks of life.

The GDG noted a single non-randomised cross-over study found that a feed volume of 9 ml / kg per feed (which is typically lower than most infants would 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 (i.e. a feeding schedule of more frequent feeds of smaller volume that would keep to appropriate total daily feed volume.)

This evidence matched the GDGs own experience and observation that conversely in infants who are inadvertently overfed an increased feed volume can appear to cause or potentiate regurgitation. However, it was the GDG’s opinion that if the feeding volume must be decreased, then an adequate total volume should be maintained 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 to monitoring a baby's growth which in the UK is well taken care of with the standard surveillance schemes through primary care augmented where necessary by secondary expertise.

The GDG 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.

6.2.6.202 Thickened feeds

The reviewed evidence supported the experience of the GDG 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 to those infants not using them. Similar findings were reported when utilizing 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 GDGs own experience when using thickened feeds to manage GOR.

The GDG discussed the practicalities of using feed thickeners. The GDG noted that there are number of feeding thickening products available; both on prescription and over the counter. These products vary across commercial brands but are basically divided in to either as a pre-thickened formula or a product added to bottle milk. The GDG 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 GDG recommended that feed thickeners should be used as an early, effective and cheap strategy to treat GOR.

6.2.6.203 Cow's 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 Cow's Milk Allergy (CMA) when they underwent a challenge test compared to when they were on an amino acid formula. There was, however, no statistical difference on the effect of cow's milk protein elimination on the pH reflux index. All the infants in this study had confirmed CMA and the GDG 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 GDG protocol had been identified so discussion was then based on clinical experience in the absence of available evidence.

The GDG's experience was that Cow's Milk Protein and Soya Protein elimination with the use of either a change in maternal diet for breast fed infants or an expensive extensively hydrolysed feed / amino acid based feed for bottle fed infants is very widespread practice in the UK for a whole variety of perceived problems in infancy.

Clearly the logical reason for the elimination of Cows Milk or Soya Milk based products must be the presumed diagnosis of Cows Milk / Soya Protein Allergy. It was accepted by the GDG that the area is controversial and not helped by the absence of any sensitive or specific diagnostic test for this form of type 4 / cell mediated hypersensitivity.

Among these situations it was the experience of the GDG that 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 infants with regurgitation with or without

reported distress in bottle fed babies. This practice consumes a not insignificant financial resource when multiplied across the UK.

The GDG concluded that based on RCTs there is no evidence base to support this practice. Further, they feel that there is likely to be a considerable placebo effect and also recognize that these milks are prescribed and are therefore free compared to the standard formula milk that must be purchased by the family in most cases. As a result, once an infant has been started on a prescribed milk substitute there is likely to be a (subconscious) disincentive to revert to the original feed unless the infant is obviously worse off or suffering a side-effect e.g. refuses the substitute or regurgitates even more. This, the GDG postulate may account for why once infants have been started on expensive prescribed milk substitutes it becomes almost impossible for health professionals to accurately gauge their true effect or in many cases stop the feed to assess the effect The GDG therefore feels that there is a pressing need for large, well designed, blinded RCTs to clarify this important question and identifies this issue as “Research Recommendation” from this guideline

Finally, it has also been hypothesised that, in breast fed infants, an elimination of cow’s milk in the mother can be beneficial for problematic reflux in the infant, but no data was found to support this. None of the GDG had any experience of using this strategy for this indication, therefore they concluded that no recommendation could be made on this.

6.2.6.294 Summary of advice

Based on the reviewed evidence, GDG experience and subsequent discussion, the GDG outlined a three staged feeding change schedule for infants who had GOR causing significant distress. The GDG recommended that initially a detailed feeding and regurgitation feeding history should be taken to ensure that an infant was not being given an inappropriate volume of feed in each individual feed, followed by a low threshold to advise reducing the volume of each feed with an increase the feed frequency (if required) and finally to advise thickening the feeds.

6.2.673 Consideration of health benefits and resource uses

The GDG noted that many types of feeding thickeners are available, both commercially in over-the-counter products and also for 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 should be left to the discretion of the pharmacist - taking into account patient preference, local acquisition cost and route of delivery.

6.2.644 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: variation 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 two questions on feeding volume and cow’s milk. The very low quality and lack of available evidence means that a strong recommendation could not be made for these interventions.

6.2.625 Other considerations

6.2.6.531 Breast feeding

The benefit of breast feeding for infants is recognised beyond any doubt. The evidence review did not investigate the merits of breast feeding in comparison with formula feeding for GORD. Therefore, the recommendations in this chapter are only for those children already being formula fed. Furthermore, the recommendations are not applicable to those children

who are being breast fed and who have overt reflux. However, it is the opinion of the GDG that whenever possible all infants should be breast fed.

6.237 Recommendations

6.2.741 Recommendations

24. In formula-fed infants with frequent regurgitation associated with marked distress:

- review the feeding history **and**
- reduce the feed volumes only if excessive for the infant's weight, **then**
- give a trial of either:
  - smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk) **or**
  - thickened formula (for example, containing rice starch, cornstarch, locust bean gum or carob bean gum).

6.2.732 Research recommendations

2. What is the efficacy of cow's milk protein elimination in GOR and/or GORD?

Why this is important

There is a widespread belief that GOR and/or GORD in formula-fed infants is often caused by intolerance to cow's milk. As a result, health professionals often prescribe a trial of hydrolysed formula as a substitute for cow's milk formula. This often leads to infants remaining on hydrolysed formula for extended periods based on a subjective assessment. Because hydrolysed formula is more expensive than cow's milk formula, this has resource implications. However, there is no evidence on the clinical or cost

6.3 Alginates 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 - the 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 preprarations 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 should be borne in mind in 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/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 infants as accumulation may lead to increase 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.

6.3.1 Review question

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

6.3.2 Description of included studies

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), one from Belgium (Buts et al, 1987) and one from Australia (Forbes et al, 1986). We are also aware of an unpublished Cochrane review currently being undertaken. No studies were identified on the use of antacids for the management of GOR/D 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 one study (Miller et al, 1999), infants under 12 months in one study (Del Buono et al, 2005), children up to the age of 3 years in one study (Buts et al, 1987) and children up to the age of 17 years in one study (Forbes et al, 1986).

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

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

- Gaviscon infant liquid: alginic acid with antacid (Forbes et al, 1986): 10ml four times a day for infants, 20ml four times a day for older children.

- Gaviscon: aluminium-containing alginate preparation (2g of alginate per sachet), (Buts et al, 1987)
- Infant Gaviscon: (Miller et al, 1999): the currently available formulation as per BNFc. 225 mg sodium alginate and 87.5 mg magnesium alginate. In breast-fed Infants under 4.5 kg (10lb) – one sachet. In breast-fed Infants over 4.5kg (10lb) – two sachets. In bottle-fed infants 1sachet per 115ml (4 fl oz) of feed. The authors state that this preparation was aluminium–free.
- Infant Gaviscon: consisting of sodium and magnesium alginate (225mg sodium alginate and 87.5 mg magnesium alginate in 225ml 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; parent reported reduction in infant distress. The GRADE table 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.

More details on each individual study can be found in the evidence tables.

6.3.13 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 findings 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[a,b,c,d,e]	None	None	Serious[f]	None	13/42 (31%)	5/46 (11%)	p=0.027[g] Odds ratio [OR] (95% CI): 3.68 (1.18 to 11.44)[h]	-	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[a,b,c,d,e]	None	None	Not assessed[i]	None	n=42 Median (range): 3.0 (0 to 22)	n=46 Median (range): 5.0 (0 to 37)	p=0.009[g]	-	Low
Reported as mean frequency of vomiting/regurgitation episodes after 14 days											
1 (Miller et al 1999)	RCT	Very serious[a,b,c,d,e]	None	None	Not assessed[i]	None	n=42 Mean: 4.5 (Standard deviation [SD] not reported)	n=46 Mean: 6.2 (SD not reported)	p=0.056[g]	-	Low
Adverse outcomes, n (%)											
Functional diarrhoea											
1 (Miller et al	RCT	Very serious[a,b,]	None	None	Very serious[j]	None	6/42 (14.3%)	5/46 (10.9%)	p>0.1[k] OR	-	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
1999)		[c,d,e]							(95% CI): 1.37 (0.38 to 4.86)[h]		
Teething syndrome											
1 (Miller et al 1999)	RCT	Very serious[a,b,c,d,e]	None	None	Very serious[j]	None	5/42 (11.9 %)	3/46 (6.5 %)	p>0.1[k] OR (95% CI): 1.94 (0.43 to 8.66)[h]	-	Very low
Diarrhoea not otherwise specified											
1 (Miller et al 1999)	RCT	Very serious[a,b,c,d,e]	None	None	Very serious[j]	None	1/42 (2.4%)	4/46 (8.7 %)	p>0.1[k] OR (95% CI): 0.26 (0.03 to 2.39)h	-	Very low
Constipation											
1 (Miller et al 1999)	RCT	Very seriousa,b,c,d,e	None	None	Very serious[j]	None	4/42 (9.5%)	1/46 (2.2 %)	p>0.1[k] OR (95% CI): 4.74 (0.51 to 44.20)[h]	-	Very low
Acute nasopharyngitis											
1 (Miller et al 1999)	RCT	Very serious[a,b,c,d,e]	None	None	Very serious[j]	None	3/42 (7.1%)	1/46 (2.2 %)	p>0.1[k] OR (95% CI): 3.46 (0.35 to	-	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
									34.64)[h]		
Colic[l]											
1 (Miller et al, 1999)	RCT	Very serious[a,b,c,d,e]	None	None	Very serious[j]	None	2/42 (4.8%)	3/46 (6.5%)	p>0.1[k] OR (95% CI): 0.72 (0.11 to 4.51)[h]	-	Very low
Parent reported reduction in infant distress											
Reported as parent/guardian assessment of symptoms, n (%)											
1 (Miller et al, 1999)	RCT	Very serious[a,b,c,d,e]	None	None	Serious[i]	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[g] p= 0.0036[g]	-	Very Low

1 *NA - not applicable*
2 [a] *Randomisation not described in detail*
3 [b] *Unclear whether there was adequate allocation concealment*
4 [c] *Unclear whether investigators were blinded to intervention*
5 [d] *Unclear whether investigators were blinded to confounding factors*
6 [e] *20 withdrawals (alginate, n=7; placebo, n=13; p>0.2) due primarily to adverse events (alginate, n=4; placebo,*
7 *n=7) and lack of efficacy (alginate, n=2; placebo, n=3)*
8 [f] *Wide confidence interval (CI crosses 2 zones)*
9 [g] *As reported in the study (Wilcoxon rank sum test)*
10 [h] *Calculated by NCC-WCH technical team based on data reported in the article*
11 [i] *Imprecision could not be investigated due to way result has been reported*
12 [j] *Very wide confidence interval (CI spans 3 zones)*
13 [k] *As reported in article (chi square or Fisher's exact test, as appropriate)*
14 [l] *Reported as adverse event in paper*

Table 43: GRADE findings 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-metry											
Total number of reflux episodes (oesophageal pH <4 for at least 25 seconds) in 24 hours											
1 (Butset al 1987)	RCT	Serious[a,b,c,d,e]	None	None	Serious[f]	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[g] p-value for after placebo versus before placebo: NS[g] Mean Difference [MD] (95% CI): -35.00 (-78.50 to 8.50)[h]	-	Low
Number of reflux episodes greater than 5 minutes											
1 (Butset al 1987)	RCT	Serious[a,b,c,d,e]	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[g]	-	Moderate

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
									p-value for after placebo versus before placebo: NS[g] MD (95% CI): -4.00 (-5.96 to -2.04)[h]		
Percent total reflux (Reflux Index)											
1 (Butset al 1987)	RCT	Serious[a,b,c,d,e]	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[g] p value for after placebo versus before placebo: NS[g] MD (95% CI): -4.00 (-6.56 to -1.44)[h]	-	Moderate
Adverse outcomes (events not specified), n (%)											

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**
1 (Buts et al 1987)	RCT	Serious[a,b,c,d,e]	None	None	Serious[i]	None	n=100/100 (0%)	n=100/100 (0%)	-	-	Low

NS – not significant
[a] *Randomisation method not described in detail*
[b] *Alternate allocation to treatments*
[c] *Not all subjects endoscoped*
[d] *Unclear whether investigators were blinded to intervention*
[e] *Unclear whether investigators were blinded to confounding factors*
[f] *Wide confidence interval (confidence interval of SMD crosses 2 zones)*
[g] *As reported in study*
[h] *Calculated by NCC-WCH technical team based on data reported in the article*
[i] *Imprecision could not be investigated due to way result have been reported*

Table 44: GRADE findings 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-metry											
Number of episodes of GER (esophageal pH <4) in 24 hours											
1 (Forbes et al 1986)	RCT	Serious[a,b,c,d]	None	None	Serious[e]	None	n=10 Mean (SD): 81 (72.7)	n=10 Mean (SD): 49 (34.8)	p: NS[f] MD (95% CI): 32.00 (-18.18 to 82.18)[g]	-	Low
Total duration of acid reflux in minutes											
1 (Forbes et al 1986)	RCT	Serious[a,b,c,d]	None	None	Very serious[h]	None	n=10 Mean (SD): 74 (123.3)	n=10 Mean (SD): 96 (34.8)	p: NS[f] MD (95% CI): -22.00 (-101.26 to 57.26)[g]	-	Very low
Adverse outcomes (events not specified), n (%)											
1 (Forbes et al 1986)	RCT	Very serious[a,b,c,d]	None	None	Not assessed[i]	None	n=100/10 (0%)	n=100/10 (0%)	-	-	Low

NS – not significant
[a] *Method of randomisation not described in detail*
[b] *Unclear whether there was adequate allocation concealment*
[c] *Not all subjects endoscoped*
[d] *Unclear whether investigators were blinded to confounding factors*
[e] *Wide confidence interval (confidence interval of SMD crosses 2 zones)*
[f] *As reported in the study (Wilcoxon signed rank test)*
[g] *Calculated by NCC-WCH technical team based on data reported in the article*
[h] *Very wide confidence interval (confidence interval of SMD crosses 3 zones)*
[i] *Imprecision could not be investigated due to way result have been reported*

Table 45: GRADE findings 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[a,b,c,d]	None	None	Not assessed[e]	None	-	Median difference (placebo -– Gaviscon infant), range: 0.06 (-1.20 to 3.80)	P = 0.784[f]	-	Low
Number of acid reflux events per hour											
1 (Del Buono et al 2005)	RCT	Very Serious[a,b,c,d]	None	None	Not assessed[e]	None	-	Median difference (placebo -– Gaviscon infant), range: -0.02 (-0.55 to 3.94)	p = 0.940[f]	-	Low
Total reflux time per hour (seconds per hour)											

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
1 (Del Buono et al 2005)	RCT	Serious[a,b,c,d]	None	None	Not assessed[e]	None	-	Median difference (placebo -– Gaviscon infant), range: -7.6 (-38.5 to 111.8)	p = 0.096[f]	-	Low

[a] *Method of randomisation not described in detail*
[b] *Unclear whether groups were comparable at baseline (baseline characteristics not reported)*
[c] *Unclear whether groups were comparable for dropout (numbers not reported)*
[d] *Unclear whether groups were comparable for missing data (numbers not reported)*
[e] *Imprecision could not be investigated due to way result have been reported*
[f] *As reported in study (Wilcoxon signed rank test) a Method of randomisation not described in detail*

6.3.4 Evidence statements (see Table 42 to Table 45)

6.3.4.1 ALUMINIUM FREE INFANT GAVISCON (Miller et al, 1999) VERSUS PLACEBO

6.3.4.1.1 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 to infants receiving placebo. This finding was statistically significant. The evidence for this finding was of very low quality.

6.3.4.112 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 to infants receiving placebo. This finding was statistically significant. The evidence for this finding was of 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 to infants receiving placebo. The evidence for this finding was of low quality.

6.3.4.133 Adverse outcomes

Functional diarrhoea

One study did not find a statistically significant difference in the occurrence of functional diarrhoea in infants receiving aluminium free infant Gaviscon compared to infants receiving placebo. The evidence for this finding was of very low quality.

Diarrhoea not otherwise specified

One study did not find a statistically significant difference in the occurrence of diarrhoea not otherwise specified in infants receiving aluminium free infant Gaviscon compared to infants receiving placebo. The evidence for this finding was of very low quality.

Constipation

One study did not find a statistically significant difference in the occurrence of constipation in infants receiving aluminium free infant Gaviscon compared to infants receiving placebo. The evidence for this finding was of very low quality.

Acute nasopharyngitis

One study did not find a statistically significant difference in the occurrence of acute nasopharyngitis in infants receiving aluminium free infant Gaviscon compared to infants receiving placebo. The evidence for this finding was of very low quality.

Colic

One study did not find a statistically significant difference in the occurrence of colic in infants receiving aluminium free infant Gaviscon compared to infants receiving placebo. The evidence for this finding was of very low quality.

6.3.4.144 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 to infants receiving placebo. The evidence for this finding was of low quality.

6.3.4.12 GAVISCON (Buts et al, 1987) VERSUS PLACEBO

6.3.4.2.1 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 to 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 to 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 to infants receiving placebo. This finding was statistically significant. The evidence was of moderate quality.

6.3.4.2.2 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.

6.3.4.13 GAVISCON INFANT LIQUID (Forbes et al, 1986) VERSUS PLACEBO

6.3.4.3.1 Reflux measured using oesophageal pH-metry

Number of episodes of GER (esophageal pH <4) in 24 hours

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

6.3.4.3.2 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.

6.3.4.14 INFANT GAVISCON (Del Buono et al, 2005) VERSUS PLACEBO

6.3.4.4.1 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 to 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 to 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 to infants receiving placebo. The evidence was of moderate quality.

6.3.5 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).

6.3.6 Evidence to recommendations

6.3.6.1 Relative value placed on the outcomes considered

Of the outcomes prioritised by the GDG, 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 GDG listed a number of parent reported outcomes (parent 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[D] in some infants. Finally, they considered adverse outcomes to be important when recommending treatment for potentially mild symptoms.

6.3.6.2 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 milk or a small amount of warm water given before feed. As Gaviscon Infant can be administered with water before conventional feeds, it can used in women who exclusively breast feed, 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 up to 2 years of age. 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 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 GDG noted that the preparations currently available were quantitatively different from those used in two 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 GDG considered these differences to be important and considered the findings of these studies were no longer relevant. The GDG therefore focused on the studies by Miller et al and Del Buono et al.

The study by Miller et al, showed that the number of regurgitation episodes in a 24 hours period was statistically lower in those treated with Gaviscon Infant compared those treated with placebo, however 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 GDG did not consider this outcome to have clinical relevance.

The study by Del Buono et al., used dual impedence 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 GDG 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 GDG 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 GDG noted that neither study included patients older than 1 year (up to 12 months and 6 months respectively) and have only made recommendations for the use of alginates in infants.

The GDG were 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 GDG concluded that whilst the evidence was limited, with only the Millar study examining frequency of overt reflux, it matched their clinical experience. The GDG 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 patient and professional, the review can happen via telephone or at a face-to-face consultation. After this therapeutic trial the infant is reviewed and the need for ongoing treatment should be agreed upon. The effect of an alginate is immediate; therefore the benefit of a course of alginates would be evident at this review. If, after one or two weeks, there is no effect 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 feed thickening agent recommended. In the absence of comparative evidence the GDG chose to recommend that a therapeutic trial of a feeding change should be tried first, if this does not show any benefit then alginates can be considered. The rationale for offering alginates as a second line treatment was because feed thickeners are a cheaper intervention; where there is no evidence to support a cost effectiveness assessment, the cheaper option should be offered first. Furthermore, the GDG 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 GDG highlighted that this order of treatment

should only be applied in infants that are bottle fed. Feeding changes are not appropriate in breast fed infants and in this situation alginates should be considered earlier.

No evidence was identified for the use of antacids to treat problematic overt regurgitation in children or young people. Furthermore, the GDG 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 GDG recommended that antacids and antacid/alginate combinations should be offered to young people suffering from heartburn. This is extrapolated from NICE clinical guideline 17: Dyspepsia (published 2004 with update under development and expected to be published September 2014). Antacids should only be offered in young people who have gone through puberty; the effect in younger children is unknown and therefore recommendations made based on adult evidence are inappropriate.

6.3.63 Consideration of health benefits and resource uses

A description of the treatment costs associated with treatment are provided in appendix A: Health Economics.

6.3.64 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/children. The other sources of bias included poorly defined methods of randomisation and analysis, and serious imprecision in results. These limited the GDG's ability to make clear conclusions based on the evidence.

6.3.7 Recommendations

6.3.71 Recommendations

25. In breast-fed infants with frequent regurgitation associated with marked distress, 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.

26. In formula-fed infants, if small, frequent feeds and thickening the formula are unsuccessful, try stopping the thickening agent 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.

6.3.72 Research recommendations

No research recommendations in this area.

7 Pharmacological treatment of GORD

Drug treatments are usually considered for GORD after attempting the more conservative treatments, such as feeding changes in infants or alginates. The groups of medications being investigated in this chapter are broadly divided in to those that may promote gastric emptying and enhance upper gut motility (pro-kinetics) and those which reduce gastric acid secretion (the H2 receptor antagonists or the more modern Proton Pump Inhibitors).

Before prescribing drug treatment it is important, ethical and logical that professionals adhere to the aphorism “Primum non nocere” roughly translated to “first, do no harm” by always considering the indication, 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 together with the availability of acceptable and reasonably priced preparations.

7.1 Review question

Effectiveness of 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?

7.2 Description of included studies

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 RCTs, with 3 using a cross-over design (Omari et al, 2007; Moore et al, 2003; Tolia et al, 1989).

Definition of GOR/D varied between studies, but 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; Winter et al 2012; Moore et al, 2003; Davidson et al, 2013; Hussain et al , 2014) two studies the effect of H_2-Receptors antagonists (Simeone et al, 1997; Cucchiara et al, 1989), six 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).

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), five in Italy (Cresci et al, 2008; Carroccio et al, 1994; Simeone et al, 1997; Cucchiara et al, 1989; Cucchiara et al, 1993), two in Australia

(Moore et al, 2003; Davidson et al, 2013) and one 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: 4 to 51 weeks (Orenstein et al, 2009), 34 to 40 weeks postmenstrual age (Omari et al, 2007), 3 to 10.2 months (Moore et al, 2003), 4.9 (2.6); 4.9 (3.2) (Winter et al, 2012), 0.5 to 12 years (Simeone et al, 1997), 29.03 months (39.73) (Cucchiara et al, 1989), 21 to 1215 days (Leung et al, 1984), Mean; range): 0.5 to 11.3 years (Bines et al, 1992), 1 to 19 months (Carroccio et al, 1993), 122 days (79) (Bellissant et al, 1997), 24.7 days (13.7) (Cresi et al, 2008) and 1 to 9 months (Tolia et al, 1989), 48.1 days (SD 29.8) (Davidson et al, 2013); 1 to 11 months (Hussain et al, 2014).

One study was included that compared H_2 receptor antagonists with Proton Pump Inhibitors (Cucchiara et al, 1993). The study compared high-dose Ranitidine with Omeprazole in the management of GORD refractory to 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.

7.153 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 findings for comparison of PPIs with placebo for the management of GORD in infants.

Quality assessment							Number of children		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[a]	None	None	Not assessed[b]	None	Lansoprazole: N = 81, -14%	n = 81, -11%	NS[c]	N/A	Moderate
Frequency of vomiting											
1 (Omari et al, 2007)	RCT, Crossover	Very Serious[a,d]	None	None	Not assessed[b]	None	Omeprazole: Median 8.5	Median 6.5 (IQR 3 to	NS[c]	N/A	Low

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proton Pump Inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
							(IQR 7 to 22.8)	14.3)			
Vomiting											
1 (Davidson et al, 2013)	RCT	Serious [e]	None	Serious [f]	Very serious [g]	None	Esomeprazole: Mean 5.21 (SD 6.75)	Mean 4.87 (SD 5.93)	MD 0.34 [-3.15, 3.83]	N/A	Very low
Frequency of regurgitation											
1 (Hussain et al, 2014)	RCT	Very Serious [a,h]	None	Serious[i]	Not assessed [b]	None	Raberprazole: NR	NR	NS[c]	N/A	Very Low
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
Number of acid GER episodes											
1 (Omari et al, 2007)	RCT, Crossover	Very Serious [a,d]	None	None	Not assessed [b]	None	Omeprazole: 59.6 (SE 26.7)	119.4 (SE 20.9)	p < 0.05[c]	N/A	Moderate
Number of acid GER episodes lasting longer than 5 minutes											
1 (Omari et al, 2007)	RCT, Crossover	Very Serious [a,d]	None	None	Not assessed [b]	None	Omeprazole: 3.0 (SE 2.0))	8.0 (SE 2.1	a < 0.01[c]	N/A	Moderate
Longest acid GER episode (minutes)											
1 (Omari et al, 2007)	RCT, Crossover	Very Serious [a,d]	None	None	Not assessed [b]	None	Omeprazole: 16.3 (SE 8.0)	48.6 (SE 10.1)	p < 0.01[c]	N/A	Moderate
% time pH < 4.0											
1 (Omari et al, 2007)	RCT, Crossover	Very Serious [a,d]	None	None	Not assessed [b]	None	Omeprazole: 4.9 (SE 3.4)	19.0 (SE 4.5)	p < 0.01[c]	N/A	Moderate
1 (Moore et al, 2003)	RCT, Crossover	Serious [a,j]	None	Serious[k]	Not assessed [b]	None	Omeprazole: 1.0 (SD 1.3)	5.3 (SD 4.9)	p < 0.01[c]	N/A	Low
Adverse outcomes											

Quality assessment							Number of children		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 events											
1 (Orenstein et al, 2009)	RCT	Serious[a]	None	None	None	None	Lansoprazole: 50[l]	37[l]	NS[c]	N/A	Moderate
1 (Hussain et al, 2014)	RCT	Very Serious [a, h]	None	Serious[i]	None	None	Rebeprazole: 83/178	42/89	NS[c]	N/A	Very Low
Serious adverse events											
1 (Orenstein et al, 2009)	RCT	Serious[a]	None	None	None	None	Lansoprazole: 10[m]	2[m]	p = 0.032 [c]	N/A	Moderate
1 (Omari et al, 2007)	RCT, Crossover	Very Serious [a,d]	None	None	None	None	Omeprazole: 0	0	NS[c]	N/A	Low
1 (Davidson et al, 2013)	RCT	SeriousI[e]	None	Serious[f]	None	None	Esomeprazole: 6	9	NS[c]	N/A	Low
Parent reported reduction in infant distress											
Global severity index (parent reported improved at 4 weeks)											
1 (Orenstein et al, 2009)	RCT	Serious[a]	None	None	Not assessed [b]	None	Lansoprazole: 45	44	NS[c]	N/A	Moderate
Improvement in validated reflux questionnaire											
Visual Analogue Scale by parents of infants irritability											
1 (Moore et al)	RCT, Crossover	Serious[j]	None	Serious[k]	Not assessed [b]	None	Omeprazole: 5.0 (SD 3.1)	5.9 (SD 2.1)	p = 0.214[c]	N/A	High
I-GERQ-R											
1 (Hussain et al, 2014)	RCT	Very Serious[j]	None	Serious[i]	Not assessed [b]	None	Raberprazole: NR	NR	NS[c]	N/A	Very Low
Parent satisfaction with this intervention											

Quality assessment							Number of children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proton Pump Inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality
Responder rate (>50% reduction in feeding or crying symptoms from baseline)											
1 (Orenstein et al, 2009)	RCT	Serious[a]	None	None	Not assessed[b]	None	Lansoprazole 44%	44%	NS[c]	N/A	Moderate
Discontinued due to non-efficacy											
1 (Orenstein et al, 2009)	RCT	Serious[a]	None	None	Very serious[o]	None	Lansoprazole: 28 of 81	29 of 81	0.97 [0.64, 1.47]	N/A	Low
Discontinued due to worsening symptoms											
1 (Winter et al, 2012)	RCT	Serious[n]	None	Serious[p]	Very serious[o]	None	Esomeprazole: 15 of 39	20 of 41	0.79 [0.48, 1.31]	N/A	Very Low

CI confidence interval; RCT randomised controlled trial; NS not significant, NA not applicable; MD mean difference; NR not reported; SE standard error; GER gastro-esophageal reflux
NS Non significant at p < 0.05.
N/A Not applicable – could not be calculated on data available.

a Poor reporting of results that not all GRADE items could be assessed
b Reporting of results did not allow imprecision to be calculated.
c As reported in the study.
d Small sample size; no washout period during crossover between treatments.
e Groups unbalanced at baseline; small sample size
f Study included neonates only
g SMD confidence intervals cross several categories on Cohen effect size. MD presented in table as more relevant.
h Method of randomisation not described in detail
i Only included infants in whom PPIs were effective in a pre-randomisation phase.
j Method of randomisation not explained in detail; no washout period; results from before crossover
k Infants had GERD and were irritable.
l Reported events were: Infection – URI, ear, LRTI, viral, constipation, eczema, fever, respiratory tract congestion, rhinorrhea, candidiasis, diarrhea, vomiting.
m Reported events were: Lower respiratory infection, diarrhea, Ileua, dehydration, otitis media, upper respiratory infection, epididymal infection, arachnoid cyst, febrile convulsion, klebsiella infection.
n Method of randomisation and concealment not explained in detail.
o Confidence intervals cross several +/- 0.25 RR
p Infants had to respond to treatment to enter the randomised part of the study.

Table 47: GRADE findings for comparison of H_2 receptor antagonists with placebo for the management of GORD in infants.

Quality assessment							Number of Children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
Reduced frequency of overt regurgitation											
Regurgitation at 4 weeks											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Mean 1.3 (SD 1.1)	Mean 2.2 (SD 1.3)	N/A[b]	N/A	Very low
Vomiting at 4 weeks											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Mean 0.8 (SD 0.9)	Mean 2.1 (SD 1.1)	N/A[c]	N/A	Very low
Regurgitation at 8 weeks											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Mean 0.3 (SD 0.7)	Mean 1.7 (SD 1.4)	N/A[b]	N/A	Very Low
Vomiting at 8 weeks											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Mean 0.4 (SD 0.7)	Mean 1.6 (SD 1.7)	N/A[c]	N/A	Very Low
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
% of reflux episodes (Reflux Index)											
1 (Simeone et al, 1997)	RCT	Very serious a	None	None	Not assessed[k]	None	Nizatidine: Median 4.3 (range 1.5 to 11.2)	Median 10.4 (4.1 to 18.8)	N/A[d]	N/A	Very Low
Number of reflux episodes											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Median 85.8 (range 42	Median 123 (range 32 to 360)	N/A[d]	N/A	Low

Quality assessment							Number of Children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
							to 227)				
Number of reflux episodes > 5 minutes											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Median 1.7 (range 0 to 6)	Median 5.4 (range 2 to 10)	N/A[d]	N/A	Very low
Duration time of longest episode											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	Not assessed[k]	None	Nizatidine: Median 11.8 (range 4 to 40)	Median 25.1 (range 3 to 73)	N/A[d]	N/A	Very low
Resolution of oesophagitis - endoscope											
Esophagitis score[g]											
1 (Cucchiara et al, 1989)	RCT	Serious[e]	None	None	Not assessed[k]	None	Cimetidine: Mean 1.6 (SD 2.43)	Mean SD 5.43 (3.81)	N/A[f]	N/A	Low
Esophagitis score improved[g]											
1 (Cucchiara et al, 1989)	RCT	Serious[e]	None	None	None	None	Cimetidine: 16 of 17	9 of 15	RR 1.57 [1.02, 2.41]	N/A	Moderate
Endoscopy score normal[h]											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	None	None	Nizatidine: 5 of 12	2 of 12	RR 2.50 [0.60, 10.46]	N/A	Low
Histology score normal[i]											
1 (Simeone et al, 1997)	RCT	Very serious[a]	None	None	None	None	Nizatidine: 9 of 12	3 of 12	RR 3.00 [1.07, 8.43]	N/A	Low
Adverse outcomes											
1 (Cucchiara et al,	RCT	Serious[e]	None	None	None	None	Cimetidine: 0	0	NS[j]	N/A	Moderate

Quality assessment							Number of Children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
1989)											
Improvement in validated reflux questionnaire											
Clinical score											
1 (Cucchiara et al, 1989)	RCT	Serious[e]	None	None	Not assessed[k]	None	Cimetidine: Mean 5.00 (SD 4.36)	Mean 9.46 (SD 4.86)	N/A[f]	N/A	Low
% improvement in clinical score from baseline											
1 (Cucchiara et al, 1989)	RCT	Very Serious[e]	None	None	Not assessed[k]	None	Cimetidine: Mean -67.39% (SD 23.17)	Mean -29.57% (SD 30.31)	p < 0.01[j]	N/A	Low

H_2RA H_2 receptor antagonists; CI confidence interval; RCT; randomised controlled trial; SD standard deviation; NA not applicable; RR relative risk
NS Non significant at p< 0.05
N/A Not applicable – could not be calculated on data available
a 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.
b 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.
c 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.
d No comparative results presented. Significantly reduced in treatment group compared to baseline, but not the placebo group.
e Method of randomisation and allocation concealment not explained in detail. Poor reporting of study results so GRADE items could not be assessed.
f Based on a categorical score 0 to 9 so cannot be analysed a continuous variable. Reduced from baseline in intervention group but not placebo.
g Scored from 0 to 9 – normal mucosa, mild degree, moderate degree, severe degree
h Classified as "Normal, erithema and edema, erythema and friability, erosions."
I Classified as "Normal, mild or moderate histology."
j As reported by authors
k Reporting of results did not allow imprecision to be calculated.

Table 48: GRADE findings for comparison of prokinetics (metoclopramide and domperidone) with placebo for the management of GORD in infants.

Quality assessment	Number of Children	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prokinetic	Comparator	Relative (95% CI)	Absolute (95% CI)	
Reduced frequency of overt regurgitation											
1 (Leung et al, 1984)	RCT	Very serious[a]	None	None	Not assessed[b]	None	Metoclopramide: 1.6 (SD 2.0)	Not reported	p < 0.05[c]	N/A	Very low
Reflux measured using oesophageal pH-monitoring or impedance monitoring											
% of reflux episodes < 4.0											
1 (Bines et al, 1992)	RCT	Very serious[d]	None	None	Not assessed[b]	None	Domperidone: Mean 11.8 (SD not reported)	Mean 15.9 (SD not reported)	NS[c]	N/A	Very Low
1 (Carroccio et al, 1993)	RCT	Serious[e]	None	None	Not assessed[b]	None	Domperidone: Median 8 (range 2 to 35)	Median 9 (range 3 to 40)	NS[c]	N/A	Low
1 (Bellissant et al, 1997)	RCT	Serious[e]	None	None	Very serious[f]	None	Metoclopramide: Mean 6.7 (SD 9.2)	Mean 8.1 (SD 11.7)	MD -1.40 [-7.99, 5.19]	N/A	Low
1 (Tolia et al, 1989)	RCT, crossover	Very serious[g]	None	None	Not assessed[b]	None	Metoclopramide: Median 10.3 (range 2.4 to 22.8)	Median 13.4 (2.8 to 30.5)	p < 0.001[c]	N/A	Low
Number of reflux episodes < 4.0											
1 (Bines et al, 1992)	RCT	Very serious[d]	None	None	Not assessed[b]	None	Domperidone: 26 (SD not reporter)	28 (SD not reported)	p = 0.001[b]	N/A	Very Low
1 (Carro	RCT	Serious[e]	None	None	Not asse	None	Domperido	Median	N/S[b]	N/A	Moderate

Quality assessment							Number of Children		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prokinetic	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality
ccio et al, 1993)					ssed[b]		ne: median 48.5 (range 2 to 181)	68 (range 38 to 130)			
1 (Cresi et al, 2008)	RCT	Serious[e]	None	None	Not assessed[b]	None	Domperidone: NR	NR	p < 0.05[c]	N/A	Low
1 (Bellissant et al, 1997)	RCT	Serious[e]	None	None	Very serious[f]	None	Metoclopramide: 63 (SD 136)	43 (SD 26)	MD 20.00 [-42.20, 82.20]	N/A	Moderate
1 (Tolia et al, 1989)	RCT, crossover	Very serious[g]	None	None	Not assessed[b]	None	Metoclopramide: 25.0 (SD 3.4)	22.4 (SD 2.5)	NS[c]	N/A	Moderate
Duration time of longest episode											
1 (Bines et al, 1992)	RCT	Very serious[d]	None	None	Not assessed[b]	None	Domperidone: 12.6	20.9	NS[c]	N/A	Very low
1 (Carroccio et al, 1993)	RCT	Serious[e]	None	None	Not assessed[b]	None	Domperidone: Median 16 (range 2 to 51)	Median 33.5 (range 8 to 103)	NS[c]	N/A	Low
1 (Bellissant et al, 1997)	RCT	Serious[e]	None	None	Very serious[g]	None	Metoclopramide: Mean 18 (SD 30)	Mean 15 (SD 17)	MD 3.00 [-12.41, 18.41]	N/A	Moderate
Number of reflux episodes > 5 minutes											
1 (Carroccio et al, 1993)	RCT	Serious[e]	None	None	Not assessed[b]	None	Domperidone: Median 7.5 (range 0 to 16)	Median 6 (range 1 to 20)	NS[c]	N/A	Low

Quality assessment							Number of 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[e]	None	None	Serious[h]	None	Metoclopramide: Mean 1.9 (SD 3.0)	Mean 3.0 (SD 3.5)	MD -1.10 [-3.14, 0.94]	N/A	Moderate
1 (Tolia et al, 1989)	RCT, crossover	Very serious[f]	None	None	Not assessed[b]	None	Metoclopramide: 2.6 (SD 0.5)	2.0 (SD 0.3)	NS[c]	N/A	Low
Adverse outcomes											
Diarrhea											
1 (Bines et al, 1992)	RCT	Very serious[d]	None	None	None	None	Domperidone: 4	2	NS[c]	N/A	Low
Any adverse event											
1 (Carroccio et al, 1993)	RCT	Serious[e]	None	None	None	None	Domperidone: 0	0	NS[c]	N/A	Moderate
1 (Tolia et al, 1989)	RCT, crossover	Very serious[f]	None	None	None	None	Metoclopramide: 0	0	NS[c]	N/A	Low
Any adverse event leading to discontinuation											
1 (Bellissant et al, 1997)	RCT	Serious[e]	None	None	None	None	Metoclopramide: 3 of 19	1 of 20	NS[c]	N/A	Moderate

CI confidence interval; RCT randomised controlled trial; SD standard deviation; NA not applicable; NS not significant;
NS Non significant at p < 0.05
N/A Not applicable – could not be calculated on data available
a 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.
b Data not reported so imprecision could not be calculated
c As reported in the study
d 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.
e Method of concealment not described in detail. Poor reporting of data so not all GRADE items could be assessed.
f wide confidence intervals - SMD crosses +/- 0.5 effect size
g 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.
h wide confidence intervals – SMD crosses -0.5 and 0 effect size

Table 49: GRADE findings for comparison of Proton pump inhibitors compared with H_2 receptor antagonists for managing gastro-oesophageal reflux symptoms

Quality assessment							Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	PPI	Relative (95% CI)	Absolute (95% CI)	Quality
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[a,b,c,d,e]	None	Serious[f]	Not assessed[g]	None	Median 59.6 (range 2 to 83.4)	Median 61.9 (range 34 to 99)	NS[h]	-	Very Low
Intragatric 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[a,b,c,d]	None	Serious[f]	Not assessed[g]	None	Median 26.2 (range 0.35 to 95.6)	Median 61.5 (range 7.2 to 98.4)	NS[h]	-	Very Low
Intragatric 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[a,b,c,d]	None	Serious[f]	Not assessed[g]	None	Median 22.3 (range 2.1 to 72.8)	Median 29.0 (range 16.4 to 62.8)	NS[h]	-	Very Low
Median intragstric pH % improvement from baseline (Better indicated by higher values)											
1 (Cucchiara et al, 1993)	randomised trials	very serious[a,b,c,d]	None	Serious[f]	Not assessed[g]	None	Median 37.4 (range 0 to 56.7)	Median 60.1 (range 9.3 to 81)	P < 0.05[h]	-	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[a,b]	None	Serious[f]	Very serious[i]	None	8/13 (61.5 %)	9/12 (75%)	RR 0.82 (0.48 to 1.41)	-	Very Low
Adverse events requiring discontinuation											

Quality assessment							Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	H_2RA	PPI	Relative (95% CI)	Absolute (95% CI)	Quality
1 (Cucchiara et al, 1993)	randomised trials	very serious[a,b]	none	Serious[f]	None	none	0/13 (0%)	0/12 (0%)	NS[h]	-	Very Low
Improvement in validated reflux questionnaire											
60% or more decrease in symptom score - Ranitidine vs. Omeprazole											
1 (Cucchiara et al, 1993)	randomised trials	very serious[a,b]	None	Serious[f]	very serious[f]	None	9/13 (69.2 %)	10/12 (83.3 %)	RR 0.83 (0.53 to 1.29)	-	Very Low
GOR symptoms score (; range of scores: 0-45; Better indicated by lower values)											
1 (Cucchiara et al, 1993)	randomised trials	very serious[a,b,c,d]	None	Serious[f]	Not assessed[g]	None	Median 9.0	Median 9.0	NS[h]	-	Very Low

H_2RA H_2 receptor antagonists; PPI protein pump inhibitor; CI confidence interval; NS not significant; RR relative risk; GOR gastro-oesophageal reflux
a High dropout rate
b Method of randomisation not defined
c Small sample size
d Data reported as medians due to skewness
e poor reporting
f Study examining children who had failed previous treatment
g imprecision not assessed
h as reported in study
i Wide confidence intervals crossing no effect and +/- 0.25

7.1.4 Evidence statements (see Table 46 to Table 49)

7.1.4.1 Proton Pump Inhibitors compared to placebo

Six studies were included in this review.

7.1.4.1.1 Reduced frequency of overt regurgitation in infants.

Four studies found that frequency of overt regurgitation did not differ in infants who received PPI compared to patients who received placebo for the treatment of pH confirmed GORD.

7.1.4.1.2 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 patients who received PPIs compared with patients who received placebo for the treatment of pH confirmed GORD.

7.1.4.13 Resolution of oesophagitis

Not reported

7.1.4.14 Resolution of faltering growth

Not reported

7.1.4.15 Adverse outcomes

Four studies found that adverse events did not differ in patients who received PPI compared to patients who received placebo for the treatment of pH confirmed GORD.

7.1.4.16 Parent reported reduction in infant distress

One study found that parent-reported reduction in distress did not differ in patients who received PPI compared to patients who received placebo for the treatment of pH confirmed GORD.

7.1.4.17 Improvement in validated reflux questionnaire

One study found that irritability score did not differ in patients who received PPI compared to patients who received placebo for the treatment of pH confirmed GORD.

7.1.4.18 Parent satisfaction with this intervention

Two studies found no difference in discontinuation rates in patients who received PPI compared to patients who received placebo for the treatment of pH confirmed GORD. The evidence for these findings was from high to low quality.

7.1.5 H_2 receptor antagonists compared to placebo in infants

7.1.5.1 Reduced frequency of overt regurgitation

One study found that compared to baseline figures that regurgitation and vomiting were reduced more in patients who received H_2 receptor antagonists than those receiving placebo. The evidence for these findings was of very low quality.

7.1.5.2 Reflux measured using oesophageal pH-monitoring or impedance monitoring

One study found that compared to baseline figures that pH monitoring indices were reduced more in patients who received H_2 receptor antagonists than those receiving placebo. The evidence for these findings was of very low quality.

7.1.5.3 Resolution of oesophagitis

Two studies found that endoscopic and histological feature of oesophagitis were reduced in patients who received H_2 receptor antagonists compared to those who received placebo. The quality of the evidence for this finding was moderate to very low.

7.1.5.4 Resolution of faltering growth

Not reported

7.1.5.5 Adverse outcomes

One study found no difference in adverse events reported by parents whose children received H_2-Receptors antagonists or placebo.

7.1.5.6 Parent reported reduction in infant distress

Not reported.

7.1.4.217 Improvement in validated reflux questionnaire

One study found that improvement in clinical score was greater in children who received H_2-receptors antagonists compared to infants who received placebo. This evidence was very low quality.

7.1.4.258 Parent satisfaction with this intervention

Not reported

7.1.473 Prokinetics (metoclopramide or domperidone) compared to placebo

7.1.4.381 Reduced frequency of overt regurgitation

One study found that frequency of regurgitation was reduced in infants who received prokinetics compared to infants who received placebo. The evidence for this finding was very low quality.

7.1.4.322 Reflux measured using oesophageal pH-monitoring or impedance monitoring

Three studies found that there was no difference in pH outcomes in infants who received prokinetics compared to infants who received placebo. Two studies found that pH-monitoring outcomes were improved in infants who received prokinetics compared to infants who received placebo. The quality of the evidence for this finding was moderate to very low.

7.1.4.373 Resolution of oesophagitis

Not reported.

7.1.4.394 Resolution of faltering growth

Not reported.

7.1.4.315 Adverse outcomes

Four studies reported no difference in adverse events between infants who received prokinetics or placebo.

7.1.4.346 Parent reported reduction in infant distress

Not reported

7.1.4.367 Improvement in validated reflux questionnaire

Not reported

7.1.4.388 Parent satisfaction with this intervention

Not reported

7.1.404 H_2 receptor antagonists compared to PPIs

7.1.4.411 Reduced frequency of overt regurgitation

Not reported

7.1.4.412 Reflux measured using oesophageal pH-monitoring or impedance monitoring

Oesophageal pH <4.0 (% improvement from baseline)

One study found no statistically significant difference in improvement based on oesophageal pH<4.0 between children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

Intragastric pH < 2.0 (% improvement from baseline)

One study found no statistically significant difference in improvement on intragastric pH<2.0 improvement between children with refractory GORD who received high dose ranitidine (H_2 Receptor Antagonist) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

Intragastric pH < 4.0 (% improvement from baseline)

One study found no statistically significant difference in improvement on intragastric pH<4.0 improvement between children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with children 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 children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

7.1.4.423 Resolution of oesophagitis

One study found no statistically significant difference in oesophagitis healing between children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

7.1.4.434 Resolution of faltering growth

Not reported.

7.1.4.445 Adverse outcomes

One study found no statistically significant difference in reported adverse events requiring discontinuation of treatment between children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

7.1.4.456 Parent reported reduction in infant distress

Not reported

7.1.4.467 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 symptoms score between children with refractory GORD who received high dose ranitidine (H_2 receptor

antagonists) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

GOR symptoms score % improvement from baseline

One study found no statistically significant difference in GOR symptom score between children with refractory GORD who received high dose ranitidine (H_2 receptor antagonist) compared with children with refractory GORD who received omeprazole (proton pump inhibitor). The evidence for this finding was of very low quality.

7.1.4.4.8 Parent satisfaction with this intervention

Not reported

7.1.5 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).

7.1.6 Evidence to recommendations

7.1.6.1 Relative value placed on the outcomes considered

The primary outcomes outlined by the GDG 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 GDG 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 Receptors antagonists, proton pump inhibitors, and prokinetics.

7.1.6.2 Consideration of clinical benefits and harms

The GDG examined the evidence for each review question separately and debated what recommendations could be made.

7.1.6.2.1 H2 receptor antagonists

One RCT reported outcomes for overt regurgitation, 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 GDG noted that no studies were identified that used ranitidine, which the most commonly prescribed H_2RA agent in the UK. However, it was the clinical opinion of the GDG that the effects of all H_2 receptor antagonists are similar and that the data found for one type of H_2 receptor antagonists treatment could be applied to all H_2 receptor antagonist treatments.

The GDG's own experience matched the evidence. The GDG agreed that H_2 receptor antagonists were of benefit for the management of reflux oesophagitis, but would 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.

7.1.6.232 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 GDG to conclude that PPIs have a similar effect and therefore outcomes found for one drug would apply to others. The GDG agreed with the evidence and concluded that they could be used to manage reflux oesophagitis, but should not be used to manage the frequency of overt regurgitation.

In addition, the GDG discussed the use of PPIs to manage heartburn in young people. The GDG had not outlined this as a specific outcome for the review, but were aware that it was the most common reflux-related symptom reported by young people and adults. The GDG highlighted evidence for the effectiveness is shown in RCTs examining the effectiveness of PPIs on heartburn in an adult population. The GDG therefore recommended that a PPI could be offered to children and young people complaining of heartburn. However, the GDG emphasised that this should be for a trial of 4 weeks to avoid unnecessary long-term use followed by review and consideration of the need for referral for a possible endoscopy depending on the outcome of treatment i.e 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 GDG concluded that it was not unreasonable in some instances to treat infants with either an H2RA 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 or otherwise unexplained faltering growth. The GDG 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 GI endoscopy and biopsy under general anaesthetic in a tertiary gastroenterology unit. However, the GDG very clearly stipulate that such treatment must be reviewed regularly with a low threshold for referral with a view to consideration of an endoscopy dependent on outcome.

A major point of discussion for the GDG 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 either using water or sodium bicarbonate. This is difficult for the parents or carers and often unpleasant for the infants and children. Very occasionally and at great cost liquid preparations of PPI can be prepared in the UK and the GDG were unable to comprehend why a liquid preparation is readily and cheaply available in the US but not in the UK. 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 this does not appear to have been successful.

7.1.6.253 Proton pump inhibitors compared with H2 receptor antagonists

Evidence from one RCT found no difference in outcome between PPIs or H_2 receptor antagonists, but both improved symptom scores.

The GDG agreed with these findings of the review. It was the experience of the GDG that in most cases the use of a PPI or a H_2 receptor antagonist will have similar outcomes; they are both acid supressing agents (although the pharmacological mechanisms differ). The GDG

concluded that the decision of which to use should be based on practical considerations, such as administration and local acquisition costs.

7.1.6.234 Prokinetics

Evidence from RCTs was available for domperidone and metoclopramide, however, these reported mixed results in terms of efficacy. One RCT found a statistically significant reduction in overt regurgitation and another two RCTs reported reduced acid reflux episodes based on 24-hour pH monitoring. However, the three other RCTs found no difference in acid reflux episodes. In addition, only one of the five 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 GDG 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 GDG was aware of specific safety advice with regards for domperidone and metoclopramide. In August 2013, the European Medicines Agency released a statement that 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, and those taking CYP3A4 inhibitors, and those adults taking more than 30mg as a daily oral dose. The GDG concluded that if metoclopramide or domperidone were used then caution should be taken and therefore initiation of treatment should only be offered by health care professionals who can make individual assessments on the cardiac risk and potential benefit on a case by case basis.

The GDG concluded that if domperidone and metoclopramide were to be offered, then it 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 health care professionals.

The GDG 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 had been identified for these drugs, and the pharmacodynamics of these agents differ from domperidone and metoclopramide. The GDG knew that erythromycin was also in widespread use in the NHS and was being used in similar indications as a prokinetic. However, the GDG was not aware of bethanechol or baclofen being used to manage GORD in children or young people.

7.1.6.33 Consideration of health benefits and resource uses

The GDG were 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 GDGs 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. Therefore, the GDG 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 GDG could not specify which individual preparation to use. Therefore, the GDG concluded that cost and practical application should be taken into account. In the case of PPIs, the GDG highlighted that liquid preparation was the simplest to

administer in practice to young children, but also the most costly (see Appendix A: Health Economics).

7.1.6 Quality of evidence

All studies included studies 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 reanalysis and meta-analysis could not be undertaken. Only one 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 the method of reporting, and this limited the interpretation of the evidence.

7.1 Recommendations

7.1.1 Recommendations

27. 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.

28. Consider a 4-week trial of an H_2RA or a PPI for infants, young children who are unable to verbally express their symptoms and those with a neurodisability and/or communication difficulties who have overt regurgitation with one or more of the following:

- unexplained feeding difficulties (for example, refusing feeds, gagging or choking)
- distressed behaviour
- faltering growth.

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

30. Assess the response to PPI or H_2RA treatment at 4 weeks, and think about referral for specialist assessment and possible endoscopy if the symptoms:

- do not resolve **or**
- recur when treatment is stopped.

31. When choosing between H2RAs and PPIs 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.

32. Treat endoscopically determined oesophagitis with an H_2RA or PPI.

33. Repeat endoscopy may be needed after PPI or H_2RA therapy to guide treatment and confirm mucosal healing.

34. 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.

7.1.712 Research Recommendations

2 No research recommendations in this area.

3

8 Enteral feeding for GORD

Enteral tube feeding involves the artificial delivery of nutrition directly in to 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 (NJT) tube in to 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/D 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. In these cases they can receive supplemental nutrition via the enteral route e.g. children with cystic fibrosis, metabolic disease or chronic liver / kidney / heart disease. 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 while swallowing, airway protection or energy deficit problems and GORD can be linked they remain distinct problems in the same child. Therefore, enteral tube feeding is frequently being used as a supportive treatment for an alternative reason in a child with GORD as opposed to as a primary treatment for GORD in that particular child.

Enteral tube feeding can only really be considered as a primary, specific intervention for GORD in the following three limited situations:

- The NG delivery of small volume frequent feeds or the NG 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.

8.1 Review question

How effective is enteral tube feeding in the management of GOR/GORD?

8.2 Description of included studies

No comparative studies were identified that met the inclusion criteria or outcomes outlined by the GDG.

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.

8.1.13 Evidence profile

None

8.1.14 Evidence statements

None

8.1.15 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).

8.1.16 Evidence to recommendations

8.1.16.1 Relative value placed on the outcomes considered

The primary outcomes outlined by the GDG 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.

8.1.16.2 Consideration of clinical benefits and harms

No evidence was identified that met the predefined inclusion criteria, and the GDG were unaware of any studies that could be included. Therefore, discussion was based on the GDGs own experience and knowledge of evidence from related areas. The GDG reiterated that the remit of discussion was enteral tube feeding as an effective treatment of GORD and not its use for other conditions, such as swallowing problems for example 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 GDG stressed that enteral tube feeding was not a cure for GORD, but provided relief from symptoms, particularly allowing weight gain. This can give health professionals time to investigate other possible causes of the symptoms and plan further treatment, such as consideration of 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 GDG, that there are potential harms related to tube feeding that should be considered before commencement. It was the experience of the

GDG that feeding exclusively via an enteral tube can create behavioural issues relating to oral food aversion when tube feeding is stopped. It was agreed that as a precautionary measure, oral stimulation should be continued throughout enteral tube feeding treatment. Dependent on the individual, a variety of tastes and textures should be explored. It is important to stress that the exclusive use of enteral tube feeding can disrupt normal feeding behaviour and therefore can lead to long term feeding difficulties.

The GDG were aware of an on-going 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 gastric enteral feeding tube, and the need to consider undertaking a fundoplication to prevent this. It was outlined by the GDG that enteral tube feeding when used 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 GDG 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 GDG were also concerned that without a clear plan for the removal of enteral feeding for GORD that it could unnecessarily be used as a long-term therapy. The GDG 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 usual need for an inpatient admission pending discharge to the community with an appropriate supporting team the GDG advise that a gastroenterology specialist be involved in reviewing the indication for this management decision.

8.1.633 Consideration of health benefits and resource uses

The GDG outlined that the main costs were related to staff time and equipment required, but that there were costs associated with not using enteral tube feeding as the child or young person would still require feeding.

The GDG 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.

8.1.634 Quality of evidence

No evidence was identified that met the predefined inclusion criteria for this review question. Therefore, recommendations were based on GDG experience and knowledge.

8.1.635 Other considerations

The GDG 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.

8.187 Recommendations

8.1.791 Recommendations

35. 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

36. 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.

37. 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.

8.1.12 Research recommendations

No research recommendations in this area.

9 Surgery for GORD

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 alternatively as an anti-vomiting procedure in children with complex, severe neurodisabilities which is 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, also known as laparoscopic or keyhole techniques, 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 relatively frequently performed, 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 six months after the procedure, but a restricted diet may be required initially. 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. Particularly in neurologically impaired children, retching can be an intractable symptom following fundoplication. 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.

9.1 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

9.1.2 Description of included studies

Four comparative studies met the inclusion criteria for this review, two RCTs (McHoney et al., 2011; Knatten et al., 2012) and two 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 one study compared fundoplication with gastrojejunal feeding tubes (Srivastava et al., 2009).

Sample sizes ranged from 44 to 456. Studies included children up to 5 years of age.

Two studies were undertaken in the USA (Diaz et al., 2005;Srivastava et al., 2009), one in the UK (McHoney et al., 2011) and one in Norway (Knatten et al., 2012).

More details on each individual study can be found in the evidence tables.

9.1.3 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.

Table 50: GRADE findings 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[a]	None	Serious	Very serious[b]	Yes[c]	3/18 (16.7 %)	1/14 (7.1 %)	Odds ratio [OR] (95% CI): 2.60 (0.24-28.14)[d]	9.5% (-17.1 to 32.8)[e]	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[f]	None	None	Very serious[b]	Yes[c]	1/20 (5%)	3/19 (16 %)	OR (95% CI): 0.28 (0.03-2.97)[d]	-10.8 (-33 to 10.5)[e]	Very low
Reported as patients with complications occurring in the first 30 days after surgery, n/N, %											
1 (Knatten	RCT	Very serio	None	None	Very serio	Yes[k]	24/44	24/44	OR (95%	-	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
et al., 2012)		us[g,h,i,j]			us[b]		(55%)	(55%)	CI): 1 (0.43-2.31)[d]		
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[g,h,i,j]	None	None	Not assessed[q]	Yes[k]	31	34	NA	-	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[g,h,i,j]	None	None	Not assessed[q]	Yes[k]	11	11	NA	-	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[g,h,i,j]	None	None	Not assessed[q]	Yes[k]	18	17	NA	-	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[g,h,i,j]	None	None	Not assessed[q]	Yes[k]	2	6	NA	-	Low
Reported as patients readmitted to hospital because of complications after discharge, n/N, %											
1 (Knatten et al., 2012)	RCT	Very serious[g,h,i]	None	None	Very serious[b]	Yes[k]	11/44 (25%)	12/44 (27%)	OR (95% CI): 0.89 (0.34-2.30)[d]	-	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[f]	None	None	Very serious[b]	Yes[c]	2/20 (16%)	3/19 (11%)	OR (95% CI): 1.42 (0.21-9.52)[d]	-5.8% (-28.7 to 16.8)[e]	Very low
Reported as late postoperative incidence of dysphagia, n/N, % (exact follow-up time point not reported)											
1 (McHone	RCT	Serious[f]	None	None	Not asse	Yes[c]	0/16 (0%)	1/16 (6.3	-	-6.3% (-28.3	Moderate

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
y et al., 2011)					ssed [q]			%)		to 13.8)[e]	
Reported as late postoperative incidence of retching o, n/N, %											
1 (McHoney et al., 2011)	RCT	Very serious[a,p]	None	None	Very serious[b]	Yes[c]	10/18 (55.6)	1/16 (6.3 %)	OR (95% CI): 18.75 (2.02 - 173.94)[d]	49.3% (18.3 to 69.8)[e]	Very low
Reported as mean time to full feed in days, mean (CI)											
1 (McHoney et al., 2011)	RCT	None	None	Serious	Not assessed [q]	None	2 (2 to 4)	2 (2 to 4)	P = 0.85[e]	-	Moderate

NA-not applicable or not calculable on the data
[a] *Unbalanced drop-out in the LNF arm, reasons not reported*
[b] *Wide confidence interval (CI crosses three zones)*
[c] *The study was not adequately powered for the clinical outcomes*
[d] *NCC-WCH calculation*
[e] *As reported by study authors*
[f] *Unclear whether a valid and reliable method was used to assess outcome*
[g] *No adequate concealment*
[h] *No blinding of the patients or postoperative care staff*
[i] *Unclear whether the groups received same level of care*
[j] *Unclear whether a valid and reliable method was used to assess outcome*
[k] *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*
[l] *Graded according to the Clavien-Dindo classification. Grade I complications do not require pharmacologic treatment, including dislocated gastrostomy, hematoma at the epigastric port site, gastroenteritis, wound infection, and feeding problems*
[m] *Graded according to the Clavien-Dindo classification. Grade II complications require pharmacologic treatment with drugs other than those allowed for Grade I, including airway complications, gastrostomy infection, blood transfusion, urinary tract infection, and gastroenteritis*
[n] *Graded according to the Clavien-Dindo classification. Grade IIIb complications implies that surgical, endoscopic, or radio logic intervention has been performed. Grade IIIb denotes interventions with the use of general anaesthesia, including food impaction, port site hernia/wound rupture, and redo gastrostomy*
[o] *Continued beyond the first six weeks after surgery*
[p] *Subjective outcome reported by parents postoperatively*
[q] *Data was not presented in a way that allowed imprecision to be calculated.*

Table 51: GRADE findings 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 (%)											

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**
1 (Diaz et al., 2005)	Retrospective cohort study	Serious[a, b]	None	Serious	Very Serious[c]	None	43/306 (14%)	12/150 (8%)	Odds ratio [OR] (95% CI): 1.88 (0.96-3.68) [d,e]	-	Very low
Reported as frequency of short-term acute bleeding, n (%),											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[a,b,f]	None	None	Not assessed[k]	None	1 (0.8%)	0	P = 0.67[d]	-	Very low
Reported as frequency of short-term acute respiratory problem, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[a,b,f]	None	None	Not assessed[k]	None	4 (1.3%)	12 (8%)	P = 0.046[d]	-	Very low
Reported as frequency of acute infection, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[a,b,f]	None	None	Not assessed[k]	None	3 (0.9%)	2 (1.3%)	P = 0.53[d]	-	Very low
Reported as frequency of acute prolonged ileus, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[a,b,f]	None	None	Not assessed[k]	None	4 (1.3%)	14 (9.3%)	P = 0.0003[d]	-	Very low
Reported as acute other, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[a,b,f]	None	None	Not assessed[k]	None	6 (1.9)	6 (4%)	P = 0.2[d]	-	Very low
Reported as total frequency of acute complications, n (%)											
1 (Diaz et al., 2005)	Retrospective cohort study	Very serious[a,b,f]	None	None	Not assessed[k]	None	18 (5.9%)	34 (22.7%)	P = 0.0001[d]	-	Very low
Reported as potential risk factors (LNF versus ONF) associated with reoperation											
1 (Diaz et al., 2005)	Retrospective cohort	Serious[g]	None	None	Very serious[c]	None	-	-	OR (95% CI):	-	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
	study								1.68 (0.84-3.3) P = 0.1427[d,g]		
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[a,b]	None	None	Very serious[c]	None	Survival/reoperation, n (%): 274 (89.5%)/ 32 (10.5%)[h]	Survival/reoperation, n (%): 144 (96%)/ 6 (4.0%)[h]	OR (95% CI): 2.80 (1.15-6.86)[i]	-	Very low
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[a,b]	None	None	Very serious[c]	None	Survival/reoperation, n (%): 265 (86.6%)/41 (13.4%)[h]	Survival/reoperation, n (%): 140 (93.3%)/10 (6.7%)[h]	OR (95% CI): 2.17 (1.05-4.45)[i]	-	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[a,b]	None	None	Very serious[c]	None	Survival/reoperation, n (%): 262 (85.6%)/44 (14.4%)[h,j]	Survival/reoperation, n (%): 138 (91.9%)/12 (8.1%)[h]	OR (95% CI): 1.93 (0.99-3.78)[i]	-	Very low

NA-not applicable or not calculable on the data
[a] *Intervention groups were not comparable at baseline in terms of undergoing diagnoses*
[b] *Unclear whether there were systematic differences between groups in the care provided*
[c] *Confidence interval crosses three zones*
[d] *As reported by study authors*
[e] *Unadjusted odds ratio*
[f] *Unclear how outcomes were ascertained, diagnosed or verified*
[g] *Odds ratio adjusted for age, gender, neurological impairment, chronic respiratory condition, cardiac disease, prematurity, and reflux alone*
[h] *Percentage as reported by study authors, number of patients calculated by NCC-WCH*
[i] *NCC-WCH calculation*
[j] *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.*
[k] *Data was not presented in the paper in a format that allowed imprecision to be assessed.*

Table 52: GRADE findings for observational comparison of fundoplication with gastro-jejunal feeding tubes (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[d]	Very serious[c,d,e]	None	None	None	None	40/323 (12%)	9/43 (21%)	Hazard ratio [HR], (95% CI): 0.30 (0.12-0.73)[f]	-	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 study[b]	Very serious[c,d,e,g]	None	None	Very serious[h]	None	48/323 (15%)	7/43 (16%)	HR (95% CI): 0.71 (0.21-1.69)[i]	-	Very low

[a] *The study was underpowered to detect true differences in this infrequent outcome*
[b] *Study subjects were children with neurologic impairment and GORD*
[c] *Intervention groups were not comparable at baseline in terms of comorbidities*
[d] *Confounders including propensity for surgical indication were adjusted for in analyses, but there still could be other unmeasured confounders*
[e] *Unclear whether the groups received same level of care before and after surgery*
[f] *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*
[g] *The distinction between AP caused by primary aspiration (e.g., secretions) or secondary aspiration (e.g., refluxed GERD) could not be made because of the nature of the retrospective study*
[h] *Confidence interval crosses three zones*
[i] *Adjusted hazard ratio from Cox model adjusting for propensity scores for surgery indication and baseline heterogeneities*

9.1.4 Evidence statements (see Table 50 to Table 52)

9.1.4.1 Fundoplication compared to laparoscopic fundoplication

One study was unable to determine if there was a difference in frequency of overt regurgitation in children treated open fundoplication compared to those treated with laparoscopic fundoplication. The quality of evidence for this finding was very low.

Results from one RCT study found no difference in short-term adverse events. Results from one retrospective observational study found that rates of reoperation were higher in children who had undergone laparoscopic fundoplication compared to those who had undergone open fundoplication at 12 and 24 months post-operation, but not by 36 months. 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.

No data was found for other outcomes.

9.1.4.12 Open compared to gastrojejunal feeding tubes

One study found that long-term mortality was reduced in children who had undergone fundoplication compared to 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.

9.1.5 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).

9.1.6 Evidence to recommendations

9.1.6.1 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 GDG 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 pH-metry or impedance monitoring) and subjective (parent reported reduction in infant distress and parent satisfaction with the intervention) outcomes were included.

9.1.6.2 Consideration of clinical benefits and harms

The GDG noted that the available evidence on fundoplication was limited in quantity, quality and scope, with few of the outcomes outlined by the GDG being reported. Therefore, the majority of the discussion was based on the GDGs own experience.

The GDG discussed whether fundoplication can be effective in the treatment of GORD in children and young people. Only one study was identified and this reported on the safety of fundoplication compared to gastro-jejunal feeding. It showed a lower mortality rate ain 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.

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 are requiring utterly 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 GDG 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 GDGs focused their 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 there was a concern 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 GDG 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 GDG 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 GDG concluded that consideration must be given to the potential benefit of having additional information from either or both pH/Impedance study 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 also ensure that the benefits are likely to outweigh the risks for the particular child and family.

Finally, the GDG assessed the evidence comparing laparoscopic with open fundoplication to treat GORD in children and young people. The available evidence from three studies low quality studies showed no difference in outcomes, based on this the GDG did not believe a recommendation on which should be used could be made. However, it was the experience of the GDG that open fundoplication had a number of disadvantages compared to laparoscopic surgery related to the larger wound: greater pain and discomfort, longer length of stay and longer recovery period being the main ones. 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 that unless the results of “open” surgery are clearly superior to “laparoscopic” surgery then equivalence in reported outcomes ought to logically favour the laparoscopic approach given the other obvious benefits.

9.1.273 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 GDG’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 to adults, and the underlying cause of GORD / severe regurgitation may be different in children (for example, caused by evolving dysmotility in cerebral palsy) compared to adults (for example, 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 specific symptom, surgical management may be considered the only option to treat GORD where 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.

9.1.6.14 Quality of evidence

Only four comparative studies were identified for this review, two RCTs and two retrospective observational studies. Unfortunately, none of the studies clearly answered the most question – "Is fundoplication 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. In the observational studies, biases included retrospective design and loss to follow-up

Given the limited amount and quality of the evidence available, it is not possible to make strong recommendations on the use of fundoplication.

9.1.6.15 Other considerations

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

9.1.7 Recommendations

9.1.7.1 Recommendations

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

39. Think about performing other investigations such as pH–impedance monitoring for infants, children and young people before deciding whether to offer fundoplication.

40. 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.

9.1.7.2 Research recommendations

3. What are the effects on pH monitoring results before and after fundoplication?

Why this is important

Fundoplication is used to manage severe GORD. At present, there is limited evidence showing 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 pH monitoring. This may help health professionals identify which children and young children will benefit from surgery.

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10 Glossary and abbreviations

10.1 Glossary

Table 53: Glossary terms

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 haemoglobin with or without symptoms outside 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, e.g. 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 'soft spot' palpable on the top of the head created by the gaps between the skull bones (usually at the front and the back). These fontanelles which normally closes in the first year of life, and if elevated ('bulging'), this may indicate a pathological rise in the pressure inside the head. This is a sign of meningitis and poor drainage of cerebrospinal fluid, known as due to anatomical issues when it may suggest

Term	Description
	'hydrocephalus'.
Case–control study	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. 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 whenever 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 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 (e.g. environmental factors) had been ruled out.
Child:	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, e.g. 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.

Term	Description
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 well 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 ingest a substance which will show up on X-ray e.g. barium, to highlight certain aspects of the anatomy. The gastrointestinal tract and elements of its function can be visualised by this method.
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.
Cow's milk protein	In dairy produce there are a number of proteins which are collectively known as 'cow's milk protein'.
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 / young people with a neurodisability who are unable to communicate clearly. Examples include crying, grimacing, other objective clinical signs of pain, and / 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.

Term	Description
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 (e.g. the stomach or intestine) in order to obtain images, 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(D). A variety of techniques are used.
Fundoplication - open vs laparoscopic	Open' refers to a surgical approach with an entry into the abdomen via a surgical incision. Laparoscopic involves instruments inserted into the abdomen with small scars and is also known as 'key-hole' surgery.
Gastro-oesophageal reflux	Gastro-oesophageal reflux 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 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 adultsthe term GORD is often used more narrowly, referring specifically to reflux oesophagitis.
H2-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.
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(D).
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 6-10 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	Older than 28 days but younger than 1 year

Term	Description
Likelihood ratio	Used to assess the benefit of undertaking a diagnostic test. It is based on sensitivity and specificity.
Medical management	Any intervention aimed at alleviating a disease or condition when instigated by a medical practitioner or team.
Melaena	Black-coloured, foul-smelling stool which is usually a sign of a significant amount of partially-broken-down blood in the stool altered blood lost further up the gut.
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/m2. Age and gender specific charts are used to determine BMI centile and BMI above the 98th centile indicates obesity in children and young people.
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 (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
Occult reflux	Reflux which does not appear out of the mouth i.e. with no associated outward signs of regurgitation or vomiting.
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' and 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

Term	Description
	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 during pregnancy abnormally resulting in a blind ended tube with no passage to the stomach.
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	When regurgitation gastric contents come up into is seen coming out of the mouth or into the mouth.
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 P = 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 kind of 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 (i.e. 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. In no way do they relate to how big the effect might be, for which we need the confidence interval.
Paediatric specialist	The term paediatric specialist refers to a healthcare professional who has had specific training or has recognised expertise in the management of children and their illnesses. Examples include paediatricians, or healthcare professionals working in children's emergency departments.
pH impedance monitoring	A combined technique in which a thin tube is placed via the nose into the oesophagus and this allows 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 a 24 hours and allows association between reflux and symptoms in real time.
pH monitoring	A technique in which a thin tube is placed via the nose into the oesophagus and this allows measurement in real time of acid reflux (by measuring of

Term	Description
	acid/neutral/alkaline).
Physiological reflux	Reflux which occurs in all infants and children to some 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 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 placebo effect 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.
Prokinetic agents	Drugs which help the stomach to empty faster by increasing the speed 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 two 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

Term	Description
	the treatment they receive during the study.)
Reflux oesophagitis	Inflammation of the oesophagus due to reflux. This and can be seen at endoscopy or only seen when biopsies taken at endoscopy are analysed under microscopic examination of the tissue.
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 the stomach contents up the oesophagus to the mouth.
Relative risk	A summary measure that represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in 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 the present/past 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(D). It should resolve with correct treatment of the GOR(D).
Secondary care	Care provided in District General Hospitals, generally led by paediatricians and the 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.
Specialist	Consultant paediatrician
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.

Term	Description
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 the multidisciplinary teampaediatric gastroenterologist-led care.
Treatment failure	When a medical intervention has failed to relieve or resolve the problem or condition.
Urgent	Requiring same day care
Young person	12 years to 17 years

10.2 Abbreviations

Table 54: Abbreviations

Abbreviation	Description
BMI	body mass index
CI	confidence interval
GI	gastrointestinal
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
H2RAs	H2-receptor antagonists
NPV	negative predictive value
OR	odds ratio
PPI	proton pump inhibitors
PPV	positive predictive value

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Appendices

The Appendices for this guideline are in a three separate documents.